CLINICAL DIABETOLOGY

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Contents

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COVID-19 in patients with gestational diabetes: review of literature

ABSTRACT

The risk of severe acute respiratory distress syndrome associated with coronavirus-2 (SARS-CoV-2) to maternal and newborn health has yet to be determined. Several studies showed that pregnancy with gestational diabetes increased the risk of maternal illness, but cases of gestational diabetes, preeclampsia and preterm birth have been reported rarely. Reports indicated placental infection and vertical transmission of COVID-19 were uncommon. Interestingly, despite the lack of SARS-CoV-2 placental infection, there were many records of major abnormalities in placental morphology. Continued research into offsprings of pregnant women with gestational diabetes infected with SARS-CoV-2 was vitally necessary. This study showed the impact of COVID infections on the fetus and the newborn in GDM pregnancy. There were very few data considering this subject and therefore, the findings have nowadays very debatable value. However, it's worthwhile to show the scientific community that nowadays we have no proof that COVID infection has a significant impact on pregnancy and the fetus. (Clin Diabetol 2020; 9; 6: 367–371)

Key words: COVID-19, patients, gestational diabetes

Introduction

Severe acute respiratory distress syndrome associated with coronavirus-2 (SARS-CoV-2), was an etiological agent of Coronavirus disease 2019 (COVID-19). It was first identified in Wuhan, China, in December 2019 and is now a global pandemic. To date, more than 4 million cases and 300,000 deaths have been registered by the World Health Organisation. There has been a significant increase in awareness of the genetic, virological, epidemiological, and clinical aspects of COVID-19, but there are far fewer studies explaining the risks and unique impact of COVID-19 on pregnant females with gestational diabetes and their newly born infants. In this study, both peer-reviewed and non-peer-reviewed preprints were included in order to identify the most up-to-date information.

Pregnancy with gestational diabetes increases the risk of adverse obstetric and neonatal outcomes due to many respiratory viral infections. The maternal immune system is altered during pregnancy in order to prevent the rejection of the fetus and to contribute to the development of the fetus [1]. Some viral infections cause more serious or prolonged illness in pregnant women with gestational diabetes [2]. COVID-19 has resulted in elevated rates of abortion, infant mortality and preterm delivery [3]. Multiple influenza studies have shown an increased risk of maternal morbidity and mortality relative to non-pregnant women. On the other hand, the majority of results for pregnant women with gestational diabetes infected with SARS-CoV-2 [5–53] do not vary from the general population. Fever is the most common symptom of COVID-19 in these patients, but many also experience cough, shortness of breath, and diarrhea. Occasionally serious infections involved mechanical ventilation [2–46] but rarely resulted in death [4, 5].

COVID in pregnant women with gestational diabetes

Although the majority of COVID infections in pregnant women with gestational diabetes were mild, data indicated substantial placental pathology

in SARS-CoV-2 pregnancy despite lack of detectable or very low levels of SARS-CoV-2 mRNA or protein [4–43]. There were, however, case studies suggesting COVID-19 virons in syncytio-trophoblasts in placental villous when examined by the electron microscopy [6–8] or (PCR) [5, 28, 36]. The significant questions that remains unanswered are, whether SARS-CoV-2 replicates in the placenta, whether it is the cause of the reported placenta abnormalities and, whether SARS-CoV-2 is an "innocent bystander." It is also important to note that the identified placenta abnormalities occur mainly in women who are asymptomatic or have mild to moderate illness, indicating that these defects are not necessarily due to severe COVID disease.

Placenta abnormalities in diabetic women

The placenta abnormalities identified in an infected diabetic pregnant women with SARS-CoV-2 include diffuse perivil fibrin, fetal vascular malperfusion in fetal vessels, choriohemangioma, maternal vascular malperfusion, and multifocal infarctions [17, 26, 36]. In some cases, SARS-CoV-2 has been found in the placenta [5, 17, 28, 36]. Lack of controls and non-specific staining issues [16] complicate the interpretation of these findings in some of these studies. Importantly, the vast majority of placenta cases were negative for SARS-CoV-2 as calculated by PCR [12, 22, 26, 27, 36, 41, 43]. The anomalies observed in placenta pathology therefore indicated that the placenta was vulnerable to maternal COVID-19 disease, even in the absence of infection, because in many cases these disorders may be due to maternal co-morbidities such as hypertension, preeclampsia, and gestational diabetes. There is, therefore, a vital need for thorough systematic studies to determine the prevalence of infection and replication of SARS-CoV-2 in the placenta and its connection with placenta abnormalities.

Easy vertical transmission?

It still remains to be seen whether SARS-CoV-2 can be transferred from a diabetic pregnant woman to her fetus, a process called vertical transmission. Importantly, the transmission is predicted to have various effects over the three trimesters of pregnancy. Transplacental transmission of the virus typically increases with advanced gestational age, while there is a decreases in the incidence of fetal injuries from embryopathy and embryo/fetal death in the first trimester, from fetal infection and immune response during the second and third trimesters. Unlike many other viral diseases, viremia in SARS-CoV-2 is observed in just 1% of symptomatic patients and is usually mild and transient [19].

Effect of COVID-19 on newly born infants

Most of the case reports documented that, the birth of a full term baby to COVID-19 positive mothers with mild to moderate illness is not carrying any significant risk to the baby itself [8–53]. Preterm births, on the other hand, are fairly common in women with severe illness, although there are sporadic reports of spontaneous preterm births [9–53]. Spontaneous abortion has also been reported twice in early pregnancy [5, 45] and fetal death has been reported 6 times [13, 18, 23, 24]. Case reports of newborns with symptoms requiring NICU admission for tachypnea, tachycardia, fever, gastrointestinal symptoms, and signs of CT pulmonary infection [2, 7, 12, 27, 41, 48, 52, 53] were reported; with 2 of 5 had NP swabs positive for SARS-CoV-2. Interestingly, some symptomatic infants tested negative for SARS-CoV-2. In one case, a positive SARS-CoV-2 infant born at 31 weeks of age needed resuscitation and was diagnosed with pneumonia, but the authors confirmed that they suspected sepsis with Enterobacter [52]. Thus, with the exception of these unusual cases, neonates were born healthy to infected mothers with SARS-CoV-2. However, it has yet to be known whether infection at an earlier stage would have a significant effect on neonatal health and whether it results in long term outcomes.

Actual mode of transmission

Newborns may be infected by viral infection from mother either directly by the virus through vertical transmission or passively, by the maternal reaction to the virus. Considerable evidence indicates the absence of vertical transmission of SARS-CoV-2. Multiple newborns were screened for SARS-CoV-2 at delivery and viral RNA was not found in cord blood, throat and nasopharyngeal swabs, urine, and feces [5, 51]. Amniotic fluid samples were also obtained from positive COVID pregnant mothers and were mainly screened negative for SARS-CoV-2 [5–49]. Neonatal testing, 24 hours or more after birth, have rarely been confirmed positive for the virus [27–52], but due to delays in testing, these infants may have already been infected after birth. There was one case report of COVID-19 neonates at birth, but the baby was symptom free with, perhaps, the exception of some minor initial nursing problems [28]. In addition, despite cautious isolation, the baby born at 33 weeks of age tested positive after 16 hours and again after 48 hours post-partum [2]. The authors indicated that this infant may have been infected either during the delivery of the ceasarean or in the uterus. The baby needed admission to the NICU for low Apgar scores and ventilator support.

Antibodies were found in neonatal blood

Most babies in these studies were delivered by a cesarean section, and it is possible that newborns could potentially be contaminated during vaginal delivery. Vaginal swabs, however, were screened negative at 37 weeks of caesarean section delivery [12] and negative for SARS-CoV-2 in 6 women at hospital admission [45]. Intriguingly, despite the absence of virus present in neonate at birth, antibodies have been detected in neonatal tissue [51]. In particular, IgM has been documented to be elevated indicating fetal exposure to the uterine virus [51]. It is important to note that IgM antibody testing results in a high risk of false-positive [19] but these findings indicate that ongoing neonatal antibody testing can be useful.

Extracellular vesicles confer viral resistance to receptor cells

Overall, there is little evidence of vertical transmission in the majority of cases of positive COVID-19 birth. The fact that viremia is present in 1% of symptomatic patients and is usually mild and temporary may play a role [42]. However, other processes are likely to be just as important or more important in the defense of the fetus against vertical transmission. Maternal-fetal interface barriers protect the fetus from infection. For example, the syncytiotrophoblasts–organize the immune response to infection and also act as a physical barrier to the viral passage [29, 47]. Immune cells in the placenta also have anti-viral potential [47]. Finally, previous studies have shown that trophoblast-derived extracellular vesicles containing a special group of miRNAs, expressed as chromosome 19 miRNA clusters, confer viral resistance to receptor cells suggesting a paracrine role that allows contact between placental cells to control their immunity to viral infections [10].

The ability of the virus to replicate and infect the placenta is also dependent on the virus. In the case of SARS-CoV-2, the entry of cells requires the binding of the spike protein to ACE2 [15]. The virus is then produced by cellular proteases such as TMPRSS2 [15] and possibly cathepsin B/L7 [37] and furin [6]. Utilizing recently reported single-cell RNAseq results, researchers have observed robust ACE2 activity in the placenta [21, 37] though not in TMPRSS2 [37]. Two studies, using single nucleotide RNAseq or single-cell RNAseq, were recently performed during gestation and found expression of ACE2 but either no or very low levels of TMPRSS2 were detected in the placenta [3, 32]. There has been no systematic assessment of the presence and role of other proteases that lead to viral entry and replication in the placenta cell. ACE2 was observed by 133 IHC in syncytio-trophoblast, cyto-trophoblast, endo-thelial and smooth muscles of the blood vessels [40].

Interestingly, ACE2 is involved in placentation, including the migration of trophoblasts, vascular remodeling, and maternal vasodilation [33, 39]. Complications such as abortion, ectopic pregnancy, and preeclampsia have also been implicated in ACE2 [40]. Therefore, if SARS-CoV-2 affects the expression of ACE2 in the placenta as shown by SARS-CoV-1 in the lung [20], there is a risk for placental defects and complications of pregnancy. The existence of ACE2 in the placenta could mean that there is a capacity to bind COVID-19 to cause viral infection, but there are mechanisms that underlie SARS-CoV-2's failure to infect and replicate in the placenta are unknown.

Conclussion

Vertical transmission of SARS-CoV-2 is considered unlikely at this time but there appears to be considerable potential for SARS-CoV-2 to affect the placental function and fetal development. Continued research is, therefore, needed focusing especially on the detection of SARS-CoV-2 at early gestational time points. Finally, careful longitudinal studies with adequate controls are needed before any conclusions about COVID-19's maternal or neonatal effects are drawn.

Conflict of interest

The author declare no conflict of interest.

REFERENCES

1. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol. 2017; 17(8): 469–482, doi: 10.1038/nri.2017.64, indexed in Pubmed: 28627518.
2. Racicot K, Mor G. Risks associated with viral infections during pregnancyViral infections during pregnancy. J Clin Invest. 2017; 127: 1591–1599.
3. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004; 191: 292–297.
4. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19. Am J Obstet Gynecol. 2020; 223(1): 109.e1–109.e16, doi: 10.1016/j.ajog.2020.04.030, indexed in Pubmed: 32360108.
5. Karami P, Naghavi M, Feyzi A, et al. WITHDRAWN: Mortality of a pregnant patient diagnosed with COVID-19: A case report with clinical, radiological, and histopathological findings. Travel Med Infect Dis. 2020 [Epub ahead of print]: 101665, doi: 10.1016/j.tmaid.2020.101665, indexed in Pubmed: 32283217.
6. Algarroba GN, Rekawek P, Vahanian SA, et al. Visualization of severe acute respiratory syndrome coronavirus 2 invading the human placenta using electron microscopy. Am J Obstet Gynecol. 2020; 223(2): 275–278, doi: 10.1016/j.ajog.2020.05.023, indexed in Pubmed: 32405074.
7. Hosier HFS, Morotti R, Deshmukh U, et al. First case of placental infection with SARS-CoV-2. J Clin Investig. 2020; 130(9): 4947–4953, doi: https://doi.org/10.1172/JCI139569.

8. Patane L, Morotti D, Giunta MR, et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019–positive mothers and neonates at birth. Am J Obstet Gynecol MFM. 2020; 2(3): 100145. , doi: 10.1016/j.ajogmf.2020.100145.

9. Alzamora MC, Paredes T, Caceres D, et al. Severe COVID-19 during pregnancy and possible vertical transmission. Am J Perinatol. 2020; 37(8): 861–865, doi: 10.1055/s-0040-1710050, indexed in Pubmed: 32305046.

10. Ashary N, Bhide A, Chakraborty P, et al. Single-Cell RNA-seq Identifies Cell Subsets in Human Placenta That Highly Expresses Factors Driving Pathogenesis of SARS-CoV-2. Frontiers in Cell and Developmental Biology. 2020; 8, doi: 10.3389/fcell.2020.00783.

11. Baergen RN, Heller DS. Placental Pathology in Covid-19 Positive Mothers: Preliminary Findings. Pediatr Dev Pathol. 2020; 23(3): 177–180, doi: 10.1177/1093526620925569, indexed in Pubmed: 32397896.

12. Baud D, Greub G, Favre G, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 Infection. JAMA. 2020; 323(21): 2198–2200, doi: 10.1001/jama.2020.7233, indexed in Pubmed: 32352491.

13. Bestle D, Heindl M, Limburg H, et al. TMPRSS2 and furin are both essential for proteolytic activation and spread of SARS-CoV-2 in human airway epithelial cells and provide promising drug targets. , doi: 10.1101/2020.04.15.042085.

14. Breslin N, Baptiste C, Gyamfi Bannerman C G. COVID 19 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM 100118. 2020.

15. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020; 395(10226): 809–815, doi: 10.1016/S0140-6736(20)30360-3, indexed in Pubmed: 32151335.

16. Chen L, Li Q, Zheng D, et al. Clinical characteristics of pregnant women with Covid-19 in Wuhan, China. N Engl J Med. 2020; 382(25): e100, doi: 10.1056/NEJMc2009226, indexed in Pubmed: 32302077.

17. Delorme-Axford E, Donker RB, Mouillet JF, et al. Human placental trophoblasts confer viral resistance to recipient cells. Proc Natl Acad Sci U S A. 2013; 110(29): 12048–12053, doi: 10.1073/pnas.1304718110, indexed in Pubmed: 23818581.

18. Dong L, Tian J, He S, et al. Possible Vertical Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn. JAMA. 2020; 323(18): 1846–1848, doi: 10.1001/jama.2020.4621, indexed in Pubmed: 32215581.

19. Fan C, Lei Di, Fang C, et al. Perinatal Transmission of COVID-19 Associated SARS-CoV-2: Should We Worry? Clin Infect Dis. 2020 [Epub ahead of print], doi: 10.1093/cid/ciaa226, indexed in Pubmed: 32182347.

20. Hirshberg A, Kern-Goldberger AR, Levine LD, et al. Care of critically ill pregnant patients with coronavirus disease 2019: a case series. Am J Obstet Gynecol. 2020; 223(2): 286–290, doi: 10.1016/j.ajog.2020.04.029, indexed in Pubmed: 32371056.

21. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2): 271–280.e8, doi: 10.1016/j.cell.2020.02.052, indexed in Pubmed: 32142651.

22. Honig A, Rieger L, Kapp M, et al. Immunohistochemistry in human placental tissue   pitfalls of antigen detection. J Histochem Cytochem. 2005; 53(11): 1413–1420, doi: 10.1369/jhc.5A6664.2005, indexed in Pubmed: 16009964.

23. Kimberlin DW, Stagno S. Can SARS-CoV-2 infection be acquired in utero? More definitive evidence is needed. JAMA. 2020; 323(18): 1788–1789, doi: 10.1001/jama.2020.4868, indexed in Pubmed: 32215579.

24. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury.

Nat Med. 2005; 11(8): 875–879, doi: 10.1038/nm1267, indexed in Pubmed: 16007097.

25. Li M, Chen L, Zhang J, et al. The SARS-CoV-2 receptor ACE2 expression of maternal-fetal interface and fetal organs by single-cell transcriptome study. PLoS One. 2020; 15(4): e0230295, doi: 10.1371/journal.pone.0230295, indexed in Pubmed: 32298273.

26. Li Y, Zhao R, Zheng S, et al. Lack of vertical transmission of severe acute respiratory syndrome coronavirus 2, China. Emerg Infect Dis. 2020; 26(6): 1335–1336, doi: 10.3201/eid2606.200287, indexed in Pubmed: 32134381.

27. Liu Y, Chen H, Tang K, et al. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. J Infect. 2020 [Epub ahead of print], doi: 10.1016/j.jinf.2020.02.028, indexed in Pubmed: 32145216.

28. Lokken E, Walker C, Delaney S, et al. Clinical characteristics of 46 pregnant women with a severe acute respiratory syndrome coronavirus 2 infection in Washington State. American Journal of Obstetrics and Gynecology. 2020, doi: 10.1016/j.ajog.2020.05.031.

29. Mulvey JJ, Magro CM, Ma LX, et al. Analysis of complement deposition and viral RNA in placentas of COVID-19 patients. Ann Diagn Pathol. 2020; 46: 151530, doi: 10.1016/j.anndiagpath.2020.151530, indexed in Pubmed: 32387855.

30. Nie R, Wang Ss, Yang Q, et al. Clinical features and the maternal and neonatal outcomes of pregnant women with coronavirus disease 2019. , doi: 10.1101/2020.03.22.20041061.

31. Pereira L. Congenital viral infection: traversing the uterine-placental interface. Annu Rev Virol. 2018; 5(1): 273–299, doi: 10.1146/annurev-virology-092917-043236, indexed in Pubmed: 30048217.

32. Pierce-Williams RAM, Burd J, Felder L, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. Am J Obstet Gynecol MFM. 2020; 2(3): 100134, doi: 10.1016/j.ajogmf.2020.100134, indexed in Pubmed: 32391519.

33. Piersigilli F, Carkeek K, Hocq C, et al. COVID-19 in a 26-week preterm neonate. The Lancet Child & Adolescent Health. 2020; 4(6): 476–478, doi: 10.1016/s2352-4642(20)30140-1.

34. Pique Regi R RR, Tarca A, Luca F, Xu Y, Alazizi A, Leng Y, Hsu C, Gomez Lopez N. Does the human placenta express the canonical cell entry mediators for SARS-CoV-2? https://elifesciences.org/articles/58716.

35. Pringle KG, Tadros MA, Callister RJ, et al. The expression and localization of the human placental prorenin/renin-angiotensin system throughout pregnancy: roles in trophoblast invasion and angiogenesis? Placenta. 2011; 32(12): 956–962, doi: 10.1016/j.placenta.2011.09.020, indexed in Pubmed: 22018415.

36. Schwartz DA. An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med. 2020 [Epub ahead of print], doi: 10.5858/arpa.2020-0901-SA, indexed in Pubmed: 32180426.

37. Shanes ED, Mithal LB, Otero S, et al. Placental Pathology in COVID-19. Am J Clin Pathol. 2020; 154(1): 23–32, doi: 10.1093/ajcp/aqaa089, indexed in Pubmed: 32441303.

38. Sungnak W, Huang Ni, Bécavin C, et al. HCA Lung Biological Network. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med. 2020; 26(5): 681–687, doi: 10.1038/s41591-020-0868-6, indexed in Pubmed: 32327758.

39. Sutton D, Fuchs K, D'Alton M, et al. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. N Engl J Med. 2020; 382(22): 2163–2164, doi: 10.1056/NEJMc2009316, indexed in Pubmed: 32283004.

40. Valdés G, Corthorn J, Bharadwaj MS, et al. Utero-placental expression of angiotensin-(1-7) and ACE2 in the pregnant guinea-pig. Reprod Biol Endocrinol. 2013; 11: 5, doi: 10.1186/1477-7827-11-5, indexed in Pubmed: 23339712.

41. Valdés G, Neves LAA, Anton L, et al. Distribution of angiotensin-(1-7) and ACE2 in human placentas of normal and pathologi-

cal pregnancies. Placenta. 2006; 27(2-3): 200–207, doi: 10.1016/j.placenta.2005.02.015, indexed in Pubmed: 16338465.

42. Wang S, Guo L, Chen L, et al. A case report of neonatal 285 COVID 19 infection in China. Clin Infect Dis. 2020; ciaa225, doi: 10.1093/cid/ciaa225.

43. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 2020; 323(18): 1843–1844, doi: 10.1001/jama.2020.3786, indexed in Pubmed: 32159775.

44. Wang X, Zhou Z, Zhang J, et al. A Case of 2019 Novel Coronavirus in a Pregnant Woman With Preterm Delivery. Clin Infect Dis. 2020; 71(15): 844–846, doi: 10.1093/cid/ciaa200, indexed in Pubmed: 32119083.

45. Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. Am J Obstet Gynecol. 2020; 223(1): 111.e1–111.e14, doi: 10.1016/j.ajog.2020.04.014, indexed in Pubmed: 32335053.

46. Yin M, Zhang L, Deng G, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection During Pregnancy In China: A Retrospective Cohort Study. BioRxiv. 2020, doi: 10.1101/2020.04.07.20053744.

47. Yockey LJ, Lucas C, Iwasaki A. Contributions of maternal and fetal antiviral immunity in congenital disease. Science. 2020; 368(6491): 608–612, doi: 10.1126/science.aaz1960, indexed in Pubmed: 32381717.

48. Yu N, Li W, Kang Q, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis. 2020; 20(5): 559–564, doi: 10.1016/S1473-3099(20)30176-6, indexed in Pubmed: 32220284.

49. Yu N, Li W, Kang Q, et al. No SARS-CoV-2 detected in amniotic fluid in mid-pregnancy. Lancet Infect Dis. 2020 [Epub ahead of print], doi: 10.1016/S1473-3099(20)30320-0, indexed in Pubmed: 32333848.

50. Zambrano LI, Fuentes-Barahona IC, Bejarano-Torres DA, et al. A pregnant woman with COVID-19 in Central America. Travel Med Infect Dis. 2020; 36: 101639, doi: 10.1016/j.tmaid.2020.101639, indexed in Pubmed: 32222420.

51. Zeng H, Xu C, Fan J, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. JAMA. 2020; 323(18): 1848–1849, doi: 10.1001/jama.2020.4861, indexed in Pubmed: 32215589.

52. Zeng L, Xia S, Yuan W, et al. Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China. JAMA Pediatr. 2020; 174(7): 722–725, doi: 10.1001/jamapediatrics.2020.0878, indexed in Pubmed: 32215598.

53. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020; 9(1): 51–60, doi: 10.21037/tp.2020.02.06, indexed in Pubmed: 32154135.

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How to manage the IVF during COVID-19 pandemic among diabetic females: a scientific perspective

ABSTRACT

Diabetes is a challenging clinical problem facing obstetricians and gynecologists when it comes to in vitro fertilization and embryo transfer (IVF-ET). During the COVID-19 pandemic we are living nowadays, COVID-19 becomes a new superimposing challenge for diabetic females need IVF-ET procedures.

The persistent lock-down of diabetic health facilities already advised by numerous organizations and contributing to challenging diabetes treatment is harmful to the whole population and in particular to patients with infertilities. Around 0.3% of all babies born last year were conceived with IVF-ET therapies worldwide. We recommend remedies to foresee more delicate infertility cases so as to prepare for a resumption of temporarily suspended fertility treatment.. In an age of crucial challenges for our national health services, complication prevention and tension management can help competent agencies and health providers identify patients that should be preferred to begin fertility treatment in a healthy environment.

What we consider as a possible possibility is the gradual restart of IVF, which needs many measures for diabetic patients. The problem of restarting IVF installations after the current lockdown is real since each nation follows a certain recovery curve. Especially as a result of silent dissemination, attention should be provided to COVID-19 infection among patients and health-care staff after the restart of IVF therapy. (Clin Diabetol 2020; 9; 6: 372–377)

Key words: IVF, COVID-19, pandemic, diabetic, females

Introduction

Since the early stages of the pandemic, diabetic patients have been at the frontline, as rising epidemiological evidence showed that they are at higher risk of serious clinical effects of COVID-19 [1]. However, the present global condition does not discourage women from pursuing an interest in building a family and dreaming of a child. Even if she is diabetic and tries IVF, there is a possible danger of in-vitro fertilization (IVF), which may end in respiratory and cardiovascular problems, termed a severe ovarian hyper-stimulation syndrome [2]. Since COVID-19 may also induce respiratory and cardiovascular complications, it is unclear how women with COVID-19 manage a serious ovarian hyper-stimulation syndrome. There are no records of these problems at the moment [3].

The risk of serious ovarian hyper-stimulation syndrome may be increased by diabetes with or without other concomitant autoimmune diseases [4, 5]. For thorough guidance before embarking on ovarian stimulation, knowledge of the association of current conditions and the potential for vascular leakage disorders is required. In this demographic, prevention steps may be essential factors [5].

It was also established that pregnancy accomplished by IVF was linked, according to a study team in Greece, with a higher risk of gestational diabetes. These methods are considered to be correlated with a greater risk of pregnancy and birth complications. More than half a million babies are projected to be born worldwide through IVF [6].

However, fertility and IVF problems allow the patient to slip into the difficulty of finding the right period for IVF after the pandemic. Either delay or resume the extraction of IVF eggs and embryos, or freeze the eggs/embryos until date of expiry of eggs/ /embryos [7].

There is currently little scientific data on the connection between coronavirus and fertility [8]. We know that diseases will sometimes contribute to fever that can influence the treatment of infertility [9]. One research has shown that fever was correlated with a reduced amount of embryos, a longer duration and a higher amount of treatment needed during their freezing or IVF cycle. However there is no proof that the impact of fever on female fertility persists longer [10].

COVID-19 and diabetes
Outcome of COVID-19 in diabetics

People with COVID-19 diabetes are more likely to have poor prognosis and mortality. Given the high worldwide incidence of diabetes, the COVID-19 demographic represents a significant susceptible group [11]. The worse prognosis of persons with diabetes is likely to be a result of the syndromic aspect of the condition: hyperglycemia, older age, comorbidity and in particular, hypertension, obesity and cardiovascular disease — all lead to growing incidence in these individuals [12]. The scenario, however, is more complicated as it involves factoring in social variables such as inequality and race, as well as factors that become important at a time when a patient with extreme COVID-19 needs to be handled. Here the specialist must not only provide treatment for the health condition of the individual with diabetes, but must also closely match glucose-lowering medications with complex virus infection treatments [13].

Diabetes management in COVID-19 patients

Once again, diabetes treatment in patients with COVID-19 represents a significant clinical challenge, one that needs a well-integrated team solution, since this is an indispensable technique to minimize the likelihood of serious problems and mortality as far as possible [14]. Careful consideration of the multiple components that lead to poor prognosis of COVID-19 in patients with diabetes might be one of the most, if not the only, way to address the current condition and make it easier for our health services to be able to meet any potential problems in a timely and successful manner [15].

Hidden relation between diabetes and COVID

Finally, the inter-relationship between diabetes and COVID-19 needs further studies in order to explain the degree to which the particular mechanisms of the virus (e.g. its pancreatic β-cell tropism) could contribute to the deterioration of glycemic regulation and in certain situations, to the striking development of diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome [16].

Glycemic control and its impact

Medical teams can maintain sufficient glycemic regulation in diabetic patients with COVID-19. This includes analysis of all possible effects that COVID-19 therapy may have had in patients with diabetes [17].

Treatment with chloroquine or hydroxychloroquine can induce hypoglycemia, especially in patients on insulin or sulfonylurea, due to their effects on insulin secretion, degradation and action [18]. Contrarily, medications such as lopinavir and ritonavir can contribute to hyperglycemia and exacerbate glycemic regulation [19]. These agents may induce hepatic and muscular toxicity, so vigilance is advised when used in conjunction with statins and in patients with fatty liver disease [20]. Pharmacokinetic reactions with antidiabetic drugs are often normal, triggering over-exposure or under-exposure to either antiviral or anti-diabetic drugs [21]. Glucocorticoids have been used as symptomatic and anti-inflammatory therapy in individuals with COVID-19 with extreme acute respiratory distress syndrome. However, their usage can exacerbate insulin resistance, retain gluconeogenesis, worsen glycemic regulation, and trigger pronounced hyperglycemia. Glucocorticoids are known to impose their hyperglycemic impact by lowering insulin sensitivity and insulin release, and also by interaction with GLP-1 effects, and by increasing the development of glucagon [22].

Diabetes and IVF
How diabetes can impact woman fertility

Women who have diabetes are usually at a higher risk for conceiving complications. There are several causes that may lead to lower fertility rates: obesity, underweight, diabetes problems, PCOS (polycystic ovarian syndrome) or autoimmune disorder. The above factors are consistent with diabetes in women, which usually contributes to lowered fertility rates [23].

Patients with PCOS are candidates for IVF

Polycystic ovary syndrome — PCOS is a medical disorder in which a large number of cysts form on the ovary and it may influence fertility due to irregular or missing cycles. PCOS is primarily linked with type 2 diabetes and obesity [24]. Cycles are considered irregular if periods occur at intervals of 35 days or more. Periods are considered to be missing when a woman who has previously had regular cycles is missing a period for 6 months or more [25].

Premature menopause and diabetes

Premature menopause — frequently correlated with type 1 diabetes, premature menopause occurs when a woman stops having periods before the age of 40. Endometrial cancer (uterine cancer). This condition is more frequent in women with type 2 diabetes and PCOS, and can contribute to infertility if not treated early [26]. Microvascular and cardiovascular risks — findings indicate that people with type 1 diabetes who have microvascular or cardiovascular complications have significantly lower fertility rates [27].

The new triad (IVF, OSS and diabetes)

Patients receiving gonadotrophin ovary stimulation for IVF cycles are vulnerable to Ovarian Stimulation Syndrome (OSS). Presence of unregulated diabetes is a risk factor that raises the likelihood of ovarian hyper-stimulation; as shown in several trials, metformin has had a beneficial impact on the prevention of such complications among diabetic females pursuing IVF pregnancy. Reduction of estradiol amounts on the day of administration of HCG. Another potential reason is that the impact of berberine or metformin on the reduction of androgen and insulin levels may lead to reduced estradiol concentrations [28–31].

Data also suggests that metformin has a clear impact on human ovarian steroidogenesis [32]. In addition, metformin has also been shown to directly suppress the activity of aromatase enzyme [29]. These findings may also explain the rapid biochemical improvements in serum testosterone and estradiol concentrations observed in our study after a short course of berberine or metformin.

Safety is a key consideration for women undergoing IVF. Hyperinsulinemia is a risk factor for OHSS, as women with PCOS who are hyperinsulinemic have a higher level of E2 and a greater incidence of ovarian hyper-stimulation during ovarian stimulation with FSH, compared to those with normoinsulinemia [29].

IVF and gestational diabetes

Pregnant mothers who used in vitro fertilization to conceive are 53% more likely to experience gestational diabetes than women who conceived spontaneously, according to research results provided at the annual meeting of the European Association for the Study of Diabetes [33].

"These results underscore the significance of early diagnosis of gestational diabetes in pregnant women with assisted reproductive technologies that may contribute to an increase in lifestyle activity from the previous to the IVF era and the first trimester of pregnancy, especially in high-risk communities, in order to reduce the risk of gestational diabetes."

In a systematic study and meta-analysis, Anagnostis at al. [33] reviewed evidence from 17 matched and 21 unmatched case-control trials conducted between 1995 and 2017, contrasting the probability of gestational diabetes in singleton pregnancy with assisted reproductive technologies (IVF and intracytoplasmic sperm injection) vs. random conception (n = 1,893,599) [34]. Studies were removed if conception was accomplished by ovulation induction or intrauterine insemination. Researchers used maternal age, parity and ethnicity to balance aided reproductive groups and spontaneous reproduction groups.

Across trials, 4,766 out of 63,760 people who experienced assisted reproduction and 158,526 out of 1,870,734 women who became pregnant naturally acquired gestational diabetes [35]. "This thorough review of the best available data to date indicates that singleton pregnancy obtained by IVF is correlated with an elevated risk of developing gestational diabetes relative to pregnancies spontaneously born." Anagnostis said in a press release. "The precise cause remains unknown, and whether this risk is related to medical action or to the inherent infertility status of couples undergoing assisted reproduction is not yet well known and needs more study."

COVID-19 and IVF
COVID-19 impact on fertility clinics

Since most coronavirus cases are related to travel in places with ongoing outbreaks, fertility clinics are advising patients to postpone IVF or other fertility care. Previously, it was proposed by the Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) that patients with a high risk of coronavirus (current symptoms, verified patient infection within 14 days of initiation of symptoms, or a positive coronavirus test result) should aim to prevent pregnancy [36].

These recommendations apply to procedures in egg or sperm donors and surrogate mothers, or IVF transfers. In context, if signs of respiratory failure (common with coronavirus) occur, anesthesia used during the extraction period can further inhibit respiration while the immune system may still be weakened. Going ahead with a transfer period may pose a danger to the applicant, clinic personnel, or other patients, and is usually really not the right option [37].

At the beginning of April, ASRM had initially suggested halting the implementation of new therapy periods, including activation of ovulation, IUIs, IVF retrievals and exchanges, and non-urgent cryopreservation of gametes owing to coronavirus pandemics. Patients and physicians were actively advised to postpone any transfers of embryos, fresh or frozen, and allowed to collaborate closely to decide how "urgent" the patient's treatment could be [38].

In other terms, whether fertility treatment was super time-sensitive (say, in the case of age or reduced ovarian reserve) and a protracted pause may have an effect on the result that might have been deemed urgent. The ASRM suggested the cessation of non-time-sensitive activities, reducing in-person experiences and promoting the usage of telehealth. However, patients that were mid-cycle would have been willing to pursue their care.

COVID-19 impact on fertility

There is currently insufficient clinical information on the relationship between coronavirus and fertility. But this is a fairly touch-and-go scenario. COVID-19 is relatively recent, so the CDC and other scientists would need to continue tracking its impact on fertility and beyond [39].

What we do know is that viruses will often trigger a fever that can affect fertility care. One research indicated that fever during the egg freeze or IVF period was correlated with a lower number of eggs recovered, a longer cycle, and a higher amount of medication needed. There is no proof, however, that fever causes longer-term effects on female fertility [40].

COVID-19 impact on pregnancy

We know that full-term babies born from women with active COVID-19 infections have performed well while serious illness (COVID-19 or otherwise) can contribute to premature labor. A very small case-analysis of COVID-19-affected women who delivered by C-section found that the virus had not been transmitted via amniotic fluid, cord blood or breastmilk, although it is still uncertain if transmission is feasible. However, in another review, preeclampsia was identified in 6 of 8 women with serious COVID-19 pneumonia admitted to ICU, although no preeclampsia symptoms were found in 34 participants with more moderate coronavirus [41].

However these details are somewhat insufficient. Abortion and stillbirth, has been shown in cases of infection with other associated coronaviruses (SARS-CoV and MERS-CoV) during pregnancy, and the CDC states that high fever during the first trimester of pregnancy may raise the risk of some birth defects. This describes the prudent attitude of ASRM to begin transfer cycles at this period, although there is no evidence yet on the effect of COVID-19 on the fetus during the first or second trimesters of pregnancy [42].

Conclusion

To our knowledge the inter-relationship among those three elements of the triad, "Diabetes, COVID and Fertility", was not addressed in literature. However, it was noticed obviously in many cases managed particularly in IVF clinics that there was a hidden relation among those three factors. Diabetic patients who attended our clinics for IVF trials during the COVID-19 pandemic experienced unexpected procedure failures and outcomes. This hypothesis obliged us to start our question by a review of literature to find that this topic was not discussed before. We recommend further researches in this new topic to find a causative and any associated risk factors.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Abdi A, Jalilian M, Sarbarzeh PA, et al. Diabetes and COVID-19: A systematic review on the current evidences. Diabetes Res Clin Pract. 2020; 166: 108347, doi: 10.1016/j.diabres.2020.108347, indexed in Pubmed: 32711003.
2. Tandulwadkar SR, Lodha PA, Mangeshikar NT. Obstetric complications in women with IVF conceived pregnancies and polycystic ovarian syndrome. J Hum Reprod Sci. 2014; 7(1): 13–18, doi: 10.4103/0974-1208.130802, indexed in Pubmed: 24829525.
3. Fabregues F, Peñarrubia J. Assisted reproduction and thromboembolic risk in the COVID-19 pandemic. Reprod Biomed Online. 2020; 41(3): 361–364, doi: 10.1016/j.rbmo.2020.06.013, indexed in Pubmed: 32660814.
4. Selter J, Wen T, Palmerola KL, et al. Life-threatening complications among women with severe ovarian hyperstimulation syndrome. Am J Obstet Gynecol. 2019; 220(6): 575.e1–575.e11, doi: 10.1016/j.ajog.2019.02.009, indexed in Pubmed: 30742828.
5. Kilpatrick CR, Ratts VS, Simckes E, et al. Severe ovarian hyperstimulation syndrome in patients with autoimmune disorders: a report of two cases. J Reprod Med. 2014; 59(11-12): 591–595, indexed in Pubmed: 25552133.
6. Kouhkan A, Khamseh ME, Pirjani R, et al. Obstetric and perinatal outcomes of singleton pregnancies conceived via assisted reproductive technology complicated by gestational diabetes

mellitus: a prospective cohort study. BMC Pregnancy Childbirth. 2018; 18(1): 495, doi: 10.1186/s12884-018-2115-4, indexed in Pubmed: 30547777.

7. Szymanska M, Horosz E, Szymusik I, et al. Gestational diabetes in IVF and spontaneous pregnancies. Neuro Endocrinol Lett. 2011; 32(6): 885–888, indexed in Pubmed: 22286793.

8. Segars J, Katler Q, McQueen DB, et al. American Society for Reproductive Medicine Coronavirus/COVID-19 Task Force. Prior and novel coronaviruses, Coronavirus Disease 2019 (COVID-19), and human reproduction: what is known? Fertil Steril. 2020; 113(6): 1140–1149, doi: 10.1016/j.fertnstert.2020.04.025, indexed in Pubmed: 32482250.

9. Diriba K, Awulachew E, Getu E. The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical maternal-fetal transmission: a systematic review and meta-analysis. Eur J Med Res. 2020; 25(1): 39, doi: 10.1186/s40001-020-00439-w, indexed in Pubmed: 32887660.

10. Anifandis G, Messini CI, Daponte A, et al. COVID-19 and fertility: a virtual reality. Reprod Biomed Online. 2020; 41(2): 157–159, doi: 10.1016/j.rbmo.2020.05.001, indexed in Pubmed: 32466995.

11. Zhu L, She ZG, Cheng Xu, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab. 2020; 31(6): 1068–1077.e3, doi: 10.1016/j.cmet.2020.04.021, indexed in Pubmed: 32369736.

12. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr. 2020; 14(4): 395–403, doi: 10.1016/j.dsx.2020.04.018, indexed in Pubmed: 32334395.

13. Tadic M, Cuspidi C, Sala C. COVID-19 and diabetes: Is there enough evidence? J Clin Hypertens (Greenwich). 2020; 22(6): 943–948, doi: 10.1111/jch.13912, indexed in Pubmed: 32472662.

14. Pugliese G, Vitale M, Resi V, et al. Is diabetes mellitus a risk factor for COronaVIrus Disease 19 (COVID-19)? Acta Diabetol. 2020; 57(11): 1275–1285, doi: 10.1007/s00592-020-01586-6, indexed in Pubmed: 32865671.

15. Rahimi L, Malek M, Ismail-Beigi F, et al. Challenging issues in the management of cardiovascular risk factors in diabetes during the COVID-19 pandemic: a review of current literature. Adv Ther. 2020; 37(8): 3450–3462, doi: 10.1007/s12325-020-01417-8, indexed in Pubmed: 32632851.

16. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract. 2020; 162: 108142, doi: 10.1016/j.diabres.2020.108142, indexed in Pubmed: 32278764.

17. Singh AK, Gupta R, Ghosh A, et al. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr. 2020; 14(4): 303–310, doi: 10.1016/j.dsx.2020.04.004, indexed in Pubmed: 32298981.

18. Unübol M, Ayhan M, Guney E. Hypoglycemia induced by hydroxychloroquine in a patient treated for rheumatoid arthritis. J Clin Rheumatol. 2011; 17(1): 46–47, doi: 10.1097/RHU.0b013e3182098e1f, indexed in Pubmed: 21169846.

19. Paengsai N, Jourdain G, Salvadori N, et al. Recommended first-line antiretroviral therapy regimens and risk of diabetes mellitus in HIV-infected adults in resource-limited settings. Open Forum Infect Dis. 2019; 6(10): ofz298, doi: 10.1093/ofid/ofz298, indexed in Pubmed: 31660327.

20. Bruno R, Sacchi P, Maiocchi L, et al. Hepatotoxicity and antiretroviral therapy with protease inhibitors: A review. Dig Liver Dis. 2006; 38(6): 363–373, doi: 10.1016/j.dld.2006.01.020, indexed in Pubmed: 16631422.

21. Liverpool COVID-19 interactions. https://www.covid19-druginteractions.org/ (5.05.2020).

22. Isidori AM, Arnaldi G, Boscaro M, et al. COVID-19 infection and glucocorticoids: update from the Italian Society of Endocrinology Expert Opinion on steroid replacement in adrenal insufficiency.

J Endocrinol Invest. 2020; 43(8): 1141–1147, doi: 10.1007/s40618-020-01266-w, indexed in Pubmed: 32335855.

23. Thong E, Codner E, Laven J, et al. Diabetes: a metabolic and reproductive disorder in women. The Lancet Diabetes & Endocrinology. 2020; 8(2): 134–149, doi: 10.1016/s2213-8587(19)30345-6.

24. Swanton A, Storey L, McVeigh E, et al. IVF outcome in women with PCOS, PCO and normal ovarian morphology. Eur J Obstet Gynecol Reprod Biol. 2010; 149(1): 68–71, doi: 10.1016/j.ejogrb.2009.11.017, indexed in Pubmed: 20022685.

25. Li HW, Lee VC, Lau EY, et al. Cumulative live-birth rate in women with polycystic ovary syndrome or isolated polycystic ovaries undergoing in-vitro fertilisation treatment. J Assist Reprod Genet. 2014; 31(2): 205–211, doi: 10.1007/s10815-013-0151-6, indexed in Pubmed: 24337962.

26. Anagnostis P, Christou K, Artzouchaltzi AM, et al. Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis. Eur J Endocrinol. 2019; 180(1): 41–50, doi: 10.1530/EJE-18-0602, indexed in Pubmed: 30400047.

27. Paschou SA, Papanas N. Type 2 Diabetes Mellitus and Menopausal Hormone Therapy: An Update. Diabetes Ther. 2019; 10(6): 2313–2320, doi: 10.1007/s13300-019-00695-y, indexed in Pubmed: 31549295.

28. Tang T, Glanville J, Orsi N, et al. The use of metformin for women with PCOS undergoing IVF treatment. Hum Reprod. 2006; 21(6): 1416–1425, doi: 10.1093/humrep/del025, indexed in Pubmed: 16501038.

29. Haas DA, Carr BR, Attia GR. Effects of metformin on body mass index, menstrual cyclicity, and ovulation induction in women with polycystic ovary syndrome. Fertil Steril. 2003; 79(3): 469–481, doi: 10.1016/s0015-0282(02)04800-8, indexed in Pubmed: 12620424.

30. Harborne L, Fleming R, Lyall H, et al. Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. Lancet. 2003; 361(9372): 1894–1901, doi: 10.1016/S0140-6736(03)13493-9, indexed in Pubmed: 12788588.

31. Kjøtrød SB, von Düring V, Carlsen SM. Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study. Hum Reprod. 2004; 19(6): 1315–1322, doi: 10.1093/humrep/deh248, indexed in Pubmed: 15117902.

32. Mansfield R, Galea R, Brincat M, et al. Metformin has direct effects on human ovarian steroidogenesis. Fertil Steril. 2003; 79(4): 956–962, doi: 10.1016/s0015-0282(02)04925-7, indexed in Pubmed: 12749437.

33. Anagnostis P, et al. Abstract 921. Presented at: European Association for the Study of Diabetes Annual Meeting; Sept. 16-20, 2019; Barcelona, Spain.

34. Maroufizadeh S, Navid B, Alizadeh A, et al. Risk of gestational diabetes mellitus following assisted reproductive technology: systematic review and meta-analysis of 59 cohort studies. J Matern Fetal Neonatal Med. 2019 [Epub ahead of print]: 1–10, doi: 10.1080/14767058.2019.1670790, indexed in Pubmed: 31570010.

35. IVF, Assisted Reproduction Techiques Linked to Increased Gestational Diabetes. (n.d.). https://www.hcplive.com/view/ivf-assisted-reproduction-techiques-linked-to-increased-gestational-diabetes (18.12.2020).

36. Requena A, Cruz M, Vergara V, et al. A picture of the covid-19 impact on IVIRMA fertility treatment clinics in Spain and Italy. Reprod Biomed Online. 2020; 41(1): 1–5, doi: 10.1016/j.rbmo.2020.04.015, indexed in Pubmed: 32451301.

37. Monteleone PAa, Nakano M, Lazar V, et al. A review of initial data on pregnancy during the COVID-19 outbreak: implications for assisted reproductive treatments. JBRA Assist Reprod. 2020; 24(2): 219–225, doi: 10.5935/1518-0557.20200030, indexed in Pubmed: 32301600.

38. Peyronnet V, Sibiude J, Deruelle P, et al. [SARS-CoV-2 infection during pregnancy. Information and proposal of management care. CNGOF]. Gynecol Obstet Fertil Senol. 2020; 48(5): 436–443, doi: 10.1016/j.gofs.2020.03.014, indexed in Pubmed: 32199996.

39. Blumenfeld Z. Possible impact of COVID-19 on fertility and assisted reproductive technologies. Fertil Steril. 2020; 114(1): 56–57, doi: 10.1016/j.fertnstert.2020.05.023, indexed in Pubmed: 32622412.

40. Zhu C, Wu J, Liang Y, et al. Fertility intentions among couples in Shanghai under COVID-19: A cross-sectional study. Int J Gynaecol Obstet. 2020 [Epub ahead of print], doi: 10.1002/ijgo.13366, indexed in Pubmed: 32880942.

41. Juan J, Gil MM, Rong Z, et al. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound Obstet Gynecol. 2020; 56(1): 15–27, doi: 10.1002/uog.22088, indexed in Pubmed: 32430957.

42. Huntley BJF, Huntley ES, Di Mascio D, et al. Rates of Maternal and Perinatal Mortality and Vertical Transmission in Pregnancies Complicated by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co-V-2) Infection: A Systematic Review. Obstet Gynecol. 2020; 136(2): 303–312, doi: 10.1097/AOG.0000000000004010, indexed in Pubmed: 32516273.

VIA MEDICA

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Is there a need for a treatment for COVID-19-induced diabetes?

Epidemiological data show that patients with diabetes who are COVID-19-positive may have a higher risk of serious complications [1]. In addition, during SARS-CoV-2 infection glycemic normalization is more difficult to achieve, with the risk of complicating the clinical scenario even more. This evidence shows that the patient with COVID-19-positive diabetes is a complex patient. SARS-CoV-2 uses the angiotensin 2 converting enzyme (ACE2) receptors expressed in different tissues including pancreatic beta cells to enter cells. We can hypothesize [2] this is the mechanism underlying the alterations of glycemic homeostasis with the risk of damage to the patient with persistent diabetes and of inducing diabetes in patients without persistent metabolic disease.

Some data also suggest a higher incidence of glycemic dysregulation in patients with SARS pneumonia compared to those with pneumonia from other viral causes [3]. However, recent evidence has shown that SARS-CoV-2 also binds to DPP4/CD26 when it enters respiratory tract cells. In addition, another recent study has clearly reported a correlation between DPP4 and ACE2, suggesting that both membrane proteins are relevant in the pathogenesis of virus entry [4, 5]. One could hypothesize the use of antidiabetic drugs to manage cases where there is COVID-19-induced glycemic dysregulation. In particular, the gliptin class may be the most indicated among antidiabetic drugs, for several reasons [6].

The inhibition of DPP4/CD26 could antagonize the mechanism of cellular penetration of the virus. In addition, gliptins, which are associated with anti-inflammatory effects and reduction of overproduction of cytokines, are drugs that can ensure glycemic normalization and have low risk of causing hypoglycemia. Epidemiological studies are necessary to confirm these hypotheses [7, 8].

Conflict of interest

None of the Authors have conflicts of interest to disclose.

REFERENCES

1. Li J, Wang X, Chen J, et al. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes Obes Metab. 2020 [Epub ahead of print], doi: 10.1111/dom.14057, indexed in Pubmed: 32314455.
2. Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004; 203(2): 631–637, doi: 10.1002/path.1570, indexed in Pubmed: 15141377.
3. Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010; 47(3): 193–199, doi: 10.1007/s00592-009-0109-4, indexed in Pubmed: 19333547.
4. Vitiello A, Ferrara F. Correlation between renin-angiotensin system and Severe Acute Respiratory Syndrome Coronavirus 2 infection: What do we know? Eur J Pharmacol. 2020; 883: 173373, doi: 10.1016/j.ejphar.2020.173373, indexed in Pubmed: 32679185.
5. Vankadari N, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microbes Infect. 2020; 9(1): 601–604, doi: 10.1080/22221751.2020.1739565, indexed in Pubmed: 32178593.
6. Qi F, Qian S, Zhang S, et al. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun. 2020; 526(1): 135–140, doi: 10.1016/j.bbrc.2020.03.044, indexed in Pubmed: 32199615.
7. Waumans Y, Baerts L, Kehoe K, et al. The dipeptidyl peptidase family, prolyl oligopeptidase, and prolyl carboxypeptidase in the immune system and inflammatory disease, including atherosclerosis. Front Immunol. 2015; 6: 387, doi: 10.3389/fimmu.2015.00387, indexed in Pubmed: 26300881.
8. Ferrara F, Vitiello A. The impact of COVID-19 in diabetic patient. Arch Med Health Sci. 2020; 8(1): 167–171, doi: 10.4103/amhs.amhs_117_20.

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Diabetes Score questionnaire for lifestyle change in patients with type 2 diabetes

ABSTRACT

Background. Designed for use in clinical settings, the Diabetes Score is a 10-item, one-page questionnaire for discussing lifestyle change. We aimed to evaluate the Diabetes Score questionnaire for its validity and acceptability among individuals with type 2 diabetes. Methods. An observational study was conducted using interviewer-administered questionnaires to adult patients with type 2 diabetes at three ambulatory clinics. We used the Diabetes Score questionnaire for measuring adherence to diet, exercise and other lifestyle recommendations. The questionnaire yields an intuitive score ranging from 0 to 100, by addition of each of the 10 items which are rated as 0, 5 or 10 by the patient. A score of more than 60 was considered satisfactory.

Results. A total of 311 patients, 56% females, with a median age of 55 years (range: 23 to 87) participated in the study. Diabetes Score correlated with glycemic control, HbA_{1c} (r = –0.20) and blood glucose (r = –0.25; P < 0.001), indicating validity. Reliability was demonstrated by internal consistency (alpha .577) and discriminant factor analysis. Based on multivaria-

te modeling, an improvement of 30 points on the Diabetes Score corresponded to a drop in HbA_{1c} by 1.0%-unit (11 mmol/mol).

Conclusion. Diabetes Score is a valid and reliable tool for empowering lifestyle and behavior modification among patients with diabetes mellitus. This brief and free-to-use questionnaire has the potential to be used in diabetes clinics to discuss behavior change. It can serve as the first-line intervention in diabetes patients while reducing the cost of diabetes care. (Clin Diabetol 2020; 9; 6: 379–386)

Key words: diabetes mellitus, behavior change, lifestyle modifications, chronic disease care, non-communicable diseases

Introduction

Increasing evidence supports the need to focus on modifiable lifestyle factors in addition to glycemic control among individuals with diabetes [1, 2]. Self-management education on healthy diet and a physically active lifestyle, as well as regular support from healthcare professionals can enable individuals to achieve their glycemic targets with less intensive medications, improve wellness and reduce long-term complications [3]. However, implementation of these behavioral interventions has been challenging in clinical settings [4, 5].

While questionnaires have been used to measure lifestyle factors among individuals with diabetes, most are lengthy, complicated and cumbersome to score. The length of these questionnaires can exceed 65 items, spanning over 14 pages [6]. Complex scoring algorithms can be burdensome, sometimes necessitating

the use of computer software [7]. A few require prior written permission or payment for usage. Intentionally "designed especially to enable scientific studies" [8], many questionnaires serve as information gathering tools for research. Other questionnaires are focused on quality of life, and contain items pertaining to patient perceptions and expectations. There appears to be a lack of a brief and easy-to-use questionnaire designed for shared decision-making and improving lifestyle among individuals with type 2 diabetes.

We sought to evaluate the Diabetes Score questionnaire for its validity and acceptability among individuals with type 2 diabetes.

Methods
Questionnaire design

The Diabetes Score is a behaviorally-oriented questionnaire developed specifically for clinical use [9]. It is a theoretically-derived health rating scale that targets condition-specific behaviors for personally meaningful reasons as postulated in the self-management theory [10, 11]. By being brief and easy-to-understand, the instrument enables individuals with diabetes to see how well they are following evidence-based guidelines for healthy lifestyle targets [Supplementary Appendix]. The questionnaire consists of 10 behaviorally-oriented items carefully designed to motivate patients to adopt a healthier lifestyle. Each item is rated by the patient as either 0, 5 or 10-points based on a rubric of lifestyle targets. The item ratings are summed up to yield an intuitive total score ranging from zero to 100 points. This allows patients and physicians to measure progress and discuss areas for improvement and target behaviors. Any form of tobacco use such as cigarette smoking leads to a 20-point reduction. Simplicity is a virtue when advocating lifestyle change. For instance, it has been shown that a structured meal plan is sufficient compared to a detailed, individualized eating plan among patients with type 2 diabetes [12]. Layout of the questionnaire is designed to be visually appealing and easy to understand. A color-coded table enables rapid interpretation of total scores.

The content of Diabetes Score questionnaire is informed by a rich evidence base on behavior change in diabetes research [13, 14]. These reviews recommend a healthful eating pattern, reduced calorie intake, regular physical activity, health education and social support as primary treatment strategies [13–15]. Consequently, the Diabetes Score questionnaire is structured to include items on nutrition, physical activity and self-care. The items are judiciously constructed to be behaviorally oriented and actionable, thus potentially empowering to patients. Non-actionable items such as current hemoglobin A_{1c} level, body mass index and blood pressure were excluded. Such items have been shown to be ineffective in motivating patients for behavior change [16].

Study design and setting

An observational study was carried out at three ambulatory clinics in three cities: Islamabad, Rawalpindi and Peshawar, Pakistan, from July 2017 to March 2018. The clinics serve a wide range of patients: one of the clinics is a community diabetes clinic, another is a teaching clinic affiliated with a medical college, and the third is an ambulatory center in a general hospital.

Participants and data collection

Researcher-administered, printed questionnaire forms were used to conduct interviews with participants after obtaining verbal informed consent. Eligibility criteria included adult patients (age more than 18 years) with an established diagnosis of diabetes mellitus. Patients were excluded if they had apparent visual, hearing or mental impairment that would limit comprehension of the interview. The primary outcome measure was the correlation of Diabetes Score with glycemic control. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Participants were asked additional questions including age, years of formal education completed, current occupation as well as four questions on perceived satisfaction with the Diabetes Score questionnaire.

Statistical analysis

A minimum sample size of at least 127 patients was calculated based on the assumption that the correlation between HbA_{1c} and Diabetes Score will be 0.1, with a power (beta) of 80% and type I error rate (alpha) of 0.05 (UCSF Sample Size Calculators, www.sample-size.net/correlation-sample-size/).

The prespecified analyses included bivariate correlation between Diabetes Score and HbA_{1c}, and multiple linear regression with HbA_{1c} as the outcome variable. Psychometric validation of the questionnaire was conducted using reliability analysis based on the alpha (Cronbach) model for internal consistency, followed by factor analysis for dimensionality of items [17]. All statistical analyses were conducted with the current version of SPSS (IBM SPSS Inc.). An alpha level of $P < 0.05$ was considered statistically significant.

Results

A total of 311 patients with type 2 diabetes mellitus participated in the study (Table 1). The median age

Table 1. Participants' sociodemographic and clinical characteristics (n = 311)

Characteristic	n (%)
Sex	
Males	132 (42.4)
Females	176 (56.6)
Age (years)	
20–29	4 (1.3)
30–39	18 (5.8)
40–49	70 (22.5)
50–59	114 (36.7)
60–69	62 (19.9)
70–79	22 (7.1)
80 or more	4 (1.3)
Education (years of schooling)	
None	91 (29.3)
Primary (up to 10 years)	62 (19.9)
Secondary (up to 12 years)	52 (16.7)
College (13 years or more)	62 (19.9)
Years since diagnosis of diabetes	
Less than 5 (newly diagnosed)	76 (24.4)
5 to 9	89 (28.6)
10 to 14	45 (14.5)
More than 15	67 (21.5)
Body mass index [kg/m^2]	
25.0–29.9 overweight	8 (2.6)
30.0–34.9 obese	34 (10.9)
35.0–39.9	62 (19.9)
40.0–44.9 morbidly obese	74 (23.8)
45.0–49.9	62 (19.9)
50.0+	55 (17.7)
HbA$_{1c}$ (%)	
< 6.50	2 (0.6)
6.50–6.99	5 (1.6)
7.00–7.99	11 (3.5)
8.00–11.99	19 (6.1)
12.0 or greater	10 (3.2)
On insulin	128 (41.2)

was 55 years (minimum 23, maximum 87 years) with a mean of 53.8 years (standard deviation [SD], 10.7). The participants' occupations ranged from white-collar professions such as teaching to labor-intensive work such as farming. Among female participants, 84% stated that they were homemakers. Many patients were fairly recently diagnosed with diabetes, with 65% having been identified less than 10 years ago. The body mass index (BMI) ranged from 26 to 71 kg/m^2, with a mean of 43 kg/m^2 (SD, 7.2). The mean waist circumference for women, 102 cm (40.2 inches), exceeded that for men, 96 cm (37.8 inches) (P = .24). Missing

values were generally low except for recent HbA$_{1c}$ and waist circumference while blood glucose levels were available for 99% of patients.

The mean Diabetes Score was 58.0 points (SD, 17.1), with a median of 60, on a scale ranging from zero to 100 points. Participants reported better adherence to dietary recommendations than for physical activity and exercise (Fig. 1). About half (46.9%) reported avoiding sweets rich in simple sugars (high glycemic index foods) and 84.6% were eating at least one serving of fruits or raw vegetables. On the other hand, 104 (33.4%) admitted that they were not engaging in vigorous aerobic exercise at all, while 82 (26.4%) were not doing any home exercises. While most patients were accessing health education, only 27.7% reported performing regular foot examinations. The highest rated item was self-reported continuity of physician visits and compliance with medications (Fig. 1). In this cohort, 12 (3.9%) of patients smoked cigarettes. Comparison of individuals grouped into high (more than 50 points) and low total Diabetes Score revealed that the latter were less educated, more overweight, and had higher blood glucose levels (Table 2).

Diabetes Score correlated with HbA$_{1c}$ (r = .20) and random blood glucose (r = .25). Diabetes Score was associated with years of schooling (r = .22) indicating an effect of education on healthy lifestyle. However, there was a lack of correlation –with age (r = −.096), or duration of diabetes (r = −.036). From multivariate analysis, we found that glycemic control (HbA$_{1c}$) was weakly predicted by the patients' Diabetes Score (regression coefficient, −0.030), BMI (0.28), and duration of diabetes (−0.15). However, none of the predictors reached statistical significance (adjusted R^2 = 0.017).

Psychometric validation

The questionnaire items showed fair internal consistency (Cronbach's alpha, 0.577; n = 311). Between items comparison showed significant differences across the questions (ANOVA, p < 0.001). As expected, inter-item correlations showed moderate associations among items on physical activity as well as between those on nutrition (r = .2 to .4), indicating construct validity of these subscales. On the other hand, there was a lack of correlation between diet items and those related to exercise (r = −.015 to .033). This was confirmed on factor analysis which yielded separate components related to exercise and diet with fairly high eigenvalues explaining variance of the total Score, 21% and 14% respectively. Sensitivity analysis indicated that removal of certain items (for example, foot examination) would improve the reliability nominally (Cronbach's alpha increased from 0.577 to 0.582).
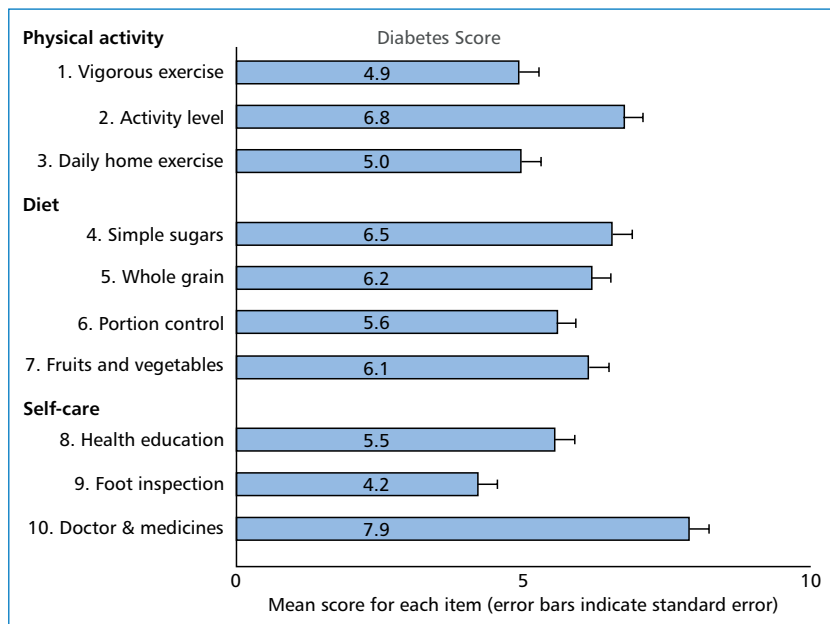
Figure 1. Mean self-ratings for each item in the Diabetes Score questionnaire (n = 311)

Table 2. Clinical characteristics of participants divided into high and low Diabetes Score groups

Characteristic	High score (> 50) Desirable (n = 197) Mean (SD)	Low score (≤ 50) Sub-optimal (n = 114) Mean (SD)	P value one-way ANOVA
Age (years)	53 (11)	55 (11)	.078
Education (years of schooling)	8.8 (5.9)	6.2 (5.9)	.001
Recent HbA$_{1c}$ (%)	9.5 (3.1)	9.5 (2.5)	.988
Random blood glucose [mg/dL]	246 (83)	318 (112)	<.001
Fasting blood glucose [mg/dL]	190 (80)	228 (85)	.017
BMI [kg/m^2]	42.3	44.5	.009
Weight [kg]	71 (12)	74 (12)	.034
Duration of diabetes (years)	9.3 (6.1)	9.1 (6.1)	.764

BMI — body mass index

Participant satisfaction with Diabetes Score

Additional questions on satisfaction with the Diabetes Score questionnaire were asked to assess participant's perceptions. More than 40% of participants liked the Diabetes Score questionnaire while only 5.8% did not (the rest were unsure or did not respond). Similarly, 41% of the participating patients indicated that they would use the questionnaire in future while only 1.3% would not. Suggestions to improve the form included adding detailed instructions, dietary advice and exercise guidelines.

Discussion

In this study, Diabetes Score correlated with glycemic control among adults with type 2 diabetes, with a 30-point improvement in the Score corresponding to a drop of 1.0%-unit (11 mmol/mol) in HbA$_{1c}$. Psychometric properties revealed internal consistency, construct validity and moderate satisfaction ratings, indicating that the instrument demonstrates validity.

It is pertinent to note that other diabetes questionnaires have been validated using the same study design with similar sample sizes of about 300 patients.

Furthermore, the correlation with HbA$_{1c}$ has also been about −.20 as their primary validation outcome. It is useful to illustrate this with a few examples. The 28-item, Type 2 Diabetes and Health Promotion Scale (T2DHPS) questionnaire was studied in 323 subjects, and had a correlation of −0.25 with HbA$_{1c}$ [18]. This questionnaire asks the respondent to make judgements which are not easily translated into behavioral actions; for example, "I have a balanced diet every day". Some items are fairly subjective: "I am content with myself generally speaking." Another questionnaire, the 16-item Diabetes Self-Management Questionnaire (DSMQ), reported as "reliable and valid", was studied in 261 hospitalized patients yielding a correlation of −0.23 with HbA$_{1c}$ [8]. The authors noted that "study participants cannot be rated as representative of the general diabetic population, which limits the generalizability of results" [8]. Some items, for example, "Check blood sugar levels frequently," appear to be not in line with current evidence for patients not on insulin [19]. An 18-item questionnaire, designed specifically as a "research tool," was tested among 252 individuals resulting in a correlation of −0.27 with HbA$_{1c}$ [20]. Generalizability is limited by certain items, such as "Maintain healthy diet during financial difficulties." Other items appear non-specific such as "Prevent low blood sugar" and "Prevent high blood sugar". The Personal Diabetes Questionnaire (PDQ) is comprehensive (spanning 14 pages) but also quite complex and time intensive, requiring 20 to 30 minutes to complete [6]"page":"321–332","volume":"91","issue":"3","source":"ScienceDirect","abstract":"Aim\nTo develop and evaluate the validity and reliability of The Personal Diabetes Questionnaire (PDQ. The questions are verbose and require patients to comprehend some fairly complicated choices. Many of the items serve as information gathering; yet there are no items for tobacco use. This lengthy questionnaire achieved a mild correlation of .21 with HbA$_{1c}$. Its generalizability is limited due to sampling of predominantly well-educated patients, as well as the use of regional colloquial words. The Summary of Diabetes Self-Care Activities (SDSCA) has multiple versions and complex scoring instructions with subscales that require separate interpretation. It appears to encourage multiple daily blood glucose testing by giving higher scores regardless of clinical indication. Items are somewhat convoluted ("On average, over the past month, how many days per week have you followed your eating plan?") and arbitrary ("On how many of the last seven days did you inspect the inside of your shoes?"). Additional items are information gathering type and some require complex judgement calls on part of the patient.

In contrast, a representative sample was obtained in our study with a broad range of age, gender, occupations, duration of diagnosis and glycemic control. The high readability (Flesch Readability score, 90) of the Diabetes Score makes it among the easiest-to-read diabetes scales. With just 10-items on a single page, the questionnaire is simple to score and relatively straightforward to interpret. These distinguishing features support its use as a clinical, shared decision-making intervention and not just as a research tool.

The Diabetes Score questionnaire items showed moderate internal consistency and reliability in our study. The correlation with HbA$_{1c}$ and random blood glucose (similar to other validated questionnaires) supports concurrent validity and its use in clinical settings. It is pertinent to point out that validation of any questionnaire is limited to the version studied in the research context [10]. Many diabetes questionnaires were modified later on, with updated versions substantially different from the originally validated ones [21]. In our extensive literature search, none of the studies reported long-term patient-oriented outcomes.

Diabetes Score showed evidence of construct validity through factor analysis indicating well separated diet and exercise subscales. Study participants with higher Diabetes Scores tended to be generally healthier with better glycemic control. Limited correlation with blood glucose levels indicated that while higher Diabetes Scores are associated with better glycemic control, the questionnaire gathers additional information not captured by HbA$_{1c}$.

Limitations of our study include lack of longitudinal follow-up, and the absence of children or patients with type 1 diabetes. The Diabetes Score questionnaire does not measure healthcare professionals' counselling skills. Furthermore, the questionnaire does not individualize dietary or exercise recommendations. The item on avoidance of sweet foods oversimplifies the concept of carbohydrate counting but is supported by recommendations to consume low-glycemic index foods [22]. To some extent, these factors are balanced by the simplicity and clinical utility of the questionnaire.

Conclusions

The 10-item Diabetes Score questionnaire is a reliable and valid questionnaire to assess adherence to lifestyle recommendations in adult patients with type 2 diabetes. Individuals with type 2 diabetes may potentially benefit from using the Diabetes Score questionnaire for behavior modification. By allowing patients to reflect upon their dietary intake and physical activity, the Diabetes Score allows a more mindful approach to setting lifestyle targets. Its initial

psychometric properties measured in this study reveal a mild correlation with glycemic control, fair reliability, reasonable evidence of construct validity and moderate patient acceptance. The simplicity of the Diabetes Score makes it attractive as a patient discussion tool for improving self-management. It may help in refocusing on patients' lifestyles and reducing excessive emphasis on tight glycemic control [23].

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Statement of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of interest

Nothing to declare.

REFERENCES

1. Jalilian H, Pezeshki MZ, Torkzadeh L, et al. Health care seeking behaviors in type 2 diabetic patients in East Azerbaijan. Clinical Diabetology. 2019; 8(6): 292–302, doi: 10.5603/dk.2019.0031.
2. Brzeziński M, Korzeniowska K, Szarejko K, et al. "PoZdro!" as an example of a successful multicenter programme for obesity management and healthy lifestyle promotion in children and adolescents - programme protocol and preliminary results from the first intervention site. Pediatr Endocrinol Diabetes Metab. 2020; 26(1): 22–26, doi: 10.5114/pedm.2020.94393, indexed in Pubmed: 32418419.
3. McGowan P. The challenge of integrating self-management support into clinical settings. Can J Diabetes. 2013; 37(1): 45–50, doi: 10.1016/j.jcjd.2013.01.004, indexed in Pubmed: 24070748.
4. Tang TS, Funnell MM, Sinco B, et al. Peer-Led, Empowerment-Based Approach to Self-Management Efforts in Diabetes (PLEASED): A Randomized Controlled Trial in an African American Community. Ann Fam Med. 2015; 13 Suppl 1: S27–S35, doi: 10.1370/afm.1819, indexed in Pubmed: 26304969.
5. Vallis M. Are Behavioural Interventions Doomed to Fail? Challenges to Self-Management Support in Chronic Diseases. Can J Diabetes. 2015; 39(4): 330–334, doi: 10.1016/j.jcjd.2015.01.002, indexed in Pubmed: 25837809.
6. Stetson B, Schlundt D, Rothschild C, et al. Development and validation of The Personal Diabetes Questionnaire (PDQ): a measure of diabetes self-care behaviors, perceptions and barriers. Diabetes Res Clin Pract. 2011; 91(3): 321–332, doi: 10.1016/j.diabres.2010.12.002, indexed in Pubmed: 21215487.
7. Uchmanowicz I, Krzemińska S, Ausili D, et al. Polish adaptation of the self-care of diabetes inventory (SCODI). Patient Prefer Adherence. 2020; 14: 1341–1350, doi: 10.2147/PPA.S253444, indexed in Pubmed: 32801664.
8. Schmitt A, Gahr A, Hermanns N, et al. The Diabetes Self-Management Questionnaire (DSMQ): development and evaluation of an instrument to assess diabetes self-care activities associated with glycaemic control. Health Qual Life Outcomes. 2013; 11: 138, doi: 10.1186/1477-7525-11-138, indexed in Pubmed: 23937988.
9. Hashim, MJ. Diabetes Score - a new behaviorally-oriented questionnaire for assessing and improving patient adherence. In: American Association of Clinical Endocrinologists Gulf Chapter 3rd Clinical Conference. Dubai; 2015.
10. Keszei AP, Novak M, Streiner DL. Introduction to health measurement scales. J Psychosom Res. 2010; 68(4): 319–323, doi: 10.1016/j.jpsychores.2010.01.006, indexed in Pubmed: 20307697.
11. Ryan P, Sawin KJ. The Individual and Family Self-Management Theory: background and perspectives on context, process, and outcomes. Nurs Outlook. 2009; 57(4): 217–225.e6, doi: 10.1016/j.outlook.2008.10.004, indexed in Pubmed: 19631064.
12. Mottalib A, Salsberg V, Mohd-Yusof BN, et al. Effects of nutrition therapy on HbA1c and cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes. Nutr J. 2018; 17(1): 42, doi: 10.1186/s12937-018-0351-0, indexed in Pubmed: 29626933.
13. Franz MJ, Boucher JL, Rutten-Ramos S, et al. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet. 2015; 115(9): 1447–1463, doi: 10.1016/j.jand.2015.02.031, indexed in Pubmed: 25935570.
14. Longo DR, Schubert SL, Wright BA, et al. Health information seeking, receipt, and use in diabetes self-management. Ann Fam Med. 2010; 8(4): 334–340, doi: 10.1370/afm.1115, indexed in Pubmed: 20644188.
15. Schellenberg ES, Dryden DM, Vandermeer B, et al. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013; 159(8): 543–551, doi: 10.7326/0003-4819-159-8-201310150-00007, indexed in Pubmed: 24126648.
16. Irwig MS, Sood P, Ni D, et al. A diabetes scorecard does not improve HbA(1c), blood pressure, lipids, aspirin usage, exercise and diabetes knowledge over 9 months: a randomized controlled trial. Diabet Med. 2012; 29(9): 1206–1212, doi: 10.1111/j.1464-5491.2012.03610.x, indexed in Pubmed: 22332914.
17. Babyak MA, Green SB. Confirmatory factor analysis: an introduction for psychosomatic medicine researchers. Psychosom Med. 2010; 72(6): 587–597, doi: 10.1097/PSY.0b013e3181de3f8a, indexed in Pubmed: 20467001.
18. Chen CP, Peng YS, Weng HH, et al. Development and preliminary testing of a brief screening measure of healthy lifestyle for diabetes patients. Int J Nurs Stud. 2013; 50(1): 90–99, doi: 10.1016/j.ijnurstu.2012.09.001, indexed in Pubmed: 23010134.
19. Havele SA, Pfoh ER, Yan C, et al. Physicians' Views of Self-Monitoring of Blood Glucose in Patients With Type 2 Diabetes Not on Insulin. Ann Fam Med. 2018; 16(4): 349–352, doi: 10.1370/afm.2244, indexed in Pubmed: 29987085.
20. Wang ML, Lemon SC, Welch G, et al. Development and validation of the Lifestyle Self-Efficacy Scale for Latinos with Diabetes (LSESLD). Ethn Dis. 2013; 23(4): 428–435, indexed in Pubmed: 24392604.
21. Toobert DJ, Hampson SE, Glasgow RE. The summary of diabetes self-care activities measure: results from 7 studies and a revised scale. Diabetes Care. 2000; 23(7): 943–950, doi: 10.2337/diacare.23.7.943, indexed in Pubmed: 10895844.
22. Watanabe T, Berry TR, Willows ND, et al. Assessing intentions to eat low-glycemic index foods by adults with diabetes using a new questionnaire based on the theory of planned behaviour. Can J Diabetes. 2015; 39(2): 94–100, doi: 10.1016/j.jcjd.2014.09.001, indexed in Pubmed: 25439502.
23. Wojszel ZB, Kasiukiewicz A. A retrospective cross-sectional study of type 2 diabetes overtreatment in patients admitted to the geriatric ward. BMC Geriatr. 2019; 19(1): 242, doi: 10.1186/s12877-019-1256-2, indexed in Pubmed: 31477024.

<p align="center">**Supplementary Appendix**</p>

Diabetes Score

What's your score?

	10 points	5 points	0 points
1. Vigorous exercise	At least 30 minutes daily 3 or more days a week	Less than 30 minutes daily Less than 3 days a week	Rarely or none
2. Activity level	Active (stairs, walks)	Mildly active	Sedentary (TV, computer, use lifts)
3. Daily home exercise	Doing daily	Irregular	Rarely or none
4. Simple sugars	Rarely eat sweets	Occasionally eat sweets	Frequent sweets
5. Whole grain	3-4 servings of whole grain	Rarely eat whole grain	Usually eat white bread or white rice
6. Portion control	Limit portion size and avoid second servings	Occasionally limit	Rarely or none
7. Fruits and vegetables	4-5 servings or pieces of fruits and raw vegetables	1-3 servings or pieces per day	Rarely or none
8. Health education	Regularly (dietician, support groups, books, websites, apps)	Occasionally	Rarely or none
9. Foot inspection	Daily	Weekly	Rarely or none
10. Doctor & medicines	3 or more visits a year to the same doctor Regular with medicines	1-2 visits a year Forgetting medicines frequently	Rarely or none Not taking 1 or more recommended medicines
Total score (☐ subtract 20 points if smoking cigarettes or using tobacco or drinking alcohol)			

Write your scores here

Score	Meaning	Date → Score↓							
80 – 100	Excellent								
60 – 80	Good								
60 – 40	Fair								
20 – 40	Not good								
0 – 20	Unhealthy								

My active lifestyle	**Walk daily.** Add an additional 1 minute of aerobic (fast brisk walk) exercise to your daily walk each week.
Monday	
Tuesday	Do home exercises such as arm stretches and lunges. Try: gardening, home cleaning, playing sports with children and friends.
Wednesday	
Thursday	Use stairs instead of escalators. Limit TV, computers, electronic devices. Avoid sitting for long periods. Be active!
Friday	
Saturday	**Be positive** – your attitude makes the difference. Smile. Think positive thoughts about yourself and the world – say positive words. Make friends with positive people
Sunday	

My meal plan	*Suggestions*
Breakfast	Fresh cut fruit, oatmeal, boiled egg, one slice of bread with vegetable oil spread (no jam or juice). Tea/coffee. Drink plenty of water.
Lunch	Salad, half-cup of rice with beans, vegetables, and seasonings. Eat four **small meals** through the day.
Snack	Green tea with a biscuit. **Reduce portion size** – eat in small amounts. Avoid second servings. Eat slowly and mindfully.
Dinner	Baked fish with steamed vegetables. A small piece of dessert. Almonds. Enjoy the taste of food. Pause between each bite.

My medicines
Morning
Afternoon
Evening

Green: All you can eat!	Water! Fresh vegetables, salads
Yellow: Eat in moderation	Cooked vegetables, beans, lentil, fish, fruits, brown bread
Red: Avoid or eat in small amounts	Rice, white bread, potatoes, meat, fried foods, pastry, nuts, desserts, jam, sweets, juice, soda

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Validation of diabetes knowledge questionnaire in Croatian with assessment of diabetes knowledge and quality of life in patients with type 2 diabetes mellitus

ABSTRACT

Background. Diabetes mellitus (DM) is one of the biggest challenges in global healthcare and society in general. Assessment of the patient's level of knowledge regarding diabetes is an important step in adapting group education programs to achieve better treatment outcomes.

The aim of this study was to validate Diabetes Knowledge Questionnaire (DKQ) in Croatian language, to evaluate knowledge about diabetes and examine the relationship between knowledge and quality of life among type 2 DM patient's in Croatia.

Methods. The study was conducted as a cross-sectional study on 500 subjects. Validation of DKQ questionnaire in Croatian language was done using forward-backward method and internal consistency was examined using Cronbach's Alpha. Quality of life was assessed using WHOQOL-BREF Questionnaire.

Results. Good reliability and internal consistency of DKQ was confirmed (α = 0,740). Overall knowledge about diabetes was satisfactory (average DKQ score was 12,13). Longer duration of disease and previous education about diabetes were observed as predictive factors of better knowledge. No association was found between diabetes knowledge and quality of life.

Conclusions. Our study confirms that DKQ is a good tool for assessing diabetes knowledge in Croatian language. Patients with DM demonstrated good diabetes knowledge but education in areas of self-care and nutrition needs to be improved which may increase quality of life. (Clin Diabetol 2020; 9; 6: 387–393)

Key words: diabetes mellitus, quality of life, knowledge, DKQ, WHOQOL-BREF

Introduction

Diabetes mellitus (DM) is one of the biggest challenges in global healthcare and society in general. As reported by the International Diabetes Federation over 463 million people worldwide are living with diabetes. It is the world's leading cause of blindness, kidney failure, heart attack, stroke and lower extremity amputation [1]. Additional concern is the rapid increase of the prevalence in both middle and low gross national income countries, where most of the world's population lives, including Croatia [2]. DM is a large-scale health, social and economic burden with huge effect on personal satisfaction and life expectancy [3, 4]. Patients with type 2 diabetes often die from heart attacks, sudden cardiac death and strokes [5–8]. Therefore, the goal of diabetes therapy is to minimize and delay the occurrence of diabetic complications and to improve the quality of life (QOL) of those affected.

Diabetes care is based on an individualized approach, which takes into consideration the needs and circumstances of the adults with type 2 diabetes. Diabetes management plan includes structured education, dietary advice, advice on other aspects of lifestyle modification (such as increasing physical activity and

losing weight) and drug treatment for blood glucose control.

Assessment of the patient's level of knowledge regarding diabetes is an important step in adapting group education programs to achieve better treatment outcomes. Knowledge is possible to evaluate by using different instruments like the Diabetes Knowledge Questionnaire (DKQ) [9] which was chosen for this study due to the proven correlation between diabetes knowledge and glycemic parameters [10, 11]. In the Republic of Croatia there is no questionnaire to assess a patient's level of knowledge about diabetes.

Quality of life is individual's subjective perception on the impact of the disease on physical health, psychological state, social relationship, environment and general well-being [12]. The studies show that QOL, for people living with chronic disease such as DM, which requires complex management and coping with diabetic complications, is decreased, compared to healthy individuals [13]. Based on clinical experience, we assumed that satisfactory knowledge about DM is a good way toward achieving good glycemic control and reducing diabetes-related complications which can have a positive impact on patients' QOL.

Therefore, the study has three objectives: (1) to validate DKQ [9] (Appendix 1) in Croatian language; (2) to identify knowledge about diabetes and (3) to study the relationship between knowledge and quality of life among type 2 diabetes mellitus patients in Croatia.

Methods

The study was conducted as a cross-sectional study on subjects with type 2 diabetes which were over 18 of age, had met criteria for the diagnosis of type 2 diabetes mellitus according to WHO guidelines (fasting plasma glucose concentration $\geq$ 7 mmol/L or plasma glucose concentration 2 hours after glucose loading [$\geq$ 11.1 mmol/L]), their antidiabetic therapy was not modified at least 3 months before joining the research and they declared themselves willing to participate in the research.

Subjects with serious mental disorders (psychotic and bipolar affective disorder) and/or Alzheimer's disease were excluded from this research.

A total number of 500 patients were included in this study. The research was conducted in accordance with the principles of the Declaration of Helsinki with approval of relevant Ethics Committees.

Written informed consent was obtained from all the participants prior to the start of the study.

DKQ is an instrument originally developed for native English speakers in a form of 60-item questionnaire.

Standard reduced version, used in our study, contains 24 questions with three response options "yes", "no" and "I don`t know". Prior to the usage of questionnaires in other languages and cultures, it is necessary to carry out an intercultural adaptation process. "Exclusive translation, without regard to cultural differences, results in systematic bias" [14, 15].

In the first part of the research, intercultural adaptation and linguistic adaptation was conducted using forward-backward technique.

Three diabetology specialists, who are excellent speakers of English language, have independently translated the original form from English to Croatian. A consensus was found between the versions that would best suit the Croatian language, all with final approval of a university professor who is also a specialist in endocrinology and diabetology. A diabetology physician who is a native speaker of English and Croatian did a backward translation of the Croatian version into English, which showed that translation did not differ from the original English version. Lastly, the final version (Appendix 2) was reviewed and approved by an expert panel consisting of diabetology specialists.

Qualified physicians first introduced DKQ to participants, who completed the questionnaire independently. For all questions and uncertainties qualified medical staff (including diabetologist, family physician or qualified nurses) was at disposal.

One point was given for each correct answer. For incorrect answers no points were taken away, nor negative points were assigned. A total of 24 points could be achieved and > 12 accurately recognized statements defined satisfactory knowledge. Individual scores for each participant were calculated.

Quality of life was measured using WHO Quality of Life-BREF (WHOQOL-BREF) questionnaire that comprises 26 items which measure following 4 domains: physical health, psychological health, social relationships and environment (domains 1–4, respectively) [12]. The responses followed a Likert scale [16] from 1 to 5 where higher score indicates better quality.

Participant's background characteristics and laboratory test results were obtained from medical records, while demographic information such as gender, age, level of education, marital and employment status was filled in by patients themselves.

Statistical evaluation of the data was carried out using SPSS statistical package, version 26.0 for Windows. The variables were reported using descriptive statistics, with decimal numbers and percentages. Internal consistency of DKQ was assessed with Cronbach's Alpha. A multiple regression analysis and Pearson's correlation coefficient were run to determine variables associated

with good knowledge of diabetes where P < 0.05 was considered as significant.

Results

A total of 500 subjects was included in this study, where 50.9% were men, 76.6% were married, 44.7% had high school graduation, and 39.3% were employed (Table 1). 70.11% were being treated by family physicians only, and 29.9% by diabetologist. Almost half of the participants were enrolled in one of the educational programs on symptoms, self-care and treatment of diabetes, out of which 55% was in the individual programs, and the rest in the group program. When asked about willingness for future participation in education, 58.1% of subjects responded positively and 30.1% would prefer group programs. Data regarding diabetes complication were obtained from participant's medical records as follows: 39% of subjects had neuropathy, 18% retinopathy and 29% nephropathy. 18% had previously suffered from heart attack, 7% had experienced at least 1 stroke and 17% were diagnosed with peripheral artery disease.

DKQ was successfully translated into Croatian language using forward-backward technique. The participants presented a good understanding of all items, thus no questions were modified. Good internal consistency of the questionnaire was demonstrated (Cronbach's Alpha [$\alpha = 0.740$]).

Overall mean score of DKQ was 12.13 ($\pm$ 4.75) indicating good knowledge. Specifically, 79.8% of examinees did not know that blood sugar level of 210 in a fasting glucose test is very high, and 78.5% that if untreated, the amount of blood sugar usually rises. 75.5% did not know that a usual cause of diabetes is lack of effective insulin in the body. Furthermore, 79.4% did not know diabetics should take extra care when cutting toenails, 68.7% that cuts and abrasions on diabetics heal more slowly, and the same percentage did not know that diabetes can damage kidneys. Moreover, 53% knew that a person with diabetes should clean a wound with an iodine solution and alcohol, 51.9% knew that diabetic diet does not consist of special foods and 44.7% knew that eating too much sugar and sweet foods do not cause diabetes.

A multiple regression was run to predict DKQ score from different variables of study participants. The model statistically significantly predicted DKQ score F (7, 491) = 25.279, P < 0.0000, R^2 = 0.265. Variables such as diabetes disease duration (P = 0.004), participant's previous enrollment in education about diabetes (P = 0.012) and treatment of disease by diabetologist versus family physician (P = 0.000) added statistically significantly to the prediction of DKQ score. The high-

Table 1. Population charateristics

Subjects characteristics	n (%)	
Sex		
Male	254 (50.9)	
Female	245 (49.1)	
Educational level		
Unfinished primary school	24 (5)	
Primary school	71 (14.8)	
High school	223 (46.4)	
BA/BSc or MS/MSc degree	163 (33.9)	
Working status		
Employee	196 (40.2)	
Self employed	16 (3.3)	
Retired	196 (40.2)	
Unemployed	78 (16)	
Miscellaneous	1 (0.2)	
Marital status		
Married	382 (78.6)	
In a partnership	16 (3.3)	
Widow/er	40 (8.2)	
Divorced	30 (6.2)	
Never married	18 (3.7)	
	Mean (min–max)	**SD**
Age	62.13 (35–90)	± 10.15
Duration of diabetes (years)	9.64 (0.1–40)	± 7.92
BMI	27.00 (13.67–36.2)	± 2.24
HbA$_{1c}$	7.57 (5.2–14.4)	± 1.01
Overall satisfaction with life	7.69 (1–10)	± 1.77
DKQ correct answers	12.13 (1–23)	± 4.75

est contributing predictor is the patient's participation in education about diabetes (.933). Higher DKQ score was detected in patients who were involved in the group programs in comparison to individual programs, however the difference was not statistically significant. Age, gender, BMI, HbA$_{1c}$ or educational background was not recognized as factors associated with good knowledge about diabetes.

Average WHOQOL-BREF score was 24.43, 22.18, 11.1 and 31.84 for domains 1–4, respectively. 33,5% subjects declared they were extremely satisfied with their life (8/10) (Likert scale where 1 signifies completely dissatisfied and 10 completely satisfied).

Discussion

One of the objectives of this study is to validate DKQ questionnaire in Croatian language. Good reliability and internal consistency was confirmed using Cronbach's Alpha ($\alpha = 0.740$). Compared to other studies with DKQ questionnaire, α is lower than in the study done in Portugal [17] and Mexico [18], but higher

than Nepal [19] and India [20]. The overall mean of correct answer was 12.13 which indicates good diabetes knowledge among our participants.

Despite good overall knowledge, questions with the low score raised several concerns. The lowest level of knowledge was related to identifying the fasting blood sugar level of 210 is too high. As self-measurement of blood glucose is recognized as one of the main factors in decreasing diabetes-related morbidity and mortality [21], blood glucose monitor is assigned to every patient diagnosed with type 2 diabetes in Croatia. Physicians are able to choose and recommend one, among more than 25 different glucose monitors currently available on the Croatian market [22], each of with slightly different settings. One of the explanations can be that using more sophisticated glucose monitors reduce the need of memorizing numbers itself, because of their possibility to perform software-based analysis and alarm when the glucose levels are too high. However, giving the age and education background of the participants, the main concern is whether the self-measurement of glucose level is conducted at all. In addition, we found that the majority of participants do not recognize signs of hyperglycemia (61.4%) and hypoglycemia (69%). These findings only highlight the need for constant education and raising the consciousness about potential signs, which could be a risk for a patient's life. Our result was expected from the similar previous studies [18, 20, 23].

Around 50% of patients thought that diabetic diet consists mainly of special foods, two thirds did not know regular exercise can have influence on need for insulin or other diabetic medication, one third of patients knew that kidneys do not produce insulin and around the same percentage knew about 2 main types of diabetes [11].

Study conducted in Mexico shows that their patients have very high awareness of cutting their toenails with care and about damage diabetes could cause to their kidneys [18], which is in high contrast to our study. A possible explanation might be that Croatian citizens respond poorly to programs for prevention or early detection of disease and are more likely to spend money on alcoholic beverages and tobacco rather than health service. In addition, health literacy and self-care awareness are lower than in the rest of European Union [24].

The most important predictors of the total knowledge scores are previous education about diabetes (P = 0.012) followed by duration of disease (P = 0.004). Similar findings were confirmed in other studies [25––27], suggesting that patients are able more effectively adapt to diabetes treatment when having appropriate education. Moreover, the duration of disease increases the knowledge due to expanded experience and the awareness of self-care. No significant correlation was detected between knowledge and age, which was confirmed by similar study [27] suggesting that patients of all ages are eligible for educational program.

In the study about the determinants of diabetes knowledge [23], lower education was observed as risk factor. Similarly, participants in our study without any education had lower DKQ results in comparison to those with higher education although statistical significance was not achieved.

In contrast to our assumption but in line with similar studies [18, 25, 26], HbA$_{1c}$ was not recognized as a factor influenced by total knowledge score (P = 0.387).

To the best of our knowledge, this is the first time to assess the level of diabetes knowledge for people in southeastern Europe, and first time to explore correlation between knowledge and quality of life using DKQ and WHOQOL-BREF, respectively.

As in other studies [28], our participants expressed high satisfaction with their quality of life in areas of physical, psychological and environmental health. On the other side, average score in the domain of social health, which concerns personal relationships, social support and sexual activity, is lower. This was expected because of lower number of questions in comparison with other domains but also the conservative upbringing and values which are still of great influence in Croatia.

Our study demonstrates that diabetic knowledge does not correlate with quality of life, which is in accordance with similar study [29]. It can be partially explained by the complex nature of the disease itself and other independent factors such as education, level of income, but also social and cultural circumstances, which highly influence people's quality of life.

Limitations of our study concerns participant's residence, which is mostly concentrated on the area of the capital city Zagreb and closer surroundings while the inclusion of more people from other parts of the country may result in different findings and accurately reflect the general population. Furthermore, involvement in the study was voluntary and it is more likely for patients with higher levels of disease awareness to be willing to participate.

Our findings reveal that DKQ is a good tool for assessing diabetic knowledge in Croatian language but also underline the need for more comprehensive initiatives targeting diabetics knowledge, especially recognizing symptoms of hypo/hyperglycemia and emphasizing exercise which can highly determine adherence to medications and improve target goals.

Conclusions

The study demonstrated good internal consistency of DKQ and as such is a reliable instrument for measuring diabetes knowledge, applicable for further studies in Croatian language. Even though Croatian diabetics have good overall knowledge about disease, improvement is especially necessary in the areas such as self-care and nutrition. We did not find a positive correlation between diabetes knowledge and quality of life. Still, we believe it would be interesting to conduct studies in other countries with different health care systems and cultures to more precisely explore this correlation.

Conflicts of interest

The authors have no conflict of interest to report.

REFERENCE

1. International Diabetes Federation. IDF DIABETES ATLAS 9th edition 2019 . https://www.diabetesatlas.org/ (1.05.2020).

2. Dunachie S, Chamnan P. The double burden of diabetes and global infection in low and middle-income countries. Trans R Soc Trop Med Hyg. 2019; 113(2): 56–64, doi: 10.1093/trstmh/try124, indexed in Pubmed: 30517697.

3. Bommer C, Sagalova V, Heesemann E, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. Diabetes Care. 2018; 41(5): 963–970, doi: 10.2337/dc17-1962, indexed in Pubmed: 29475843.

4. Preston SH, Choi D, Elo IT, et al. Effect of Diabetes on Life Expectancy in the United States by Race and Ethnicity. Biodemography Soc Biol. 2018; 64(2): 139–151, doi: 10.1080/19485565.2018.1542291, indexed in Pubmed: 31178981.

5. Aune D, Schlesinger S, Norat T, et al. Diabetes mellitus and the risk of sudden cardiac death: A systematic review and meta-analysis of prospective studies. Nutr Metab Cardiovasc Dis. 2018; 28(6): 543–556, doi: 10.1016/j.numecd.2018.02.011, indexed in Pubmed: 29730085.

6. Chen R, Ovbiagele B, Feng W. Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. Am J Med Sci. 2016; 351(4): 380–386, doi: 10.1016/j.amjms.2016.01.011, indexed in Pubmed: 27079344.

7. Li W, Li M, Gao C, et al. Impact of type 2 diabetes mellitus on recurrent myocardial infarction in China. Diab Vasc Dis Res. 2016; 13(6): 395–404, doi: 10.1177/1479164116653606, indexed in Pubmed: 27390227.

8. Israel CW, Lee-Barkey YH. Sudden cardiac death in diabetes mellitus. Herz. 2016; 41(3): 193–200, doi: 10.1007/s00059-016-4421-9, indexed in Pubmed: 27071967.

9. Garcia AA, Villagomez ET, Brown SA, et al. The Starr County Diabetes Education Study: development of the Spanish-language diabetes knowledge questionnaire. Diabetes Care. 2001; 24(1): 16–21, doi: 10.2337/diacare.24.1.16, indexed in Pubmed: 11194219.

10. Dawson AZ, Walker RJ, Egede LE. Differential Relationships Between Diabetes Knowledge Scales and Diabetes Outcomes. Diabetes Educ. 2017; 43(4): 360–366, doi: 10.1177/0145721717713316, indexed in Pubmed: 28595504.

11. Bukhsh A, Lee SW, Pusparajah P, et al. Psychometric Properties of the Urdu Version of Diabetes Knowledge Questionnaire. Front Public Health. 2017; 5: 139, doi: 10.3389/fpubh.2017.00139, indexed in Pubmed: 28702453.

12. The World Health Organization. https://www.who.int/substance_abuse/research_tools/whoqolbref/en/ (1.05.2020).

13. Tavakkoli L, Dehghan A. Compare the Quality of Life in Type 2 Diabetic Patients with Healthy Individuals (Application of WHOQOL-BREF). Zahedan Journal of Research in Medical Sciences. 2017; In Press(In Press), doi: 10.5812/zjrms.5882.

14. Beaton D, Bombardier C, Ferraz MB. Recommendations for the cross-cultural adaptation of the DASH & QuickDASH outcome measures. Institute for Work & Health. 2007; 1(1): 1–45.

15. Beaton DE, Bombardier C, Guillemin F, et al. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000; 25(24): 3186–3191, doi: 10.1097/00007632-200012150-00014, indexed in Pubmed: 11124735.

16. Likert RA. Technique for the measurement of attitudes. Archives of Psychology. 1932; 140: 1–55.

17. Menino E, Dos M, Clarisse M. Validation of Diabetes Knowledge Questionnaire (DKQ) in the Portuguese Population. Diabetes Obes Int J. 2017; 2(1): 1–8.

18. Alarcon LC. Level of knowledge in patients with type 2 diabetes mellitus and its relationship with glycemic levels and stages of Grief according to Kübler-Ross. Journal of Diabetes & Metabolism. 2015; 06(02), doi: 10.4172/2155-6156.1000495.

19. Gyawali B, Mishra SR, Neupane D, et al. Diabetes management training for female community health volunteers in Western Nepal: an implementation experience. BMC Public Health. 2018; 18(1): 641, doi: 10.1186/s12889-018-5562-y, indexed in Pubmed: 29783961.

20. Rao AR, Sreelakshmi P, Prabhu DD, et al. malayalam questionnaire for the assessment of knowledge regarding diabetes. Kerala Med J. 2016; 9(1): 7–11.

21. Martin S, Schneider B, Heinemann L, et al. Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemiological cohort study. Diabetologia. 2006; 49(2): 271–278, doi: 10.1007/s00125-005-0083-5, indexed in Pubmed: 16362814.

22. Croatian Health Insurance Fund. https://www.hzzo.hr/zdravstveni-sustav-rh/medicinski-proizvodi/ (18.09.2020).

23. Oba S, Yamamoto M, Horikawa Y, et al. Gifu Diabetes Study Group. Knowledge of diabetes and its determinants: a cross-sectional study among adults in a Japanese community. BMJ Open. 2019; 9(5): e024556, doi: 10.1136/bmjopen-2018-024556, indexed in Pubmed: 31152029.

24. Croatian bureau of statistics. Basic characteristics of household consumption, 2017. https://www.dzs.hr/Hrv_Eng/publication/2018/14-01-02_01_2018.htm (10.05.2020).

25. Mahfouz EM, Kamal NN, Mohammed ES, et al. Effects of mothers' knowledge and coping strategies on the glycemic control of their diabetic children in Egypt. Int J Prev Med. 2018; 9: 26, doi: 10.4103/ijpvm.IJPVM_336_17, indexed in Pubmed: 29619150.

26. Dussa K, Parimalakrishnan S, Sahay R. Assessment of diabetes knowledge using diabetes knowledge questionnaire among people with type 2 diabetes mellitus. Asian J Pharm Clin Res. 2015 ; 8(2): 254–256.

27. Ozcelik F, Yiginer O, Arslan E, et al. Association between glycemic control and the level of knowledge and disease awareness in type 2 diabetic patients. Pol Arch Med Wewn. 2010; 120(10): 399–406, indexed in Pubmed: 20980945.

28. Gholami A, Jahromi LM, Zarei E, et al. Application of WHOQOL-BREF in Measuring Quality of Life in Health-Care Staff. Int J Prev Med. 2013; 4(7): 809–817, indexed in Pubmed: 24049600.

29. Mujika-Zabaleta A, Forbes A, While A, et al. Relationship between diabetes knowledge, glycaemic control and quality of life: pilot study. Diabetes Prim Care. 2010; 12: 376–381.

APPENDIX 1

DKQ Croatian version

1. Konzumacija velikih količina šećera i druge slatke hrane uzrokuje šećernu bolest.	DA	NE	NEZNAM
2. Uobičajeni uzrok šećerne bolesti je smanjeni učinak inzulina u organizmu.	DA	NE	NEZNAM
3. Uzrok šećerne bolesti je nemogućnost bubrega da spriječe izlučivanje šećera u urinu.	DA	NE	NEZNAM
4. Bubrezi proizvode inzulin.	DA	NE	NEZNAM
5. Ako se šećerna bolest ne liječi, količina šećera u krvi raste.	DA	NE	NEZNAM
6. Ako sam dijabetičar, moja djeca imaju veći rizik da budu dijabetičari.	DA	NE	NEZNAM
7. Šećerna bolest se može izliječiti.	DA	NE	NEZNAM
8. Razina šećera u krvi natašte iznad 11 mmol/L je previsoka.	DA	NE	NEZNAM
9. Najbolji način za provođenje samokontrole je analiza urina.	DA	NE	NEZNAM
10. Redovita tjelovježba će povećati potrebu tijela za inzulinom ili lijekovima za šećernu bolest.	DA	NE	NEZNAM
11. Postoje dva glavna tipa šećerne bolesti: tip 1 (inzulin - ovisan) i tip 2 (inzulin - neovisan).	DA	NE	NEZNAM
12. Prejedanje dovodi do inzulinske reakcije (pada šećera u krvi).	DA	NE	NEZNAM
13. Lijekovi su puno važniji za dobru kontrolu šećerne bolesti od pravilne prehrane i redovite tjelovježbe.	DA	NE	NEZNAM
14. Šećerna bolest često dovodi do loše cirkulacije.	DA	NE	NEZNAM
15. Porezotine i ogrebotine sporije cijele kod osoba s šećernom bolesti.	DA	NE	NEZNAM
16. Osobe sa šećernom bolesti trebaju biti oprezne prilikom podrezivanja noktiju na stopalima.	DA	NE	NEZNAM
17. Osoba sa šećernom bolesti trebala bi očistiti porezotinu jodom i alkoholom.	DA	NE	NEZNAM
18. Način pripreme hrane jednako je važan kao i odabir namirnica.	DA	NE	NEZNAM
19. Šećerna bolest može oštetiti moje bubrege.	DA	NE	NEZNAM
20. Šećerna bolest može dovesti do gubitka osjeta u mojim prstima, šakama i stopalima.	DA	NE	NEZNAM
21. Znojenje i tresavica su znakovi visoke razine šećera u krvi.	DA	NE	NEZNAM
22. Učestalo mokrenje i žeđ su znakovi niske razine šećera u krvi.	DA	NE	NEZNAM
23. Uski elastični zavoji ili čarape nisu štetni za dijabetičare.	DA	NE	NEZNAM
24. Dijabetička dijeta se uglavnom sastoji od posebnih namirnica.	DA	NE	NEZNAM

APPENDIX 2

DKQ English version

1. Eating too much sugar and other sweet foods is a cause of diabetes.	YES	NO	I DON'T KNOW
2. The usual cause of diabetes is lack of effective insulin in the body.	YES	NO	I DON'T KNOW
3. Diabetes is caused by failure of the kidneys to keep sugar out of the urine.	YES	NO	I DON'T KNOW
4. Kidneys produce insulin.	YES	NO	I DON'T KNOW
5. In untreated diabetes, the amount of sugar in the blood usually increases.	YES	NO	I DON'T KNOW
6. If I am diabetic, my children have a higher chance of being diabetic.	YES	NO	I DON'T KNOW
7. Diabetes can be cured.	YES	NO	I DON'T KNOW
8. A fasting blood sugar level of 210 is too high.	YES	NO	I DON'T KNOW
9. The best way to check my diabetes is by testing my urine.	YES	NO	I DON'T KNOW
10. Regular exercise will increase the need for insulin or other diabetic medication.	YES	NO	I DON'T KNOW
11. There are two main types of diabetes: Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent).	YES	NO	I DON'T KNOW
12. An insulin reaction is caused by too much food.	YES	NO	I DON'T KNOW
13. Medication is more important than diet and exercise to control my diabetes.	YES	NO	I DON'T KNOW
14. Diabetes often causes poor circulation.	YES	NO	I DON'T KNOW
15. Cuts and abrasions on diabetics heal more slowly.	YES	NO	I DON'T KNOW
16. Diabetics should take extra care when cutting their toenails.	YES	NO	I DON'T KNOW
17. A person with diabetes should cleanse a cut with iodine and alcohol.	YES	NO	I DON'T KNOW
18. The way I prepare my food is as important as the foods I eat.	YES	NO	I DON'T KNOW
19. Diabetes can damage my kidneys.	YES	NO	I DON'T KNOW
20. Diabetes can cause loss of feeling in my hands, fingers, and feet.	YES	NO	I DON'T KNOW
21. Shaking and sweating are signs of high blood sugar.	YES	NO	I DON'T KNOW
22. Frequent urination and thirst are signs of low blood sugar.	YES	NO	I DON'T KNOW
23. Tight elastic hose or socks are not bad for diabetics.	YES	NO	I DON'T KNOW
24. A diabetic diet consists mostly of special foods.	YES	NO	I DON'T KNOW

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Examination of the relationship of knowledge of diabetes, attitude toward diabetes, and health literacy with diabetes management self-efficacy using hierarchical multiple regression modeling

ABSTRACT

Background. Self-efficacy in diabetes management can empower patients and result in their more active participation in the treatment process. In addition, a patient's behavior is influenced by their knowledge of and attitude toward their illness. Therefore, the goal of the present study was to examine the association of knowledge of diabetes, attitude toward diabetes, and health literacy with diabetes management self-efficacy in patients with type 2 diabetes.

Methods. This descriptive-correlational study was conducted in 2019. The sample included 115 patients with diabetes (59 women and 56 men) attending diabetes centers of Sanandaj, Kurdistan, Iran, who were selected using a convenience sampling method. The Brief Diabetes Knowledge Test (DKT), the Diabetes Attitude Scale (DAS), the Health Literacy for Iranian Adults (HELIA) scale, and the Diabetes Management Self-Efficacy Scale (DMSES) were used to gather data. The data was analyzed using descriptive statistics, Pearson correlation coefficient, and stepwise regression analysis. All the analyses were perfumed using SPSS, version 16. The significance level was set at 0.05 for all the tests.

Results. The mean age of participants was 46.61 ± 13.73 years. Health literacy (r = 0.585) and attitude (r = 0.396) were significantly correlated with self-efficacy (P = 0.001). According to the results of stepwise regression analysis, 34.3% and 36.6% of the variance of self-efficacy was explained by health literacy alone and health literacy together with attitude, respectively. One standard deviation change in health literacy and attitude was associated with 0.51 and 0.71 standard deviation change in self-efficacy, respectively.

Conclusion. Health literacy and attitude toward diabetes are positively associated with self-efficacy in diabetes management, and improving these variables can improve self-efficacy in patients with type 2 diabetes. (Clin Diabetol 2020; 9; 6: 394–399)

Key word: diabetes, self-efficacy, knowledge, attitude, health literacy

Introduction

Diabetes is the most common chronic metabolic disease that has become a silent epidemic in today's world [1]. In 2014, about 387 million people around the world had diabetes, and it has been projected that by 2035, 529 million people will have this disease

[2]. According to statistics, diabetes control is not at the desired level globally, and a significant increase is projected to occur in the global prevalence of diabetes. This is especially concerning for Middle-East countries; it has been projected that in near future, Iran will have the highest prevalence of diabetes in Middle-East after Pakistan [3]. The prevalence of diabetes in Iran is 9.3% [4]; however, given the fact that a lot of diabetic patients are not aware of their condition, the prevalence of diabetes seems to be higher than the reported prevalence rates [5]. Currently, more than 3 million people in Iran have diabetes, and if effective measures are not taken to address this problem, this number will be doubled by 2030 [6].

Diabetes management is complex and requires measures beyond blood sugar control, and a broad range of interventions are needed to improve the outcomes for this group of patients [7]. Improvement of self-care skills in diabetes like any other chronic disorder requires behavioral changes in patients [2]. Self-efficacy is an important factor in diabetes management, and can lead to increased quality of life, reduced risk of hospitalization, and less risky behaviors in diabetic patients [8]. Self-efficacy includes self-motivated behaviors allowing a patient to understand factors influencing their condition, make effective decisions, and engage in effective behaviors to improve their own health [6]. Patients with higher levels of self-efficacy tend to actively participate in self-care programs, and are more successful in managing their symptoms [8]. Self-efficacy empowers patients and increases their sense of control; therefore, diabetic patients with higher levels of self-efficacy feel more control on their problem, and try harder to adhere to treatment [9]. Huang et al. [10] found that self-efficacy was the strongest predictor of adherence to treatment in diabetic patients. Diabetic patients have the most important role in managing their illness; therefore, their level of knowledge of diabetes is an important factor in the effective management of their symptoms [11].

Knowledge is the best protective factor against diabetes, so that Moodley [12] considers it to be the most effective weapon against diabetes. Patients with adequate knowledge of diabetes are more likely to take responsibility for their own health [13], and have a greater sense of empowerment [14]. Attitude motivates behavior, and any change in the attitude of patients results in changes in their behaviors [15]. In addition to knowledge and attitude, health literacy may also be related to diabetes management self-efficacy. Health literacy is defined in terms of cognitive or social skills determining one's motivation or ability to obtain, understand, or use information in order to maintain or improve their own health [16]. Herath maintains that health literacy is an integral part of diabetes management [13]. Higher levels of health literacy allow diabetic patients to better understand information related to proper diets, insulin injection, blood sugar control, and acceptance of the disease, and increase the participation of patients in making decisions about treatment methods [17]. Schilinger [18] found that patients with adequate health literacy had more control over their blood sugar levels and experienced fewer diabetes complications compared to those with inadequate levels of health literacy.

Knowledge, attitude, and health literacy are influenced by culture; therefore, the present study is aimed at examining the relationship of knowledge of diabetes, attitude toward diabetes, and health literacy with diabetes management self-efficacy in patients with type 2 diabetes attending diabetes centers of Sanandaj, Kurdistan, Iran in 2019.

Methods

This was a descriptive-correlational study. The statistical population included all patients with type 2 diabetes attending diabetes centers of Sanandaj in 2019, and the sample included 115 patients who were selected for this population, using a convenience sampling method. Sample size was calculated based on the following formula:

$$N = (\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{0.5\ln\frac{1+r}{1-r}})^2 + 3,$$

according to $\alpha = 0.05$ and a correlation coefficient of r = 0.3.

The inclusion criteria were willingness to participate in the study, medical record in the diabetes center, aged 16–65 years, and ability to read and write. Incomplete questionnaires were discarded. The data was collected using the demographic questionnaire, the Brief Diabetes Knowledge Test (DKT), the Diabetes Attitude Scale (DAS), the Health Literacy for Iranian Adults (HELIA) scale, and the Diabetes Management Self-Efficacy Scale (DMSES).

The Brief Diabetes Knowledge Test (DKT): This test was developed by Fitzgerald et al. [19] at Michigan Diabetes Research Center. It has 23 items with four response options, one of which is the correct answer (scored 1) and the rest are incorrect answers (scored 0). Total score ranges from 0 to 23, with higher scores indicating higher diabetes knowledge [19, 20]. Because a Persian version of the test was not available, after obtaining permission from the original developers of the test, it was translated into Persian using the forward-backward method, and 10 experts in nursing confirmed its qualitative content validity. Then, the dif-

ficulty and discrimination coefficients were examined. 10 items with difficulty coefficients below 0.2 were discarded, and the reliability of the final scale with 16 items was found to be 0.661, using the Kuder-Richardson coefficient.

The Diabetes Attitude Scale (DAS): This scale was translated into Persian and validated in Iran by Mahjouri et al. [21]. It has 33 items that are rated on a 5-point Likert-type scale ranging from 1 (totally disagree) to 5 (totally agree), and higher scores indicate better attitude toward diabetes.

The Health Literacy for Iranian Adults (HELIA) scale: This scale was developed by Montazeri et al. [22], and has 33 items that are rated on a 5-point Likert-type scale.

The Diabetes Management Self-Efficacy Scale (DMSES): This scale was translated into Persian and validated in Iran by Haghayegh et al. [23]. It has 19 items rated on a 10-point Likert-type scale ranging from 1 (I cannot at all) to 10 (I surely can). Higher scores on this scale indicate greater self-efficacy in diabetes management. The reliability of DAS, HELIA, and DMSES questionnaires was 0.752, 0.896, and 0.853, respectively.

After explaining the objectives of the study to the participants and obtaining their consents for participation, the questionnaires were administered. It should be noted that the participants were not required to write their real names on the questionnaires. The present study was approved by the ethics committee at Kurdistan University of Medical Sciences (no. IR.MUK. REC.1398.212)

Statistical analysis

The data was described using percentage, mean, and standard deviation. Independent t-test and one-way analysis of variance were used to compare quantitative data between two groups and more than two groups, respectively. Chi-squared test and Pearson correlation coefficient were used to examine the relationship between qualitative data and the relationship between quantitative data, respectively. Stepwise multiple regression was used to determine the important factors in predicting diabetes management self-efficacy. Significance level was set at 0.05 for all the tests. All the analyses were performed using SPSS, version 16.

Results

The study sample included 115 patients with type 2 diabetes (59 women and 56 men) with a mean age of 46.61 ± 13.73 years. The mean disease duration was 9.24 ± 5.67 years. Further details are provided in Table 1.

Table 1. Demographic properties of the participants

Variable	N	%
Gender		
Male	56	48.7
Female	59	51.3
Marital situation		
Single	18	15.7
Married	97	84.3
Literacy		
Primary	70	60.9
High school	29	25.2
University	16	13.9
Employment status		
Employed	67	58.3
Un employed	48	41.7
Drug		
Insulin	47	40.9
Pills	56	48.7
Insulin + pills	12	10.4

According to the results of Pearson correlation coefficient, self-efficacy in diabetes management was significantly associated with attitude (r = 0.396) and health literacy (r = 0.585). In other words, better attitude toward diabetes and higher health literacy were related to higher self-efficacy in diabetes management (P < 0.001) (Table 2).

Stepwise regression analysis was employed to determine the predictive power of knowledge of diabetes, attitude toward diabetes, and health literacy in diabetes management self-efficacy. According to Pearson correlation results, health literacy and attitude were significantly related to self-efficacy; therefore, the two variables were included in the regression model to predict self-efficacy. Health literacy was included in the first step, and health literacy and attitude were included in the second step. In the first step, health literacy significantly predicted self-efficacy (F = 58.883, P = 0.001), and explained 34.3% of the variance of this variable. In the second step, health literacy and attitude together explained 36.6% of the variance of self-efficacy (F = 32.366, P = 0.001). In this step, attitude alone explained 2.3% of the variance of self-efficacy (Table 3).

As shown in the table above, regression coefficients indicate that one standard deviation change in health literacy and attitude is associated with 0.510 and 0.172 standard deviation change in self-efficacy, respectively. Regression coefficients also show that health literacy (P = 0.001) and attitude (P = 0.001) have a significant positive effect on self-efficacy. In other words, higher

Table 2. Correlation coefficients between diabetes management self-efficacy with knowledge of diabetes, attitude toward diabetes, and health literacy in patients with type 2 diabetes

Variables	M	SD	Knowledge	Attitude	Health literacy	Self-efficacy
Knowledge	7.41	2.82	–			
Attitude	121.07	9.28	0.18	–		
Health literacy	134.69	12.70	0.05	0.44*	–	
Self-efficacy	152.56	24.93	0.02	0.396*	0.585*	–

*P < 0.001

Table 3. The results of stepwise multiple regression

Model	Source of changes	SS	df	MS	F	R	R^2	$A_{dj} R^2$	P
Health literacy	Regression	24277.783	1	24288.783	58.88	0.585	0.343	0.337	0.001
	Residual	46590.478	113	412.305					
	Sum	70868.261	114						
Health literacy	Regression	25957.064	2	12978.532	32.36	0.605	0.366	0.355	0.001
& Attitude	Residual	44911.197	112	400.993					
	Sum	70868.261	114						

Table 4. Stepwise regression analysis for variables predicting diabetes management self-efficacy

Model	Variable	Unstandardized coefficients		Standardized coefficients	t	P
		B	Standard error	Beta		
1	(constant)	−2.095	20.244		−0.104	0.918
	Health literacy	1.148	0.150	0.585	7.674	0.001
2	(constant)	−37.882	26.540		−1.427	0.156
	Health literacy	1	0.164	0.510	6.079	0.001
	Attitude	0.461	0.255	0.172	2.046	0.001

health literacy and a better attitude toward diabetes are associated with higher diabetes management self-efficacy (Table 4).

Discussion

The goal of the present study was to examine the association of knowledge of diabetes, attitude toward diabetes, and health literacy with diabetes management self-efficacy. According to the study results, diabetes management self-efficacy was significantly associated with attitude and health literacy. In addition, health literacy and attitude explained 34.3% and 2.3% (together 36.6%) of the variance of diabetes management self-efficacy, respectively. Osborn et al. [24] also found a significant positive association between self-efficacy and health literacy in diabetic patients. Masoompour et al. [25] also showed a significant positive relationship between health literacy and self-efficacy in patients with diabetes. Sedighi Pashaki et al. [26] maintain that proper management of diabetes requires multi-

disciplinary cooperation among healthcare providers from different fields and also cooperation between healthcare providers and patients, and that the concept of health literacy is highlighted with a greater focus on patient-centered care and patient empowerment. Diabetic patients with enough health literacy are less likely to have problems in reading medication labels and health-related educational brochures, interpreting medical test results, and providing informed consent for medical procedures [27]. They are also more able to manage their illness effectively. On the other hand, the relationship between health literacy and self-efficacy is not limited to diabetes, and is also observed in other chronic disorders. For example, a study among patients with colorectal cancer showed a significant relationship between health literacy and patient self-efficacy [28]. Bohanny et al. [29] found that receiving diabetes education, job status, and health literacy explained 11.8% of the variance of self-efficacy in patients.

We found no significant association between knowledge and self-efficacy. In contrast with this finding, Abedini [11] maintains that patients' lack of knowledge of their own conditions can increase the prevalence of diabetes complications. Santos also considers knowledge to be one of the most important factors in diabetes management, because the patient needs to have enough knowledge about diabetes treatments, role of carbohydrates, and proper diets [30]. Patients with enough knowledge about their illness are more likely to take responsibility for their own health [13]. In the present study, the diabetic patients obtained less than half of the total knowledge score that seems inadequate. Murata believes that lack of knowledge of diabetes undermines the ability of diabetic patients to manage their illness [14]. Therefore, we cannot expect from patients with insufficient knowledge of their illness to show self-efficacy in diabetes management; this indicates the importance of providing patients with proper training. Given the fact that patients' knowledge of their conditions is influenced by cultural factors, learning readiness, cognitive performance, family support, and barriers to care [23], proper training programs should be provided for diabetic patients, so that they can be empowered to effectively manage their illness. Economic problems in Iran can affect patients' attitudes toward diabetes. Even if patients have good knowledge about the disease, when they cannot afford adequate treatment of the disease, this knowledge cannot help them. It seems that knowledge can be effective when the patient has sufficient financial support. On the other hand, seeing other diabetics with lower limb amputation, blindness, kidney failure, and dialysis dependence makes these patients who do not yet have the complications of diabetes pay more attention to self-care behaviors to better manage their disease.

In the present study, attitude toward diabetes was a moderate predictor of self-efficacy in diabetes management. Consistent with this finding, previous studies have shown a significant relationship between attitude and diabetes management self-efficacy [31, 32]. Given that attitude can be influenced by knowledge, this finding can be attributed to the participants' low knowledge of diabetes. Patients with inadequate knowledge of factors related to their illness, including its causes and types, proper diets, and proper exercise, cannot have the right attitude toward their conditions [33]. Attitude motivates behavior, and having a proper attitude can change patients' behaviors and improve their self-efficacy [15]. It seems that the emotional nature of the Kurds was clearer in this study because attitude (not knowledge) had an effect on the self-efficacy of their disease management.

One important limitation of the present study was that the data was gathered using self-report questioners. Therefore, participants' answers to the questionnaires may have been influenced by their mental and emotional state. Iran is a country of different cultures and ethnicities, and this study was conducted on Kurds living in western Iran. The results of this study can be generalized to all Kurdish populations in Iran, but since these concepts are influenced by the culture and context of different societies, it is recommended to study in Arab, Turkish, Lor, Balouch, Lak and Fars cultures to be able to comment on this with more confidence.

Conclusion

Overall, the study results indicated the positive association of diabetes management self-efficacy with health literacy and attitude toward diabetes in patients with type 2 diabetes. Therefore, self-efficacy of diabetic patients in managing their own illness can be improved through designing strategies to improve their health literacy and attitude toward diabetes.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Pashaki MS, Mezel JA, Mokhtari Z, et al. The prevalence of comorbid depression in patients with diabetes: A meta-analysis of observational studies. Diabetes Metab Syndr. 2019; 13(6): 3113–3119, doi: 10.1016/j.dsx.2019.11.003, indexed in Pubmed: 31790965.
2. Tharek Z, Ramli AS, Whitford DL, et al. Relationship between self-efficacy, self-care behaviour and glycaemic control among patients with type 2 diabetes mellitus in the Malaysian primary care setting. BMC Fam Pract. 2018; 19(1): 39, doi: 10.1186/s12875-018-0725-6, indexed in Pubmed: 29523075.
3. Olfatifar M, Karami M, Shokri P, et al. Prevalence of chronic complications and related risk factors of diabetes in patients referred to the Diabetes Center of Hamedan Province. Scientific Journal of Hamedan Nursing and Midwifery Faculty. 2017; 25(2): 69–74, doi: 10.21859/nmj-25029.
4. Haghdoost AA, Rezazadeh-Kermani M, Sadghirad B, et al. Prevalence of type 2 diabetes in the Islamic Republic of Iran: systematic review and meta-analysis. East Mediterr Health J. 2009; 15(3): 591–599, indexed in Pubmed: 19731775.
5. Shomali M, Mohamadi S, Ervanloo S. An investigation of nurses' knowledge regarding diabetes Zanjan University of Medical Sciences. Journal of Diabetes Nursing. 2015; 3(1): 59–68.
6. Rahimi MIN. Rezvan Madani F, Eghbalian A. Knowledge and practice level of self-directed care among diabetics in Kermanshah

City in 2014: A Short Report. The Journal of Rafsanjan University of Medical Sciences. 2015; 14(2): 167–72.

7. Shahraki RA, Kamrani AA, Sahaf R, et al. Effects of Nationwide Program for Prevention and Control of Diabetes initiated by the ministry of health on elderly diabetic patients' knowledge, attitude and practice in Isfahan. Salmand. 2019: 84–95, doi: 10.32598/sija.14.1.84.

8. Hatef M, Sharif Nia H, Mousavinasab N, et al. Self-efficacy and prediction of associated factors in patients with chronic diseases. Journal of Mazandaran University of Medical Sciences. 2018; 28(162): 86–94.

9. Niguse H, Belay G, Fisseha G, et al. Self-care related knowledge, attitude, practice and associated factors among patients with diabetes in Ayder Comprehensive Specialized Hospital, North Ethiopia. BMC Res Notes. 2019; 12(1): 34, doi: 10.1186/s13104-019-4072-z, indexed in Pubmed: 30658687.

10. Huang YM, Shiyanbola OO, Smith PD. Association of health literacy and medication self-efficacy with medication adherence and diabetes control. Patient Prefer Adherence. 2018; 12: 793–802, doi: 10.2147/PPA.S153312, indexed in Pubmed: 29785094.

11. Abedini Z. Shouri Bidgoli A, Ahmari Tehran H. Study of knowledge and practice of patient self directed care among diabetics patients. Qom Univ Med Sci J. 2008; 2(2): 37–42.

12. Moodley LM, Rambiritch V. An assessment of the level of knowledge about diabetes mellitus among diabetic patients in a primary healthcare setting. South African Family Practice. 2014; 49(10), doi: 10.1080/20786204.2007.10873652.

13. Herath HMM, Weerasinghe NP, Dias H, et al. Knowledge, attitude and practice related to diabetes mellitus among the general public in Galle district in Southern Sri Lanka: a pilot study. BMC Public Health. 2017; 17(1): 535, doi: 10.1186/s12889-017-4459-5, indexed in Pubmed: 28571566.

14. Murata GH, Shah JH, Adam KD, et al. Factors affecting diabetes knowledge in Type 2 diabetic veterans. Diabetologia. 2003; 46(8): 1170–1178, doi: 10.1007/s00125-003-1161-1, indexed in Pubmed: 12856126.

15. Sheeran P, Maki A, Montanaro E, et al. The impact of changing attitudes, norms, and self-efficacy on health-related intentions and behavior: A meta-analysis. Health Psychol. 2016; 35(11): 1178––1188, doi: 10.1037/hea0000387, indexed in Pubmed: 27280365.

16. Zahedi S, Darvishpoor Kakhaki A, Hosseini M, et al. The correlation between self-care and health literacy in patients undergoing hemodialysis. Iranian Journal of Diabetes and Lipid Disorders. 2018; 17(4): 180–188.

17. Abbaszadeh Bazzi M, Karimiaval M. Relationship between health literacy and self-care behaviors in diabetic patients type ii referred to the center of diabetes control and prevention in Zabol. Journal of Health Literacy. 2018; 3(1): 10–19.

18. Schillinger D, Grumbach K, Piette J, et al. Association of health literacy with diabetes outcomes. JAMA. 2002; 288(4): 475–482, doi: 10.1001/jama.288.4.475, indexed in Pubmed: 12132978.

19. Fitzgerald JT, Funnell MM, Anderson RM, et al. The reliability and validity of a brief diabetes knowledge test. Diabetes Care. 1998; 21(5): 706–710, doi: 10.2337/diacare.21.5.706, indexed in Pubmed: 9589228.

20. University of Michigan Health System: Michigan Diabetes Research Center (MDRC); 2019. http://diabetesresearch.med.umich.edu/Tools_SurveyInstruments.php.

21. Mahjouri MY, Esfahani E, Larijani B. Evaluation of psychometric properties of the third version of the Iranian Diabetes Attitude Scale (IR-DAS-3). Iranian Journal of Diabetes and Lipid Disorders. 2011; 10(1): 1–6.

22. Montazeri A, Tavousi M, et al. Health Literacy for Iranian Adults (HELIA): development and psychometric Properties. Payesh. 2014; 13(5): 589–599.

23. Haghayegh AS, Ghasemi N, Neshatdoost HT, et al. Psychometric Properties Of Diabetes Management Self-Efficacy Scale (Dmses). IJEM. 2010; 12(2): 111–115.

24. Osborn CY, Cavanaugh K, Wallston KA, et al. Self-efficacy links health literacy and numeracy to glycemic control. J Health Commun. 2010; 15 Suppl 2: 146–158, doi: 10.1080/10810730.2010.499980, indexed in Pubmed: 20845200.

25. Masoompour M, Tirgari B, Ghazanfari Z. The Relationship between health literacy, self-efficacy, and self-care behaviors in diabetic patients. Evidence Based Care. 2017; 7(3): 17–25.

26. Pashaki MS, Eghbali T, Niksima SH, et al. Health literacy among Iranian patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab Syndr. 2019; 13(2): 1341–1345, doi: 10.1016/j.dsx.2019.02.020, indexed in Pubmed: 31336489.

27. Saeed H, Saleem Z, Naeem R, et al. Impact of health literacy on diabetes outcomes: a cross-sectional study from Lahore, Pakistan. Public Health. 2018; 156: 8–14, doi: 10.1016/j.puhe.2017.12.005, indexed in Pubmed: 29353668.

28. von Wagner C, Semmler C, Good A, et al. Health literacy and self-efficacy for participating in colorectal cancer screening: The role of information processing. Patient Educ Couns. 2009; 75(3): 352–357, doi: 10.1016/j.pec.2009.03.015, indexed in Pubmed: 19386461.

29. Bohanny W, Wu SFV, Liu CY, et al. Health literacy, self-efficacy, and self-care behaviors in patients with type 2 diabetes mellitus. J Am Assoc Nurse Pract. 2013; 25(9): 495–502, doi: 10.1111/1745-7599.12017, indexed in Pubmed: 24170654.

30. Santos FR, Bernardo V, Gabbay MAL, et al. The impact of knowledge about diabetes, resilience and depression on glycemic control: a cross-sectional study among adolescents and young adults with type 1 diabetes. Diabetol Metab Syndr. 2013; 5(1): 55, doi: 10.1186/1758-5996-5-55, indexed in Pubmed: 24289093.

31. Goodarzi M, Ebrahimzadeh I, Rabbi A, et al. Asghari jafarAbadi M. The relationship between knowledge, attitude and practice with self-efficacy in type 2 diabetic patients in Karaj. Iranian Journal of Diabetes and Lipid Disorders. 2012; 11(3): 269–81.

32. Reisi M, Mostafavi F, Javadzade SH, et al. Assessment of some predicting factors of self-efficacy in patients with type 2 diabetes. Iranian Journal of Endocrinology and Metabolism. 2015; 17(1): 44–52.

33. Abolghasemi R, Sedaghat M. The patient's attitude toward type 2 diabetes mellitus, a qualitative study. J Relig Health. 2015; 54(4): 1191–1205, doi: 10.1007/s10943-014-9848-9, indexed in Pubmed: 24599712.

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Pains and needs of patients with type 2 diabetes as targets for novel technologies

ABSTRACT

Background. As diabetes affects multiple spheres of life the aim of this study was to explore the pain points of diabetes management as perceived by persons with type 2 diabetes and to identify their expectations towards new technologies.

Methods. Patients with type 2 diabetes treated with oral hypoglycemic agents and/or insulin were surveyed. Respondents were asked to rate (i) the impact of diabetes on their daily life and (ii) their needs for improvements in different aspects of diabetes management on a five level Likert-type scale.

Results. One hundred and fifty-four persons with type 2 diabetes were included. Most frequently reported challenges were: fear of diabetes complications development or progression (98.7% of patients), presence of diabetes complications (65.6%), frequent hyperglycemia (53.2%), and diabetes limiting one's daily activities (50%). Most frequently expressed needs were: to evaluate glucose concentrations without finger pricking (98.1%), contact with a physician using mobile solutions and/or telemedicine (98.1%), and automation of insulin dosing (91.6%) and of calories/

/carbohydrates' evaluation in meals (84.4%). Needs for telemedicine development, automation of insulin dosing and that the others help patients with diabetes management were more frequently reported by persons with: higher HbA$_{1c}$, positive severe hypoglycemia history, concomitant chronic complications or diseases, and by those who were on insulin therapy.

Conclusions. Although many diabetes technologies which meet the needs of patients with type 2 diabetes are already available, the study uncovers a high requirement for integrating them into disease management. The challenge pertains to implementation of the right technological solutions fulfilling needs of particular groups of patients and to helping them to embrace novelties into their daily lives. (Clin Diabetol 2020; 9; 6: 400–410)

Key words: digital health, eHealth, patients, telemedicine, type 2 diabetes, artificial pancreas

Introduction

Diabetes affects more than 400 million people worldwide and significantly affects their and their families' quality of life, especially when accompanied by chronic complications [1, 2]. It is not clear whether and which diabetes-related inconveniences are perceived by patients as mostly affecting their daily life. Discrepancies have been identified between the fields that persons with diabetes and their relatives would prioritize and the scientific activities in diabetology [3, 4]. The importance of a participative approach involving patients in the design and implementation of health innovation is increasingly recognized [5].

Over the last years multiple digital i.e. electronic health (eHealth) technologies aimed at improvement of diabetes patients' quality of live and glycemic control have been developed [6]. Such solutions include: (i) mobile health (mHealth), e.g. text messaging, smartphone applications (e.g. "apps" helping to count calories/carbohydrates content in meals or replacing diabetes management log-books), and wearable technologies enabling glucose levels assessment without finger *pricking*, i.e. real-time continuous glucose monitoring (rtCGM) systems and intermittently scanned CGM (iCGM)), (ii) telemedicine technologies (e.g. enabling remote contact with care providers for a discussion of electronically submitted CGM profiles), (iii) new specialized devices — from insulin pens memorizing insulin doses to automated insulin delivery (artificial pancreas) systems closing the loop between CGM assessments and a continuous subcutaneous insulin infusion (CSII) [7–11].

Although most new technological solutions are initially used by persons with type 1 diabetes, they may add value also to a more personalized and cost-effective management of persons with type 2 diabetes [10]. For instance, HbA_{1c} levels decreased significantly in patients with type 2 diabetes who used rtCGM and were on insulin pump therapy, and feasibility and safety of using insulin pump therapy and a fully automated insulin delivery system was shown for persons with type 2 diabetes [12–14].

As patient's perception might add valuable input to the enhancement of existing and the development of new diabetes technologies, the objective of this study was to identify the pain points in diabetes management that are still experienced by persons with type 2 diabetes in the era of digital health implementation and to identify their expectations towards new technologies.

Methods

This was a cross-sectional, questionnaire-based study. The study was carried out in one hospital diabetes department and in one local diabetes outpatient clinic; data were collected between June 2017 and March 2018. Inclusion criteria were: age from 18 up to 90 years, type 2 diabetes duration 6 months or more, treatment with oral hypoglycemic agents and/or insulin injections. Patients with type 2 diabetes treated only with diet and lifestyle modification were excluded. Glycated hemoglobin (HbA_{1c}) levels, body mass and height were collected from patients' medical documentation. The included patients had previously received basic education (lasting up to 45–90 minutes) in diabetes management (i.e. about nutrition, self-monitoring of blood glucose, and for patients treated with insulin —

about insulin action and injection technique) provided by their physicians and/or nurses trained in diabetes care. None of patients used CGM or insulin pump.

The questionnaire developed for the purpose of this survey included questions grouped into following categories: A — demographic and medical care related data, B — impact of diabetes on daily life, and C — new technologies and "my diabetes", i.e. how new technological solutions could help participants in their diabetes management and in their everyday live. In part B respondents were asked to rate the importance of problems concerning diabetes on a five level Likert-type scale (1 — definitely not a problem, 2 — rather not a problem, 3 — moderate problem, 4 — big problem, 5 — huge problem). Answers were further grouped as indicating a nonsignificant (scores 1 and 2) or significant (scores 3, 4, 5) problem. In part C patients rated their need for improvements in diabetes management (including introduction of existing and emerging new technological solutions) on five level Likert-type scale (1 — no need, 2 — little need, 3 — moderate need, 4 — big need, 5 — huge need), and again answers were further grouped as indicating nonsignificant (scores 1 and 2) or significant (scores 3, 4, 5) need for improvement. The questionnaire is freely available online at the following link: https://dochub.com/anetagruchala /7J4mQvgRvJYmlQ0Rj2pO5n/questionnaire-assessing-pains-and-needs-of-persons-with-type-2-diabetes-online-pd?dt=yVfo6wPasAgDDHfLq95b. Participants answered the questions in the presence of one of the investigators (AG), as some of them needed assistance with reading or writing due to their disabilities.

The study protocol was approved by the ethics committee of the Medical University of Lodz, Poland (RNN/197/17/KE). Written informed consent was obtained from each participant, and filled questionnaires were fully anonymous.

Statistical analysis was performed with Statistica version 13.1 software. Chi-square and Fisher exact tests were used for the analysis of frequency of answers (ranging particular issues as a significant problem/ /need *vs.* a nonsignificant problem/need) stratified according to patients' clinical characteristics. In all cases, the results were considered statistically significant at $P < 0.05$. In the analyses of the impact of diabetes duration on patients' answers Pearson Chi-square test was used to compare the frequency of answers between patients with diabetes duration below or equal to the median diabetes duration for the total group (≤ 12 years) versus patients with diabetes duration above the median (> 12 years). Moreover, associations between diabetes duration and patients' answers to particular questions considered as continuous variables (answers

Table 1. Characteristics of the study group (n = 154, 69 men and 85 women)

Characteristics	Mean ± standard deviation or number (percentage)
Age (years)	65.6 ± 8.3
Diabetes duration (years)	14.4 ± 9.5
BMI [kg/m^2]	30.4 ± 3.7
HbA$_{1c}$ (%)	9.0 ± 1.7
HbA$_{1c}$ [mmol/mol]	75 ± 10.7
Diabetes medication	129 (83.8%) — insulin therapy with or without oral hypoglycemic agents
	25 (16.2%) — oral hypoglycaemic agents (without insulin)
Professional activity	50 (32.5%) — professionally active
	35 (22.7%) — disabled
	69 (44.8%) — retired
Presence of chronic diabetes complications	102 (66.2%)
Positive history of severe hypoglycemia	34 (22.1%)
Presence of at least one concomitant chronic disease	128 (83.1%)

from 1 to 5) were analyzed; associations with Spearman's rank correlation coefficient $\rho \geq 0.4$ at P < 0.05 were regarded clinically significant.

Results

One hundred and eighty-nine patients (18–90 years, type 2 diabetes) were offered the possibility to participate in the study. Nineteen patients refused to participate. Sixteen patients who primarily agreed were excluded due to non-conformity with the protocol (too short diabetes duration, not treated with insulin or oral hypoglycemic medications at the time of survey). One hundred and fifty-four patients with type 2 diabetes (85 women and 69 men; aged from 46 to 80 years, with diabetes duration from 1 to 39 years; 112 surveyed in a hospital, 42 surveyed in an outpatient clinic) were included into the final analysis. Characteristics of the study group are presented in Table 1.

Diabetes-related problems

Problems most frequently rated by participants as significant were: fear of development or progression of chronic diabetes complications (graded as significant by 98.7% of patients), presence of chronic diabetes complications (65.6%), frequent hyperglycemia (53.2%), diabetes as a factor limiting one's daily activities (50%) (Table 2).

In order to assess whether the clinical characteristics of patients determine types of problems reported by them, subgroups of participants were compared depending on HbA$_{1c}$ (below and above the median, i.e. 8.7%), history of severe hypoglycemia (no such episode *vs.* at least one severe hypoglycemia with loss of consciousness, seizure or coma), presence of chronic diabetes complications (no *vs.* yes), presence of one or more chronic concomitant diseases (no *vs.* yes), and treatment with insulin (no *vs.* yes) (Table 3). Limitation of daily activity related to diabetes was significantly higher in patients: with HbA$_{1c}$ above median (65.8% *vs.* 34.6%, P < 0.001), with a history of severe hypoglycemia (88.2% *vs.* 39.2%, P < 0.001), with chronic diabetes complications (65.7% *vs.* 19.2%, P < 0.001) and on insulin therapy (57.4% *vs.* 12.0%, P < 0.001). Fear of hypoglycemia and hypoglycemia occurrence were more frequently reported as a problem by persons with a history of severe hypoglycemia, by persons with chronic complications and by those treated with insulin. Patients with diabetes duration longer than median for the total group (over 12 years) claimed significantly more frequently (P < 0.05) compared to patients with shorter diabetes duration that the following issues posed a significant problem for them: diabetes limiting daily activities 74% *vs.* 34%, necessity to prick fingers 78% *vs.* 42%, frequent hypoglycemia episodes 78% *vs.* 46%, low blood glucose levels at night 79% *vs.* 47%, fear of hyperglycemia 77% *vs.* 42%, presence of chronic diabetes complications 73% *vs.* 17%, dependence on family members' help 76% *vs.* 34%, costs of diabetes complications therapy being a burden 74% *vs.* 15%. Moreover, there was a positive correlation (P < 0.05) between longer diabetes duration and fear of chronic diabetes complications ($\rho = 0.57$), diabetes limiting patient's daily activities ($\rho = 0.43$), dependence on family members' help ($\rho = 0.46$), and costs for diabetes complications therapy being perceived as a burden ($\rho = 0.43$).

Diabetes-related needs

Almost a half of the participants (46.8%) indicated that they were dependent on help of a family member

Table 2. Percentage of participants who rated potential problems related to their diabetes and its management as non--significant and significant. Respondents rated the importance of problems on a five level Likert-type scale: 1 — definitely not a problem, 2 — rather not a problem, 3 — moderate problem, 4 — big problem, 5 — huge problem, and answers were further grouped as indicating a nonsignificant (scores 1 and 2) or significant (scores 3, 4, 5) problem. Problems rated as significant by the highest percentage of participants are listed first

Problem related to diabetes and its management	Participants who rated a problem as significant (%)	Participants who rated a problem as non-significant (%)	Total number of answers
Fear of chronic complications of diabetes — problems with eyes, kidney, heart, atherosclerosis, diabetic foot, amputation etc.	98.7	1.3	154
Presence of chronic diabetes complications — problems with eyes, kidney, heart, atherosclerosis, diabetic foot, amputation etc.	65.6	34.4	154
High blood glucose levels (often occurring)	53.2	46.8	154
Limitation of daily activity caused by diabetes	50.0	50.0	154
Necessity to check blood glucose level with blood glucose meter — pricking fingers	39.0	61.0	154
Fear of hypoglycemia	34.4	65.6	154
Lack of freedom concerning meals	31.2	68.8	154
Low blood glucose levels (often occurring)	26.0	74.0	154
Estimation of calories or carbohydrates in meals	23.4	76.6	154
Insufficient knowledge about diabetes	23.4	76.6	154
Low blood glucose levels at night	22.1	77.9	154
Feeling uncomfortable or ashamed while performing activities related to diabetes management (checking blood glucose levels, injecting insulin) in presence of other people	20.1	79.9	154
Lack of freedom in physical activities	16.9	83.1	154
Necessity to check blood glucose level with blood glucose meter — remembering to do it	14.3	85.7	154
Necessity to inject insulin — counting insulin doses	5.4	94.6	129
Necessity to inject insulin — technique of the injection (pushing the plunger etc.)	3.1	96.9	129
Necessity to check blood glucose level with blood glucose meter — recording results in a log-book	2.6	97.4	154
Necessity to inject insulin — setting the insulin dose on the pen injector	2.3	97.7	129
Necessity to take oral diabetes medication	1.8	98.2	113
Necessity to inject insulin — pain during injection	0.8	99.2	129
Necessity to check blood glucose level with blood glucose meter — operating blood glucose meter	0.7	99.3	154

in their diabetes management. More than one quarter (28.6%) would like to have a nurse/non-family caregiver support in diabetes management at home.

Detailed results of patients' perception of needs for improvement in diabetes management expressed as percentages of answers indicating significant need and non-significant need are presented in Table 4. The most frequently reported significant needs were: to evaluate glucose concentrations without finger pricking (98% of patients) and to have contact with a physician using mobile solutions and/or telemedicine to share data including doses of insulin, blood glucose levels,

Table 3. Percentage of participants who reported particular problems related to their diabetes and its management. Participants were stratified according to their glycated hemoglobin levels (HbA$_{1c}$ below or over the median; median HbA$_{1c}$ 8.7%), their history of severe hypoglycemia, the presence of chronic diabetes complications, the presence of concomitant disease/s, and the treatment with insulin. Significance of the differences between subgroups was analyzed using the Chi-squared and Fisher exact test; P value < 0.05 was considered statistically significant (emphasized with the bold font)

Potential problem	HbA$_{1c}$			History of severe hypoglycemia			Chronic diabetes complications			Concomitant chronic disease			Insulin therapy		
	≤ 8.7%	> 8.7%	P	No	Yes	P	No	Yes	P	No	Yes	P	No	Yes	P
Fear of chronic complications of diabetes — problems with eyes, kidney, heart, atherosclerosis, diabetic foot, amputation etc.	100.0	97.4	0.242	99.2	97.1	0.394	96.2	100.0	0.113	96.2	99.2	0.310	100.0	98.5	1.0
High blood glucose levels (often occurring)	38.5	68.4	**< 0.001**	50.8	61.8	0.351	34.6	61.8	**0.005**	34.6	57.0	0.061	44.0	55.0	0.428
Limitation of daily activity caused by diabetes	34.6	65.8	**< 0.001**	39.2	88.2	**< 0.001**	30.8	65.7	**< 0.001**	30.8	54.0	0.053	12.0	57.4	**< 0.001**
Necessity to check blood glucose level with blood glucose meter — pricking fingers	30.8	47.4	**0.035**	40.0	35.3	0.766	15.4	47.1	**0.007**	15.4	43.8	**0.008**	24.0	41.9	0.147
Fear of hypoglycemia	29.5	39.5	0.192	19.2	88.2	**< 0.001**	30.8	43.1	**0.003**	30.8	35.2	0.839	0	41.1	**< 0.001**
Lack of freedom concerning meals	30.8	31.6	0.914	29.2	38.2	0.425	15.4	35.3	0.173	15.4	34.4	0.065	0	37.2	**< 0.001**
Low blood glucose levels (often occurring)	25.6	26.3	0.924	13.3	70.6	**< 0.001**	23.1	34.3	**0.002**	23.1	26.7	0.901	0	31.0	**< 0.001**
Estimation of calories or carbohydrates in meals	23.1	23.7	0.919	25.0	17.7	0.506	23.1	24.5	0.792	23.1	23.4	0.830	32.0	21.7	0.393
Insufficient knowledge about diabetes	16.7	30.3	0.071	20.8	32.4	0.241	23.1	23.5	0.890	23.1	23.4	0.830	20.0	24.0	0.859
Low blood glucose levels at night	20.5	23.7	0.779	11.7	58.8	**< 0.001**	19.2	29.4	**0.002**	19.2	22.7	0.901	0	26.4	**0.001**
Feeling uncomfortable or ashamed while performing activities related to diabetes management (checking blood glucose levels, injecting insulin) in presence of other people	16.7	25.0	0.282	19.2	26.5	0.492	15.4	19.6	0.770	15.4	21.9	0.600	0	24.8	**0.002**
Lack of freedom in physical activities	18.0	15.8	0.887	16.7	17.7	0.900	19.2	15.7	0.743	19.2	16.4	0.775	0	20.2	**0.008**
Necessity to check blood glucose level with blood glucose meter — remembering to do it	15.4	13.2	0.819	15.0	11.8	0.785	7.7	17.7	0.143	7.7	15.6	0.373	16.0	14.0	0.759
Necessity to inject insulin — counting insulin doses	3.9	5.3	0.717	3.3	8.8	0.181	11.5	3.9	0.690	11.5	3.1	0.094	0	5.4	NA
Necessity to inject insulin — technique of the injection (pushing the plunger etc.)	3.9	1.3	0.620	1.7	5.9	0.212	3.9	2.0	0.600	3.9	2.3	0.527	0	3.1	NA
Necessity to check blood glucose level with blood glucose meter — recording results in a log-book	1.3	4.0	0.364	2.5	2.9	1.000	0	3.9	0.300	0	3.1	1.000	4.0	2.3	0.511
Necessity to inject insulin — setting the insulin dose on the pen injector	2.6	1.3	1.000	0	8.8	**0.010**	7.7	0	**0.037**	7.7	0.8	0.074	0	2.3	NA
Necessity to take oral diabetes medication	1.3	1.3	1.000	0.8	2.9	0.394	0	2.0	0.550	0	1.6	1.000	4.0	0.8	0.299
Necessity to inject insulin — pain during injection	0	1.3	0.494	0.8	0	1.000	3.9	1.0	1.000	3.9	0	0.169	0	0.8	NA
Necessity to check blood glucose level with blood glucose meter operating blood glucose meter	0	1.3	0.494	0	2.9	0.221	0	0	0.338	0	0.8	1.000	0	0.8	1.000

NA — not applicable

Table 4. Percentage of participants who rated needs for improvement related to diabetes and its management as non-significant and significant. Respondents rated the importance of their needs on a five level Likert-type scale: 1 — no need, 2 — little need, 3 — moderate need, 4 — big need, 5 — huge need, and answers were further grouped as indicating nonsignificant (scores 1 and 2) or significant (scores 3, 4, 5) need for improvement. Needs rated as significant by the highest percentage of participants are listed first

Needs for improvement related to diabetes and its management	Participants who rated a need as significant (%)	Participants who rated a need as non-significant (%)	Total number of answers
Glucose levels assessment without finger pricking	98.0	2.0	154
Telemedicine development to share data including doses of insulin, blood glucose levels, meals etc. with a physician (possibility to communicate via mobile phone, computer, internet etc.)	98.0	2.0	154
Creating/improving a device, which automatically adjusts insulin doses based on glucose levels (an "artificial pancreas")	91.6	8.4	154
Counting calories/carbohydrates in a meal	84.4	15.6	154
Shortening time of blood glucose measurement with a blood glucose meter	83.8	16.2	154
Memory of insulin doses in an insulin pen	83.0	17.0	129
Reminding about necessity of injecting insulin	81.4	18.6	129
Reducing pain related to pricking fingers for measurement of blood glucose level	80.5	19.5	154
Mobile phone apps automatically sending glucose level data to family members	63.0	37.0	154
Telemedicine development to share data including doses of insulin, blood glucose levels, meals etc. with family members (possibility to communicate via mobile phone, computer, internet etc.)	62.3	37.7	154
Relatives' help in diabetes management	46.8	53.3	154
Nurse/non-family caregiver support in diabetes management at home	28.6	71.4	154

etc. (98%). Patients would like to have a possibility to contact a diabetologist between medical appointments via: phone calls (97.8% of patients), text messages (52.6%), emails (35%), or other means of electronic communication (35.8%). Need for development of an "artificial pancreas" ("a device, which automatically provides adjusted doses of insulin based on glucose levels") was reported by 91.6%, and need for counting the calories/carbohydrates amount in meals in an easy way by 84.4% of participants. Other needs claimed as significant by more than 50% of participants were: shorter time of blood glucose measurement with blood glucose meter, memory of insulin doses in insulin pens, reminding about necessity of injecting insulin, reducing pain related to pricking fingers for measurement of blood glucose levels, mobile phone apps automatically sending glucose level data to family members, telemedicine development to share data related to

diabetes management with family members (possibility to communicate via mobile phone, computer, internet).

Needs for telemedicine development (to improve communication with family members to share diabetes therapy-related information with them), "artificial pancreas" development, relatives' help in diabetes management and for a nurse/non-family caregiver support in diabetes management at home (participants generally did not have such support at the time of the study) were more frequently reported by patients with HbA_{1c} above median (compared to these with HbA_{1c} below median), positive history of severe hypoglycemia (compared to these without severe hypoglycemia history), chronic diabetes complications, or concomitant chronic diseases (compared to these without comorbidities), and by those who were on insulin therapy (compared to participants treated only with oral hypoglycemic agents) (Table 5). There was

Table 5. Percentage of participants who rated particular needs for improvement related to diabetes and its management as significant, according to glycated hemoglobin level (HbA₁c below or over the median; median HbA₁c 8.7%), history of severe hypoglycemia, presence of chronic diabetes complications, presence of concomitant disease/s, and treatment with insulin. Significance of the differences between subgroups was analyzed using the χ^2 and Fisher exact test; P value < 0.05 was considered statistically significant (emphasized with the bold font)

Need for improvement related to diabetes and its management	HbA₁c			History of severe hypoglycemia			Chronic diabetes complications			Concomitant chronic disease			Insulin therapy		
	≤ 8.7%	> 8.7%	P	No	Yes	P	No	Yes	P	No	Yes	P	No	Yes	P
Glucose levels assessment without finger pricking	97.4	98.7	1.000	98.3	97.1	0.530	98.1	98.0	1.000	96.2	98.4	0.428	100.0	97.7	1.000
Telemedicine development to share data including doses of insulin, blood glucose levels, meals etc. with a physician (possibility to communicate via mobile phone, computer, internet etc.)	98.7	97.4	0.618	98.3	97.1	0.530	98.1	98.0	1.000	88.5	100.0	**0.004**	100.0	97.7	1.000
Creating/improving a device, which automatically adjusts insulin doses based on glucose levels (an "artificial pancreas")	69.2	96.1	**< 0.001**	78.3	97.1	**0.010**	51.9	98.0	**< 0.001**	80.8	93.8	0.074	28.0	93.0	**< 0.001**
Counting calories/carbohydrates in a meal	87.2	81.6	0.462	83.3	88.2	0.599	86.5	83.3	0.777	69.2	87.5	**0.041**	92.0	83.0	0.370
Shortening time of blood glucose measurement with a blood glucose meter	83.3	84.2	0.943	83.3	85.3	0.992	76.9	87.3	0.158	69.2	86.7	0.056	72.0	86.1	0.148
Memory of insulin doses in an insulin pen	83.9	80.9	0.829	81.3	85.3	0.788	82.9	82.1	0.873	61.9	86.2	**0.018**	0	82.2	NA
Reminding about necessity of injecting insulin	82.3	79.4	0.850	81.3	79.4	0.984	77.1	82.1	0.700	61.9	84.4	**0.036**	0	80.6	NA
Reducing pain related to pricking fingers for measurement of blood glucose level	77.0	84.2	0.348	80.0	82.4	0.952	82.7	79.4	0.786	73.1	82.0	0.436	80.0	80.6	0.838
Mobile phone apps automatically sending glucose level data to family members	60.3	65.8	0.477	55.8	88.2	**< 0.001**	50.0	69.6	**0.017**	34.6	68.8	**0.002**	36.0	68.2	**0.005**
Telemedicine development to share data including doses of insulin, blood glucose levels, meals etc. with family members (possibility to communicate via mobile phone, computer, internet etc.)	59.0	65.8	0.383	55.8	85.3	**0.003**	50.0	68.6	**0.024**	30.8	68.8	**< 0.001**	36.0	67.4	**0.006**
Relatives' help in diabetes management	43.1	56.9	0.077	6.1	40.3	**< 0.001**	11.5	64.7	**< 0.001**	19.2	52.3	**0.002**	12.0	53.5	**< 0.001**
Nurse/non-family caregiver support in diabetes management at home	20.5	36.8	**0.025**	23.3	47.1	**0.007**	5.8	40.2	**0.001**	3.9	33.6	**0.010**	16.0	31.0	0.152

NA — not applicable

a positive correlation between longer diabetes duration and perceiving technological development in diabetes management as more significant ($\rho = 0.50$). However, the correlations with diabetes duration were negative for patients' need for enabling them a contact with the diabetologist between medical appointments ($\rho = -0.55$ for e-mail contact, $\rho = -0.47$ for text messages and $\rho = -0.56$ for contact via other electronic media). Moreover patients with diabetes duration longer than median for the total group (over 12 years) reported significantly more frequently (P < 0.05) compared to patients with shorter diabetes duration a significant need for development in telemedicine (67% *vs.* 33%), mobile apps use (66% *vs.* 33%) and development of an "artificial pancreas" (61% *vs.* 22%), while similarly wishing more frequently for a nurse support at home (77% *vs.* 45%).

In the total group advancements in diabetes technologies which help patients with type 2 diabetes and their families in daily management of the disease were perceived by 0.6% of participants as huge, by 5.8% as big, by 47.4% as moderate, by 29.9% as small, and 16.3% of responders did not notice any development in this field.

Discussion

This study was focused on diabetes and diabetes management-related issues which were challenging for persons with type 2 diabetes and could be targeted by existing and emerging technological solutions. Studies describing these aspects are sparse, some included small groups of patients, and in others study groups were heterogeneous, without well-defined diabetes therapy used by participants. Our study included a relatively large and homogeneous group of patients with type 2 diabetes who used either oral hypoglycemic medication and/or insulin.

We found that 50% of participants reported diabetes-related limitations in daily activity (Table 2). Results of Rekeneire's et al. cross-sectional analysis of 3075 well-functioning older individuals from the USA, aged 70–79, comparing limitations in everyday activity between participants with and without diabetes were consistent with our study, since they observed such limitations in 53% of patients with diabetes [15]. Moreover, they have shown that suboptimal glycemic control (higher HbA_{1c}) and longer diabetes duration played an important role in the disablement process. This is also *in agreement* with our results as we have found that frequency of limitations was higher in patients with higher HbA_{1c} (65.8% in a subgroup with $HbA_{1c} \geq 8.7\%$ *vs.* 34.6% in a subgroup with $HbA_{1c} < 8.7\%$, i.e. below median, P < 0.001). The presented

study group was age-diverse, while de Rekeneire et al. [15] included only elderly population. Moreover, in our study most patients had chronic complications (66.2%) or other comorbidities (83%) and all were treated with oral hypoglycemic agents and/or insulin, while in their group only 64.4% of participants used any hypoglycemic medication. The percentage of daily limitation occurrence was similar even though our study population was younger (65.6 ± 8.3 years *vs.* 73.6 ± 2.9 years). Such results suggest that the need for a more intensive diabetes therapy goes along with comorbidities and with a higher risk of daily activity limitation. In the Medical Outcomes Study Short Form 36 — Item Health Survey (SF36) that included 694 patients with type 2 diabetes from two clinics in Iran, limitation of daily activity was observed in 67.5% of participants but, unlike in our survey, the authors did not establish whether disability was related to diabetes and the type of its therapy [16]. Adding to previous reports our data demonstrated that for multiple aspects there exists a dependency between diabetes duration and the perception of problems experienced by the patients. Overall, patients with longer diabetes duration state that they deal with more problems, the most evident being fear of chronic diabetes complications, diabetes limiting patient's daily activities and dependence on family members' help.

Papaspurou et al. [17] described fears and needs of persons with type 2 diabetes in a qualitative study, using interpretative phenomenological approach. Fears for chronic diabetes complications claimed by participants of their study overlapped fears declared by vast majority of our study group (98.7%). Moreover, they indicated fears for familial predisposition to the disease, deprivation and stigmatization which were not considered in our research. Needs of patients with diabetes reported in that study were partly similar to our results, in particular need for easier communication with medical teams. Grammes et al. [18] studied 64 adults with type 2 diabetes on insulin therapy with a questionnaire identifying potential reasons of patient fear and they found that 46.9% of participants dealt with fear of hypoglycemia, and this percentage was even higher than in our group (34.4%).

Patients' needs concerning new technologies identified in the present survey focused primarily on improvement of glucose concentration measurements (without finger pricking), easier or more frequent communication with a physician (in Poland it is usually a doctor who coordinates diabetes care however this need represents the willingness to contact either the doctor or other specialist from the diabetes care team, e.g. a nurse), support in insulin therapy (automation

of insulin dosing, reminding about insulin injections, memorizing insulin doses) and food counting. Studies assessing needs or expectations of patients with type 2 diabetes towards new technologies as well as randomized clinical trials evaluating mHealth interventions have focused mostly on telemedicine solutions that used short-text-messages, telephone calls and mobile apps supporting self-monitoring of blood glucose or on software supporting CGM (e.g. FGM) systems use [19–21]. Watterson et al. [19] proved that many type 2 diabetes patients admitted that a specialized text-messaging program supported them in their daily live with diabetes: 78% of respondents answered that they learned useful information from text messages, and text messages helped 89% of them to better manage diabetes [19]. These results are in accordance with ours, as 52.6% of our respondents wanted to have a possibility to contact a diabetologist between medical appointments via text messages.

In our analysis the study group was well defined (age, sex, BMI, diabetes duration, type of diabetes therapy, presence of chronic complications of diabetes, history of severe hypoglycemia, presence of concomitant chronic diseases). The majority of participants had chronic diabetes complications or concomitant chronic diseases, almost one in four had a history of severe hypoglycemia. The reported needs for development and introduction of new technologies targeting different aspects of diabetes management was high since 95% of the total study group indicated the need to check glucose levels without pricking fingers and for sharing diabetes therapy-related data with the therapeutic team (Table 4). Possibly the considerable health burden, which implies limitations in daily activity, contributed to a strong demand for improvement as patients with HbA$_{1c}$ above median, positive severe hypoglycemia history, presence of chronic diabetes complications, presence of a concomitant chronic disease and patients on insulin therapy, reported needs for telemedicine development (improvement of diabetes management related communication with family members) and for "artificial pancreas" development more frequently than patients without these health problems (Table 5). Our observation is however discordant with the results of a study that included patients from T1DM Exchange registry, as patients with type 1 diabetes with the most positive attitudes toward diabetes technology (frequent pump and CGM use) had the lowest HbA$_{1c}$ compared to persons with very low new device uptake [22]. This may imply that disease trajectories of patients with type 2 diabetes who are willing to use new technologies are different from those of patients with type 1 diabetes who embrace new diabetes devices. Our data demon-

strate that for multiple aspects there exists a dependency between diabetes duration and the perception of problems experienced by the patients. Overall patients with longer diabets duration state that they deal with more problems. Moreover, in our study patients with longer diabetes duration seemed to be less interested in telemedicine contact with the diabetes team, albeit, at the same time they more frequently claimed to perceive technological developments. Furthermore, it is worth emphasizing that with longer disease duration there is a higher need for family members or nurse help, while costs become a more significant burden.

Homogeneity of our sample may be viewed as a limitation of the study, as criterion of including only patients who required hypoglycemic medication (insulin or oral hypoglycemic agents) skew the study group characteristics to higher morbidity, not representative for the general population of persons with type 2 diabetes. Another limitation is that the questionnaire was piloted only in a few patients. However this allowed the decision to be made that in case of the surveyed group an investigator filled in the questionnaire during an interview with participants, and thanks to this the survey was easier to carry out among patients and it was more reliable. Additionally, to minimize the pollster bias, the same investigator interviewed all patients.

A favorable lesson learned from our survey is that certain needs expressed by persons with type 2 diabetes can be addressed, as many technological solutions claimed by them already exist (e.g. CGM systems, insulin pens memorizing insulin doses, artificial pancreas systems and tele-diabetological care tools) [23]. Surprisingly almost half (46%) of participants perceived the recent advancement in diabetes technology as only small or none. Such observation reveals the need to unfold the high potential of digital technologies by adapting them to expectations of persons with type 2 diabetes in the context of value-based diabetes management regimens. This requires elaboration of reasonable reimbursement strategies which can be facilitated by open collaboration within the framework of public-private partnerships such as the European Institute of Innovation and Technology (EIT) Health (www.eithealth.eu), the JDRF, and the KOMIT (https://komit-nrw.de/) or other national institutions which secure an early involvement of all relevant stakeholder groups, including patients, healthcare system and payers.

Conclusions

Diabetes technologies that meet many of the needs of patients with type 2 diabetes already exist and many others will be probably available in the foreseeable future. This study demonstrated that needs of subgroups

of patients with comorbidities or other concomitant health burdens are in several aspects different than needs of patients with less health burdens and this heterogeneity must be taken into consideration in ongoing research on new diabetes technologies. Such strategy should enhance acceptance of existing and new solutions in daily diabetes management by people with comorbidities. Overall, implementation of several existing solutions that diabetes patients claim for, might be challenging owing to economic or organizational factors (e.g. use of CGM systems by patients who don't have reimbursement for them), but others, relatively low-cost approaches can be easily promoted. For instance, the majority of population, also elderly, own smartphones or even computers, however, many are probably either not aware of the existence of medical applications supporting diabetes management (e.g. facilitating calories counting, meal planning, sharing glucose data with health personnel) or they do not know how to take advantage of them. Taking into account needs and expectations of people with type 2 diabetes identified in this study we conclude that encouraging healthcare professionals to promote innovations should be coupled with easing patients' access to modern devices through wider reimbursement or insurers co-payment for them (e.g. for CGM systems). Based on the gathered information, we conclude that the challenge pertains to both, the implementation of the right technological solutions fulfilling needs of particular groups of patients, and to helping them to embrace novelties into their daily lives.

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Conflict of interest

The authors have no conflict of interest to disclose.

REFERENCES

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017; 128: 40–50, doi: 10.1016/j.diabres.2017.03.024, indexed in Pubmed: 28437734.

2. Rubin R, Peyrot M. Quality of life and diabetes. Diabetes/Metabolism Research and Reviews. 1999; 15(3): 205–218, doi: 10.1002/(sici)1520-7560(199905/06)15:3<205::aid-dmrr29>3.0.co;2-o.

3. Arnolds S, Heckermann S, Koch C, et al. How do patients' preferences compare to the present spectrum of diabetes research? Exp Clin Endocrinol Diabetes. 2013; 121(1): 60–63, doi: 10.1055/s-0032-1323776, indexed in Pubmed: 22972031.

4. Arnolds S, Heckermann S, Heise T, et al. Spectrum of diabetes research does not reflect patients' scientific preferences: a longitudinal evaluation of diabetes research areas 2010–2013 vs. a cross-sectional survey in patients with diabetes. Exp Clin Endocrinol Diabetes. 2015; 123(5): 299–302, doi: 10.1055/s-0034-1398591, indexed in Pubmed: 25658664.

5. Barber S, French C, Matthews R, et al. The role of patients and carers in diffusing a health-care innovation: A case study of "My Medication Passport". Health Expect. 2019; 22(4): 676–687, doi: 10.1111/hex.12893, indexed in Pubmed: 31131523.

6. Bailey TS, Walsh J, Stone JY. Emerging technologies for diabetes care. Diabetes Technol Ther. 2018; 20(S2): S278–S284, doi: 10.1089/dia.2018.0115, indexed in Pubmed: 29916738.

7. Gonder-Frederick LA, Shepard JA, Grabman JH, et al. Psychology, technology, and diabetes management. Am Psychol. 2016; 71(7): 577–589, doi: 10.1037/a0040383, indexed in Pubmed: 27690486.

8. Fatehi F, Menon A, Bird D. Diabetes care in the digital era: a synoptic overview. Curr Diab Rep. 2018; 18(7): 38, doi: 10.1007/s11892-018-1013-5, indexed in Pubmed: 29748905.

9. Cefalu WT, Tamborlane WV. The artificial pancreas: are we there yet? Diabetes Care. 2014; 37(5): 1182–1183, doi: 10.2337/dc14-0491, indexed in Pubmed: 24757224.

10. Schliess F, Heise T, Benesch C, et al. Artificial pancreas systems for people with type 2 diabetes: conception and design of the European CLOSE Project. J Diabetes Sci Technol. 2019; 13(2): 261–267, doi: 10.1177/1932296818803588, indexed in Pubmed: 30241444.

11. Benhamou PY, Franc S, Reznik Y, et al. Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial. The Lancet Digital Health. 2019; 1(1): e17–e25, doi: 10.1016/s2589-7500(19)30003-2.

12. Park C, Le QA. The Effectiveness of continuous glucose monitoring in patients with type 2 diabetes: a systematic review of literature and meta-analysis. Diabetes Technol Ther. 2018; 20(9): 613–621, doi: 10.1089/dia.2018.0177, indexed in Pubmed: 30095980.

13. Bally L, Thabit H, Hartnell S, et al. Closed-loop insulin delivery for glycemic control in noncritical care. N Engl J Med. 2018; 379(6): 547–556, doi: 10.1056/NEJMoa1805233, indexed in Pubmed: 29940126.

14. Reznik Y, Cohen O, Aronson R, et al. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. The Lancet. 2014; 384(9950): 1265–1272, doi: 10.1016/s0140-6736(14)61037-0.

15. De Rekeneire N, Resnick HE, Schwartz AV, et al. Health, Aging, and Body Composition study. Diabetes is associated with subclinical functional limitation in nondisabled older individuals: the Health, Aging, and Body Composition study. Diabetes Care. 2003; 26(12): 3257–3263, doi: 10.2337/diacare.26.12.3257, indexed in Pubmed: 14633811.

16. Faraji Gavgani L, Sarbakhsh P, Asghari Jafarabadi M, et al. Identifying factors associated with functional limitation among diabetic patients in Northwest of Iran: application of the generalized additive model. Int J Endocrinol Metab. 2018; 16(2): e12757, doi: 10.5812/ijem.12757, indexed in Pubmed: 30008756.

17. Papaspurou M, Laschou VC, Partsiopoulou P, et al. Fears and health needs of patients with diabetes: a qualitative research in rural population. Med Arch. 2015; 69(3): 190–195, doi: 10.5455/medarh.2015.69.190-195, indexed in Pubmed: 26261390.

18. Grammes J, Stock W, Mann CG, et al. Focus group study to identify the central facets of fear of hypoglycaemia in people with Type 2 diabetes mellitus. Diabet Med. 2017; 34(12): 1765–1772, doi: 10.1111/dme.13506, indexed in Pubmed: 28856721.

19. Watterson JL, Rodriguez HP, Shortell SM, et al. Improved diabetes care management through a text-message intervention for low-income patients: mixed-methods pilot study. JMIR Diabetes. 2018; 3(4): e15, doi: 10.2196/diabetes.8645, indexed in Pubmed: 30377141.

20. Dobson R, Whittaker R, Jiang Y, et al. Effectiveness of text message based, diabetes self management support programme (SMS4BG): two arm, parallel randomised controlled trial. BMJ. 2018; 361: k1959, doi: 10.1136/bmj.k1959, indexed in Pubmed: 29773539.

21. Shan R, Sarkar S, Martin SS. Digital health technology and mobile devices for the management of diabetes mellitus: state of the art. Diabetologia. 2019; 62(6): 877–887, doi: 10.1007/s00125-019-4864-7, indexed in Pubmed: 30963188.

22. Tanenbaum ML, Adams RN, Iturralde E, et al. From wary wearers to d-embracers: personas of readiness to use diabetes devices. J Diabetes Sci Technol. 2018; 12(6): 1101–1107, doi: 10.1177/1932296818793756, indexed in Pubmed: 30132692.

23. Kempf K, Altpeter B, Berger J, et al. Efficacy of the Telemedical lifestyle intervention Program TeLiPro in advanced stages of type 2 diabetes: a randomized controlled trial. Diabetes Care. 2017; 40(7): 863–871, doi: 10.2337/dc17-0303, indexed in Pubmed: 28500214.

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Gestational diabetes diagnosed in third trimester of pregnancy: an observation at a Hospital of Women and Children in Vietnam

ABSTRACT

Background. Gestational diabetes mellitus (GDM) remains a significant concern within the medical community due to its high risk, as well as its serious side effects on both the mothers and the fetuses. This study aims to assess the prevalence and the risk factors of gestational diabetes mellitus in pregnant women at Da Nang Hospital for Women and Children.
Methods. A cross-sectional study was conducted on 706 pregnant women at 2428 weeks of gestation at Da Nang hospital to determine the prevalence of gestational diabetes. Multivariate regression analysis was used to clarify the independent risk factors associated with gestational diabetes. All participants were interviewed and tested for the oral glucose tolerance test (OGTT) to identify the number of gestational diabetes, which was diagnosed according to the American Diabetes Association (ADA) diagnostic criteria in 2014. Results. Gestational diabetes prevalence was 10.2%; categorized by the number of matched diagnostic criteria: 1 criterion: 7.1%; 2 criteria: 2.1%; 3 criteria: 1.0%. There are four independent risk factors for gestational diabetes determined through multivariate regression analysis: maternal age > 30 years (OR = 2.376), a history of gestational diabetes (OR = 12.211), pre-pregnancy BMI $\geq$ 23 kg/m^2 (OR = 10.775), a history of fetal macrosomia > 3800 g (OR = 4.655). The risk of gestational diabetes in the group with risk factors was 6.21 times higher than that in the group with no risk factors. **Conclusion. More attention should be paid to the risk factors for gestational diabetes, such as maternal age > 30 years, a history of gestational diabetes, pre-pregnancy BMI $\geq$ 23 kg/m^2, a history of fetal macrosomia > 3800 g in all pregnant women. (Clin Diabetol 2020; 9; 6: 411–415)**

Key words: gestational diabetes mellitus, risk factors, prevalence

Introduction

Gestational diabetes or gestational diabetes mellitus (GDM) is a condition in which diabetes is diagnosed during pregnancy that is not clearly overt diabetes. Gestational diabetes mainly occurs during the 24th–28th week of pregnancy, when a fetus produces a great number of hormones that prevent insulin receptors from functioning properly and disturbs the blood sugar levels.

Generally, gestational diabetes manifests few symptoms, and it is most commonly diagnosed by screening during pregnancy. Diagnostic tests detect inappropriately high levels of glucose in blood samples. Gestational diabetes accounts for 9.6 to 13 percent of all pregnancies [1].

The risk of perinatal mortality does not increase while the risk of fetal macrosomia does. Other perinatal risks include shoulder dystocia, birth injuries such as

bone fractures and nerve palsies, and hypoglycemia. Long-term adverse health outcomes which are reported among infants born by mothers with gestational diabetes include sustained impairment of glucose tolerance, subsequent obesity (although not when adjusted for size), and impaired intellectual achievement. For women, gestational diabetes is a strong risk factor for diabetes. GDM carries risks for both the mother and her neonates. The risks associated with gestational diabetes are well recognized, and there is a certain treatment to lower maternal glucose levels in order to reduce these risks [2].

Along with the growth of diabetes, comes the continuing spread rate of gestational diabetes mellitus (GDM). At the moment, GDM remains a significant concern within the medical community due to its high risk, as well as its side effects on both the mothers and the fetuses. It is also the reason why the American Diabetes Association (ADA) in 2014 has issued the diagnostic criteria to manage and prevent GDM's complications [3]. We designed this study to assess the prevalence and risk factors of gestational diabetes mellitus in pregnant women at Da Nang Hospital for Women and Children.

Methods
Study population

From January 2018 to March 2019, consecutive women who had either a singleton or twin pregnancy with gestation between 24 and 28 weeks (third trimester) at Da Nang Hospital for Women and Children were enrolled in this study. They visited the Obstetric Department for a regular examination. Women with previously treated gestational diabetes or active chronic systemic disease (except essential hypertension) were excluded.

The present study was approved by the ethics committee of Hue University of Medicine and Pharmacy, Vietnam. All participants were provided written informed consent. Subjects were provided with written information about the study and were briefed orally again before their oral glucose tolerance test. People whose glucose levels exceeded cut-off values for eligibility were diagnosed with gestational diabetes.

Oral glucose tolerance test

A 75-g oral glucose tolerance test (OGTT) was performed in women at 24–28 weeks of gestation who were not previously diagnosed with overt diabetes. Plasma glucose was measured when the patient is fasting and at 1 and 2 hours after the test. The OGTT was performed in the morning after an overnight fast of at least eight hours. The diagnosis of GDM is made when one or more following plasma glucose value are

met or exceeded, according ADA 2014 guidelines: 1) Fasting: $\geq$ 92 mg/dL (5.1 mmol/L); 2) first hour: $\geq$ 180 mg/dL (10.0 mmol/L); 3) second hour: $\geq$ 153 mg/dL (8.5 mmol/L) [3].

All participants were advised to follow a 48 hours normal diet before the oral glucose tolerance test and to fast for 8 hours the night before the test. Blood samples were obtained after the overnight fast and one and two hours after the receipt of the 75-g oral glucose load.

Outcome variables

Clinical outcomes among the women included: maternal age, gestational age at birth, birth weight, and body mass index (BMI).

We explored some of the risk factors such as GDM medical history; maternal age; a family medical history of type 1 diabetes; pre-pregnancy BMI; a history of fetal macrosomia and pathological obstetrics (e.g. stillbirth, miscarriage); polycystic ovary syndrome.

Statistical analysis

Statistical analyses were based on the SPSS software, version 16.0. Continuous variables were analyzed by means if they were normally distributed and by medians of nonparametric tests if their distribution was abnormal. A P value of 0.05 was considered to indicate statistical significance.

Results

From January 2018 to March 2019, oral glucose tolerance test (OGTT) was performed in 706 pregnant women at Da Nang Hospital for Children and Women. According to ADA 2014 diagnostic criteria, in this study, GDM accounted for 72 (10.2%). Among pregnancies affected by GDM, according to ADA 2017, the group with $\geq$ 1 criterion accounted for 7.1% (the highest percentage).

In bivariate analysis, factors correlated with GDM were maternal age $\geq$ 30 years (OR 1.8, 95%CI 1.1–2.9, P = 0.02); BMI $\geq$ 23 kg/m^2 (OR 10.8, 95% CI 6.3–18.4, P < 0.001) and a history of fetal macrosomia > 3800 g (OR 5.2, 95% CI 2.7–10.2, P < 0.001) (Table 1). With multivariable regression, there were independent risk factors (IRFs) of GDM indicated in this research, including GDM history, pre-pregnancy BMI $\geq$ 23 kg/m^2; a history of fetal macrosomia > 3800 g (as shown in Table 2). The percentage of previous birth weight > 3800 g and maternal age > 30 years were highest (37.8% and 37.1%) (Fig. 1). The group with risk factors was more likely to suffer from GDM than the group without those, statistical significance differentiation (14.6 *vs.* 2.7, P < 0.001) (Table 3).

Table 1. Bivariate analysis of the relationship between risk factors and GDM

Variable	Gestational diabetes mellitus n (%)	No gestational diabetes mellitus n (%)	OR (95% CI)	P value
Age ≥ 30 years				
Yes	36 (13.7%)	226 (86.3%)	1.8 (1.1–2.9)	0.02
No	36 (8.1%)	408 (91.9%)		
BMI ≥ 23 kg/m^2				
Yes	47 (33.3%)	94 (66.7%)	10.8 (6.3–18.4)	< 0.001
No	25 (4.4%)	540 (95.6%)		
History of macrosomia > 3800 g				
Yes	35 (18.8%)	151 (81.2%)	5.2 (2.7–10.2)	< 0.001
No	13 (4.2%)	293 (95.8%)		

Table 2. Multivariable regression of risk factors associated with gestational diabetes mellitus

Risk factors	Regression coefficient	P	OR	The interval where OR = 95%
GDM history	2.502	< 0.001	12.211	3.29–45.28
Maternal age > 30	0.865	0.016	2.376	1.17–4.81
Pre-pregnancy BMI				
≥ 23 kg/m^2	2.377	< 0.001	10.775	5.27–22.00
History of macrosomia > 3800 g	1.538	< 0.001	4.655	2.24–9.68

*Does not include cases with first-time pregnancies; **does not include cases with twin or more pregnancies
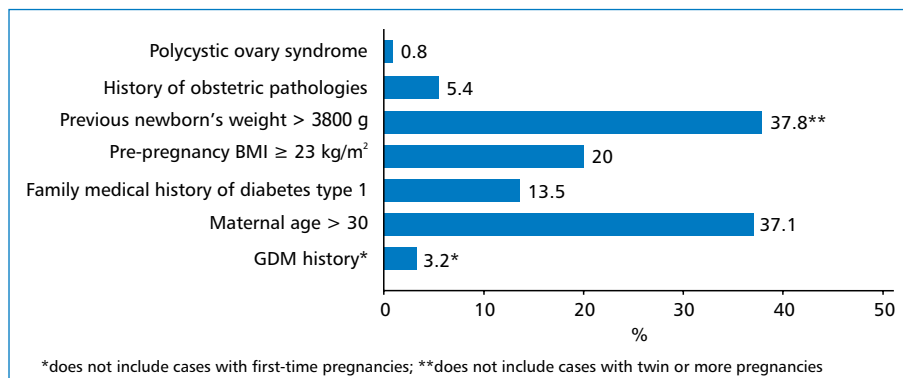
Figure 1. The percentage with respect to independent risk factors

Table 3. The percentage of affected GDM between the group with and without independent risk factors

Risk factors	Number	Gestational diabetes mellitus		No gestational diabetes mellitus	
		n	%	n	%
Yes	445	65	14.6	380	85.4
No	261	7	2.7	254	97.3
P; OR		P < 0.001; OR = 6.21			

Discussion
Prevalence of GDM

In this study, the incidence of GDM was 10.2%, a figure similar to the 10.6% found in the Vietnamese population in Australia [4]. Our findings on prevalence of GDM are fairly similar to a recent study that reported the prevalence of GDM in 8 Eastern and Southeast Asian countries — 10.1% (95% CI 6.5–15.7) [1]. However, the prevalence of GDM in our study was higher than that in

some studies in Vietnam. Thao et al carried out a study in 415 pregnancies (pregnant women) at Bach Mai Hospital showed that the proportion of GDM was 7.9% based on ADA 2003 diagnostic criteria [5]. A research undertaken by Nga in 2009 in 1327 pregnant women at Bach Mai Hospital and Central Maternity Hospital demonstrated the percentage of GDM was 7.8% [6].

The prevalence of GDM in our study was found to be lower when compared with Chinese women who live in China (13.7%) [7] or in Australia (13.9%) [8]. A meta-analysis included 84 studies from 20 Asian countries. They demonstrated the prevalence of GDM was 11.5% (95% CI 10.9–12.1) [9]. We have no clear reason for this difference, but we speculate that it may due to maternal age and BMI disparities, as well as ethnic background [10].

The epidemiological studies aim to determine the prevalence of GDM in a community, which is important to design effective screening strategies, improve the risk factors and manage effectively on pregnant women with hyperglycemia. These benefits reflected the increased use of induction of labor for the mothers and the increased rate of admission to the neonatal nursery for the infants, both of which may be depend on the experience of the physicians. The earlier gestational age at birth, as a result of the induction of labor, may have contributed to the reduction in serious perinatal outcomes. Others have reported an increased rate of cesarean delivery associated with the diagnosis and treatment of gestational diabetes.

Risk factors of GDM

The risk factors of GDM were analyzed in this current review. Multiparity ≥ 2, a previous history of GDM, congenital anomalies, stillbirth, abortion, preterm delivery, macrosomia, having concurrent pregnancy-induced hypertension, polycystic ovary syndrome, age≥ 25, BMI ≥ 25, and a family history of diabetes are the significant risk factors predictive of GDM in current pregnancy (OR values ranged from 1.90 to 8.42). Most of the guidelines, including those of ADA in 2016, recommend universal screening for GDM in second trimester [11]. According to the American Maternity Association, maternal age ≥ 25 years were considered the average risk factors for GDM. Meanwhile, the Australasian Diabetes in Pregnancy Society (ADIPS) originally recommended that pregnant women aged over 40 years were at high-risk of GDM [12].

Our study showed that those with a history of previous GDM, pre-pregnancy BMI ≥ 23 kg/m² and a history of fetal macrosomia > 3800 g are more likely to develop GDM compared those without a history of these conditions, respectively. This finding is consistent with previous studies. Idris et al. conducted the study in 366 Malaysian women showing that the rate of GDM in the age groups < 24, 25–35, ≥ 35 years was: 3%; 14,6%; 38.6% respectively [13]. Studying risk factors in pregnant women in Asia, Wagaarachchi found that the prevalence of GDM among women aged ≥ 35 years was 7.8%, 2.5 times higher than in the age group < 35 years, at 3.1% [2]. According to the study carried out by Rajput in 2011 in 607 pregnant women diagnosed with GDM, the percentage of GDM in patients aged 25 years and older is 3.8 times than that in the group below 25 years old [14]. Yang's research (2009) in 16286 pregnant women has proven the statistically significant difference between the groups of age ≥ 35 and < 35 (OR: 1.97, P < 0.001) [15]. In our research, the percentage of GDM in the group over 30 years old was higher than that in the group 30 and below (13.7% *vs.* 8.1%, P < 0.05). The odds ratio of GDM between the group > 30 years old and group ≤ 30 was 1.8. All the above results come to a general conclusion that the rate of GDM tends to increase with age.

Weight loss at birth was both a consequence of GDM and a risk factor for postpartum pregnancy. Europeans consider a baby with a birth weight ≥ 4000 g to be large for gestational age (LGA); in Vietnam, a baby with a birth weight ≥ 3600 g can be considered to be LGA. Therefore, a history of fetal macrosomia was one of the risk factors for GDM, because increased blood glucose levels go through the placenta causing increased glucose concentration in the fetus and large fetal weight. Insulin had an anabolic effect that stimulates growth either directly or indirectly through growth factors.

All of these warned that the incidence of high-risk pregnancies in the future would increase, and doctors should be aware of the high-risk factors for pregnant women during antenatal care and screening for early detection of GDM.

Conclusion

The prevalence of GDM is rather high (10.2%). The risk factors associated with GDM were identified: maternal age (≥ 30 years) and a history of macrosomia. Overall, the ratio of GDM between groups with and without independent risk factors was 6.21.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Nguyen CL, Pham NM, Binns CW, et al. Prevalence of gestational diabetes mellitus in Eastern and Southeastern Asia: a systematic review and meta-analysis. J Diabetes Res. 2018; 2018: 6536974, doi: 10.1155/2018/6536974, indexed in Pubmed: 29675432.

2. Wagaarachchi PT, Fernando L, Premachadra P, et al. Screening based on risk factors for gestational diabetes in an Asian population. J Obstet Gynaecol. 2001; 21(1): 32–34, doi: 10.1080/01443610020022087, indexed in Pubmed: 12521908.

3. American Diabetes A. Standards of medical care in diabetes 2014. Diabetes Care. 2014; 37(Supplement): S14.

4. Cheung NW, Wasmer G, Al-Ali J. Risk factors for gestational diabetes among Asian women. Diabetes Care. 2001; 24(5): 955–956, doi: 10.2337/diacare.24.5.955, indexed in Pubmed: 11347764.

5. Thao N, Nga VB. Determining the prevalence of gestational diabetes and investigating the risk factors of pregnant women managing pregnancy in Bach Mai Hospital's obstetrics department. Vietnam Medical Journal. 2007; 27(3): 135–139.

6. Nga VB. Researching fasting blood glucose threshold for screening gestational diabetes and initial assessing of treatment effectiveness. Vietnam Medical Journal. 2009; 29(2): 319–322.

7. Lao TT, Tam KF. Gestational diabetes diagnosed in third trimester pregnancy and pregnancy outcome. Acta Obstet Gynecol Scand. 2001; 80(11): 1003–1008, doi: 10.1034/j.1600-0412.2001.801106.x, indexed in Pubmed: 11703196.

8. Beischer NA, Oats JN, Henry OA, et al. Incidence and severity of gestational diabetes mellitus according to country of birth in women living in Australia. Diabetes. 1991; 40 Suppl 2: 35–38, doi: 10.2337/diab.40.2.s35, indexed in Pubmed: 1748263.

9. Lee KW, Ching SM, Ramachandran V, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018; 18(1): 494, doi: 10.1186/s12884-018-2131-4, indexed in Pubmed: 30547769.

10. Yuen L, Wong VW. Gestational diabetes mellitus: Challenges for different ethnic groups. World J Diabetes. 2015; 6(8): 1024–1032, doi: 10.4239/wjd.v6.i8.1024, indexed in Pubmed: 26240699.

11. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes — 2020. Diabetes Care. 2020; 43(Suppl 1): S14–S31, doi: 10.2337/dc20-S002, indexed in Pubmed: 31862745.

12. Australian Diabetes in Pregnancy Society. ADIPS consensus guidelines for the testing and diagnosis of gestational diabetes mellitus in Australia. 2013.

13. Idris N, Hatikah C, Murizah MZ. Universal versus selective screening for detection of gestational diabetes mellitus in a Malaysian population. Malays Fam Physician. 2009; 4(2-3): 83.

14. Rajput R, Yadav Y, Nanda S, et al. Prevalence of gestational diabetes mellitus & associated risk factors at a tertiary care hospital in Haryana. The Indian journal of medical research. 2013; 137(4): 728.

15. Yang H, Wei Y, Gao X, et al. China National GDM Survey Working Group. Risk factors for gestational diabetes mellitus in Chinese women: a prospective study of 16,286 pregnant women in China. Diabet Med. 2009; 26(11): 1099–1104, doi: 10.1111/j.1464-5491.2009.02845.x, indexed in Pubmed: 19929987.

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Uncontrolled type 2 diabetes mellitus in Kandahar, Afghanistan: a cross-sectional analytical study

ABSTRACT

Background. Type 2 diabetes mellitus (T2DM) is one of the leading causes of mortality and morbidity worldwide. Main objective of this study was to determine the factors affecting uncontrolled T2DM.

Methods. This was a cross-sectional analytical study conducted in Kandahar, Afghanistan during July–December, 2018. Data was collected from 748 T2DM patients aged > 20 years. Data was analyzed with SPSS software using descriptive statistics, Chi square test, and binary logistic regression.

Results. Among 748 T2DM patients, 390/748 (52.1%) were females with 246/258 (95.3%) having low or middle socio-economic status. Family history of DM was present in 402/746 (53.9%) patients with 370/740 (50%) patients having uncontrolled DM. Vanaspati or animal fat was used by 728/748 (97.3%) of the patients, with 194/746 (26%) patients doing regular exercise. Oral hypoglycemic drugs were used by 666/720 (92.5%) of the patients. Comorbidities were present in 612/748 (81.8%) of the patients, with 348/748 (46.5%) having hypertension while 566/746 (75.9%) of the patients were either overweight or obese. Binary logistic regression revealed female gender (Adjusted Odds Ratio [AOR] 2.1, 95% CI 1.3–3.5), job without vigorous

activity (AOR 2.2, 95% CI 1.3–3.6), and late diagnosis of DM (AOR 9.2, 95% CI 1.2–73.4) as the risk factors for uncontrolled T2DM.

Conclusion. Uncontrolled DM is prevalent in Kandahar. Proper control of the risk factors for uncontrolled DM will help in decreasing the severity and complications of DM. Diabetic services improvement, especially public awareness programs on media, is highly recommended to improve diabetic care in Kandahar. (Clin Diabetol 2020; 9; 6: 416–425)

Key words: diabetes mellitus, DM, Kandahar, Afghanistan, risk factors, determinants

Introduction

Type 2 diabetes mellitus (T2DM) is one of the leading cause of mortality and increases the risks of cardiovascular disease, blindness, kidney failure, and lower limb amputation [1]. In 2014, according to World Health Organization (WHO), approximately 422 million people worldwide had diabetes mellitus (DM) as compared to 108 million in 1980, particularly in low- and middle-income countries [1]. Approximately 90% of diabetes patients have T2DM, which is mostly related to lifestyle [2]. DM can cause many long-term complications in different parts of the body and can increase the overall risk of premature death [3]. Due to the increasing prevalence of obesity, especially among younger adults, T2DM is now more frequently diagnosed in young adults and adolescents, especially in high-income countries [4, 5]. In 2010, prevalence of DM in Afghanistan among the age group of 20–79 years was estimated to be 8.6%, whereas by 2030 it is estimated to reach 9.9% [6]. Moreover, studies reported that the prevalence of DM was 9.9% in Herat [7]

11.8% in Jalalabad [8], 13.2% in Kabul [9], and 22.4% in Kandahar [10]. Main objective of this study was to determine the factors affecting uncontrolled T2DM, as well as the sociodemographic, behavior, physical activity, and nutrition status of patients with T2DM in Kandahar, Afghanistan.

Methods

This was a cross-sectional analytical study. Data was collected during 6-month-period (July–December, 2018) using researcher-made questionnaire with questions regarding general characteristics, socio-economic status, physical activity, and nutrition of the diabetic patients.

The study population was composed of patients with T2DM with age > 20 years who visited public and private health facilities in Kandahar, Afghanistan. All the patients were living in urban area (Kandahar city).

Research question: What are the factors affecting uncontrolled T2DM in Kandahar city, Afghanistan?

Primary objective was to determine the factors affecting uncontrolled T2DM in Kandahar city, Afghanistan.

Secondary objective was to determine the sociodemographic, behavior, physical activity, and nutrition status of patients with T2DM in Kandahar city.

Inclusion criteria:
— patient with laboratory confirmed T2DM;
— both male and female patients with age > 20 years;
— permanent residents of Kandahar city.

Exclusion criteria:
— type 1 DM;
— patients who refused to consent for interview.

Sample size was calculated using the following formula:

Where n is the sample size, p is the prevalence of outcome expressed as a proportion, E is the margin of error which is 0.05 in this case, 1.96 is the standard normal z-value corresponding to the 95% confidence interval.

The sample size and power calculations have been performed in Stata 15 (College Station, Texas, USA). Our sample size was 748 patients.

Written informed consents were taken from all the participants prior to the study. Information of the participants will not be disclosed. Ethical approval was taken from Kandahar University Ethics Committee with code number of KDRU-EC-2019.329.

Data was analyzed with SPSS version 22 (Chicago, IL, USA). Descriptive statistics, such as percentages and proportions, were used to describe the sociodemographic and other variables of the study participants. Chi square test (using crude odd ratio [COR]) was used to study the association of different factors in uncontrolled diabetic patients. All variables that showed statistically significant association were put in binary logistic regression (using adjusted odd ratio [AOR]) to determine the factors affecting uncontrolled T2DM. P value of < 0.05 was considered statistically significant.

Definitions

Diabetes: A patient with fasting blood glucose of ≥ 126 mg/dL.

Fasting: Not having anything to eat or drink (except water) for at least 8 hours before the test.

Late diagnosis of T2DM: A diabetes patient with at least one diabetes related comorbidities or complications within 6 months before diagnosis.

Uncontrolled diabetes: Fasting blood glucose level of ≥ 126 mg/dL and random blood glucose of ≥ 200 mg/dL on previous three continuous occasions of the patient's visit to hospital.

Results

This was a cross-sectional study with data collected from 748 T2DM patients who visited the public and private health facilities of Kandahar city during a period of 6 months. Mean (SD) age of all patients, males, and females were 57.3 (12.6) years, 58.0 (13.3) years, and 56.6 (11.8) years, respectively (Table 1). Approximately half (360/736 [48.9%]) of the patients were in the age group of 40–59 years. Females (390/748 [52.1%]) were more than males (358/748 [47.9%]), with almost all (386/390 [99.0%]) of the female patients being housewives. Socio-economic status of most (246/258 [95.3%]) of the patients was low or middle income. More than half (402/746 [53.9%]) of the patients had a family history of DM (Table 2).

Uncontrolled DM was observed in 370/740 (50%) of the patients. Overall, 94/746 (12.6%) of the patients were smoking, with 74/358 (20.7%) males and 20/388 (5.2%) females. Mouth sniff (locally called Naswar) was being used by 266/746 (35.7%) of the patients, with 184/356 (51.7%) in males. Fruits and vegetables were used daily by 62/620 (10%) and 96/674 (14.2%) of the patients. Nearly all (728/748 [97.3%]) of the patients were using Vanaspati or animal fat, with 194/746 (26%) of the patients doing regular exercise. For treatment, 666/720 (92.5%) of the patients were treated with oral hypoglycemic drugs, 34/720 (4.7%) with insulin, while 20 (2.8%) of the patients did not use any drugs for treatment. Comorbidities were present in 612/748 (81.8%) of the patients. Hypertension was present in 348/748 (46.5%) of the patient, while 566/746 (75.9%) of the patients were either overweight or obese (Table 3).

Table 1. Characteristics of the continuous variables

Variable	Total			Males			Females		
	n	Mean ± SD	Range	n	Mean ± SD	Range	n	Mean ± SD	Range
Age	736	57.3 ± 12.6	20–103	358	58.0 ± 13.3	28 – 103	378	56.6 ± 11.8	20–85
Number of family members	736	16.1 ± 6.9	2–40	358	17.4 ± 7.3	3 – 40	378	14.8 ± 6.3	2–35
Number of years smoking in the past	182	13.4 ± 10.3	1–45	118	15.5 ± 9.8	1–45	64	9.6 ± 10.2	1–40
Packs of cigarettes smoked per week	80	2.6 ± 1.6	1–7	70	2.5 ± 1.3	1 – 6	10	3.8 ± 2.9	1–7
Number of days eating fruit in a week	620	3.6 ± 1.7	0–7	306	4.0 ± 1.6	0–7	314	3.3 ± 1.8	0–7
Number of days eating vegetables in a week	674	4.1 ± 1.6	0–7	330	3.9 ± 1.4	2–7	344	4.2 ± 1.7	0–7
Number of days doing exercise in a week	190	6.0 ± 1.1	3–7	150	5.8 ± 1.0	3–7	40	6.9 ± 0.2	6–7
Blood sugar [mg/dL]	744	227.8 ± 81.2	71–580	356	214.5 ± 70.6	71–461	388	240.0 ± 88.2	72–580
Systolic BP [mm Hg]	748	135.9 ± 24.4	70–190	358	136.9 ± 24.4	70–190	390	135.1 ± 24.5	80–190
Diastolic BP [mm Hg]	748	83.8 ± 12.2	35–120	358	84.2 ± 12.3	35–120	390	83.3 ± 12.2	55–110
Pulse rate (/minute)	748	86.1 ± 12.3	23–131	358	84.6 ± 12.1	23–112	390	87.5 ± 12.2	61–131
Weight [kg]	748	73.2 ± 13.2	48–130	358	75.2 ± 11.7	52 – 107	390	71.5 ± 14.3	48–130
Height [cm]	746	164.9 ± 8.5	105–191	358	168.7 ± 6.8	150–191	388	161.5 ± 8.4	105–181
Waist circumference	726	85.9 ± 17.5	55–168	354	82.8 ± 11.7	59–120	372	88.9 ± 21.2	55–168
BMI	746	27.1 ± 5.6	18–57	358	26.6 ± 4.7	18–39	388	27.6 ± 6.3	18–57
For how long are you taking anti- diabetic medication (years)?	668	6.9 ± 5.0	0–25	312	6.9 ± 4.8	0–25	356	7.0 ± 5.3	0–25

BMI — body mass index; mm Hg — millimeter of mercury; SD — standard deviation

Table 2. Socio-demographic characteristics

Variable	Total, n (%)	Males, n (%)	Females, n (%)
Age (years)			
20–39	58 (7.9)	32 (8.9)	26 (6.9)
40–59	360 (48.9)	178 (49.7)	182 (48.1)
60–79	284 (38.6)	122 (34.1)	162 (42.9)
>80	34 (4.6)	26 (7.3)	8 (2.1)
Total	736 (100)	358 (100)	378 (100)
Gender			
Male	358 (47.9)	358 (100)	0 (0)
Female	390 (52.1)	0 (0)	390 (100)
Total	748 (100)	358 (100)	390 (100)
Literacy			
Literate	362 (48.4)	280 (78.2)	82 (21.0)
Illiterate	386 (51.6)	78 (21.8)	308 (78.0)
Total	748 (100)	358 (100)	390 (100)
Marital status			
Currently married	486 (65.0)	278 (77.6)	208 (53.3)
Widowed	242 (32.4)	70 (19.6)	172 (44.1)
Never married	16 (2.1)	10 (2.8)	6 (1.6)
Divorced	4 (0.5)	0 (0)	4 (1.0)
Total	748 (100)	358 (100)	390 (100)
Occupation			
Government employee	16 (2.1)	16 (4.5)	0 (0.0)
Non-government employee	62 (8.3)	60 (16.8)	2 (0.5)
Self-employed	160 (21.4)	158 (44.1)	2 (0.5)
Unemployed/Housewife	510 (68.2)	124 (34.6)	386 (99.0)
Total	748 (100)	358 (100)	390 (100)
Number of family members			
< 5	28 (3.8)	12 (3.3)	16 (4.2)
5–9	110 (14.9)	48 (13.4)	62 (16.4)
10–19	408 (55.4)	176 (49.2)	232 (61.4)
20–30	160 (21.7)	102 (28.5)	58 (15.3)
> 30	30 (4.1)	20 (5.6)	10 (2.7)
Total	637 (100)	358 (100)	378 (100)
Socio-economic status			
Low income	148 (57.4)	144 (62.1)	4 (15.4)
Middle income	98 (37.9)	76 (32.7)	22 (84.6)
High income	12 (4.7)	12 (5.2)	0 (0.0)
Total	258 (100)	232 (100)	26 (100)
Family history of DM			
Yes	402 (53.9)	172 (48.3)	230 (59.0)
No	344 (46.1)	184 (51.7)	160 (41.0)
Total	746 (100)	356 (100)	390 (100)
Relative with history of DM			
Brother	124 (30.8)	62 (35.6)	62 (27.2)
Mother	108 (26.9)	34 (19.5)	74 (32.5)
Father	80 (19.9)	54 (31.0)	26 (11.4)
Sister	60 (14.9)	12 (6.9)	48 (21.0)
Son	14 (3.5)	8 (4.6)	6 (2.6)
Others*	16 (4.0)	4 (2.4)	12 (5.3)
Total	402 (100)	174 (100)	228 (100)

*Other relatives: uncle, cousin, daughter, grandfather

Table 3. Behavioral characteristics, DM-related characteristics, and physical measurements

Variable	Total, n (%)	Males, n (%)	Females, n (%)
Current smoker			
Yes	94 (12.6)	74 (20.7)	20 (5.2)
No	652 (87.4)	284 (79.3)	368 (94.8)
Total	746 (100)	358 (100)	388 (100)
Has the doctor advised to stop smoking during last 12 months?			
Yes	84 (91.3)	70 (97.2)	14 (70)
No	8 (8.7)	2 (2.8)	6 (30)
Total	92 (100)	72 (100)	20 (100)
Currently using mouth sniff			
Yes	266 (35.7)	184 (51.7)	82 (21.0)
No	480 (64.3)	172 (48.3)	308 (78.0)
Total	746 (100)	356 (100)	390 (100)
Ex-smoker			
Yes	192 (25.7)	126 (35.4)	66 (16.9)
No	554 (74.3)	230 (64.6)	324 (83.1)
Total	746 (100)	356 (100)	390 (100)
Eating fruit			
Every day in a week	62 (10.0)	26 (8.5)	36 (11.5)
3–6 days in a week	436 (70.3)	234 (76.5)	202 (64.3)
< 3 days in a week	122 (19.7)	46 (15.0)	76 (24.2)
Total	620 (100)	306 (100)	314 (100)
Eating vegetables			
Every day	96 (14.2)	32 (9.7)	64 (18.6)
3–6 days in a week	508 (75.4)	280 (84.8)	228 (66.3)
< 3 days in a week	70 (10.4)	18 (5.5)	52 (15.1)
Total	674 (100)	330 (100)	344 (100)
Type of oil used for cooking			
Vanaspati/animal fat	728 (97.3)	342 (95.5)	386 (99.0)
Vegetable oil	20 (2.7)	16 (4.5)	4 (1.0)
Total	748 (100)	358 (100)	390 (100)
Job with vigorous activity			
Yes	270 (36.1)	192 (53.6)	78 (20.0)
No	478 (63.9)	166 (46.4)	312 (80.0)
Total	748 (100)	358 (100)	390 (100)
Exercise regularly			
Yes	194 (26.0)	156 (43.8)	38 (9.7)
No	552 (74.0)	200 (56.2)	352 (90.3)
Total	746 (100)	356 (100)	390 (100)
Type of exercise			
Walking	178 (23.9)	138 (38.8)	38 (9.7)
Running	10 (1.3)	12 (3.4)	0 (0.0)
Body building	6 (0.8)	6 (1.7)	0 (0.0)
No exercise	552 (74.0)	200 (56.2)	352 (90.3)
Total	746 (100)	356 (100)	390 (100)
Late diagnosis of DM			
Yes	732 (98.1)	346 (97.2)	386 (99.0)
No	14 (1.9)	10 (2.8)	4 (1.0)
Total	746 (100)	356 (100)	390 (100)
Taking antidiabetic medicine			
Yes	700 (95.6)	332 (99.0)	368 (95.3)
No	32 (4.4)	14 (4.0)	18 (4.7)
Total	732 (100)	346 (100)	386 (100)

→

Table 3 (cont.). Behavioral characteristics, DM-related characteristics, and physical measurements

Variable	Total, n (%)	Males, n (%)	Females, n (%)
Yes	700 (95.6)	332 (99.0)	368 (95.3)
No	32 (4.4)	14 (4.0)	18 (4.7)
Total	732 (100)	346 (100)	386 (100)
Type of DM medication			
Oral hypoglycemic	666 (92.5)	314 (92.4)	352 (92.6)
Insulin	34 (4.7)	18 (5.3)	16 (4.2)
Non	20 (2.8)	8 (2.3)	12 (3.2)
Total	720 (100)	340 (100)	380 (100)
DM now under control			
Yes	370 (50)	208 (59.1)	162 (41.8)
No	370 (50)	144 (40.9)	226 (58.2)
Total	740 (100)	352 (100)	388 (100)
Co-morbidities present			
Yes	612 (81.8)	272 (76.0)	340 (87.2)
No	136 (18.2)	86 (24.0)	50 (12.8)
Total	748 (100)	358 (100)	390 (100)
Co-morbid diseases			
HTN	329 (53.8)	109 (40.0)	220 (64.7)
MI	68 (11.1)	10 (3.6)	58 (17.1)
COPD	60 (9.8)	49 (18.2)	11 (3.2)
Anxiety	47 (7.7)	35 (12.9)	12 (3.5)
IHD	47 (7.7)	30 (11.0)	17 (5.0)
Others*	61 (9.9)	39 (14.3)	22 (6.5)
Total	612 (100)	272 (100)	340 (100)
Blood pressure			
Normal	400 (53.5)	198 (55.3)	202 (51.8)
Stage 1 (mild) hypertension	154 (20.6)	70 (19.6)	84 (21.5)
Stage 2 (moderate) hypertension	144 (19.2)	58 (16.2)	86 (22.1)
Stage 3 (severe) hypertension	50 (6.7)	32 (8.9)	18 (4.6)
Total	748 (100)	358 (100)	390 (100)
BMI			
Normal	180 (24.1)	94 (26.2)	86 (22.2)
Overweight	160 (21.4)	74 (20.7)	86 (22.2)
Obese	406 (54.5)	190 (53.1)	216 (55.6)
Total	746 (100)	358 (100)	388 (100)

DM — diabetes mellitus; COPD — chronic obstructive pulmonary disease; HTN — hypertension; IHD — ischemic heart disease; MI — myocardial infarction
*Other comorbid diseases: stroke, chronic kidney injury, dyslipidemia

Chi-square test of the variables was done to determine the factors associated with uncontrolled T2DM. Statistically significant factors associated with uncontrolled T2DM were age ≥ 60 years (COR 1.6, 95% CI 1.2–2.1; P = 0.002), female gender (COR 2.0, 95% CI 1.5–2.7; P < 0.001), unemployed/housewife (COR 2.0, 95% CI 1.4–2.7; P < 0.001), eating fruit < 3 days in a week (COR 1.7, 95% CI 1.2–2.6; P = 0.006), job without vigorous activity (COR 2.7, 95% CI 2.0–3.7; P < 0.001), not doing regular exercise (COR 1.7, 95% CI 1.2–2.4; P = 0.001), late diagnosis of DM (COR 9.2, 95% CI 1.2–73.4; P = 0.011), not taking antidiabetic drugs (COR 2.3, 95% CI 1.1–5.0; P = 0.025), taking insulin (COR 2.0, 95% CI 1.0–4.1; P = 0.049), and DM that has affected routine of the patient (COR 1.6, 95% CI 1.1–2.3; P = 0.016) (Table 4).

Binary logistic regression of the above-mentioned statistically significant variables revealed female gender (AOR 2.1, 95% CI 1.3–3.5; P = 0.004), job without vigorous activity (AOR 2.2, 95% CI 1.3–3.6; P = 0.003), and late diagnosis of DM (AOR 9.2, 95% CI 1.2–73.4; P = 0.035) as the risk factors for uncontrolled T2DM (Table 5).

Table 4. Chi-square test of the factors affecting uncontrolled T2DM

Variable	Total, n (%)	Controlled T2DM, n (%)	Uncontrolled T2DM, n (%)	COR	95% CI	P value
Age (years)						
< 60	418 (55.9)	224 (62.2)	188 (51.1)			
≥ 60	318 (42.5)	136 (37.8)	180 (48.9)	1.6	1.2–2.1	0.002
Total	736 (100)	360 (100)	368 (100)			
Gender						
Male	358 (47.9)	208 (56.2)	144 (38.9)			
Female	390 (52.1)	162 (43.8)	226 (61.1)	2.0	1.5–2.7	< 0.001
Total	748 (100)	370 (100)	370 (100)			
Literacy						
Literate	362 (48.4)	170 (45.9)	212 (57.3)			
Illiterate	386 (51.6)	200 (54.1)	158 (42.7)	0.6	0.5–0.8	0.002
Total	748 (100)	370 (100)	370 (100)			
Marital status						
Single	262 (35.0)	112 (30.3)	150 (40.5)			
Married	486 (65.0)	258 (69.7)	220 (59.5)	0.6	0.5–0.9	0.003
Total	748 (100)	370 (100)	370 (100)			
Occupation						
Employed	238 (31.8)	144 (38.9)	90 (24.3)			
Unemployed/Housewife	510 (68.2)	226 (61.1)	280 (75.7)	2.0	1.4–2.7	< 0.001
Total	748 (100)	370 (100)	370 (100)			
Number of family members						
< 5	28 (3.8)	8 (2.2)	20 (5.6)			
≥ 5	708 (96.2)	360 (97.8)	340 (94.4)	0.4	0.2–0.9	0.018
Total	637 (100)	368 (100)	360 (100)			
Socio-economic status						
Low/Middle income	246 (95.3)	154 (96.3)	90 (93.8)			
High income	12 (4.7)	6 (3.7)	6 (6.2)	1.7	0.5–5.5	0.360
Total	258 (100)	160 (100)	96 (100)			
Family history of DM						
Yes	402 (53.9)	178 (48.1)	222 (60.0)			
No	344 (46.1)	192 (51.9)	148 (40.0)	0.6	0.5–0.8	0.001
Total	746 (100)	370 (100)	370 (100)			
Current smoker						
Yes	94 (12.6)	44 (12.0)	48 (13.0)			
No	652 (87.4)	324 (88.0)	322 (87.0)	0.9	0.6–1.4	0.676
Total	746 (100)	368 (100)	370 (100)			
Has the doctor advised to stop smoking during last 12 months?						
Yes	84 (91.3)	40 (90.9)	44 (91.7)			
No	8 (8.7)	4 (9.1)	4 (8.3)	0.9	0.2–3.9	0.898
Total	92 (100)	44 (100)	48 (100)			
Currently using mouth sniff						
Yes	266 (35.7)	128 (34.8)	138 (37.3)			
No	480 (64.3)	240 (65.2)	232 (62.7)	0.9	0.7–1.2	0.477
Total	746 (100)	368 (100)	370 (100)			
Eating fruit						
3–7 days in a week	498 (80.3)	270 (84.4)	222 (75.5)			
< 3 days in a week	122 (19.7)	50 (15.6)	72 (24.5)	1.7	1.2–2.6	0.006
Total	620 (100)	320 (100)	294 (100)			
Eating vegetables						
3–7 days in a week	604 (89.6)	314 (89.7)	284 (89.9)			
< 3 days in a week	70 (10.4)	36 (10.3)	32 (10.1)	1.0	0.6–1.6	0.946
Total	674 (100)	350 (100)	316 (100)			

→

Table 4 (cont.). Chi-square test of the factors affecting uncontrolled T2DM

Variable	Total, n (%)	Controlled T2DM, n (%)	Uncontrolled T2DM, n (%)	COR	95% CI	P value
Type of oil used for cooking						
Vanaspati/animal fat	728 (97.3)	364 (98.4)	356 (96.2)			
Vegetable oil	20 (2.7)	6 (1.6)	14 (3.8)	2.4	0.9–6.3	0.070
Total	748 (100)	370 (100)	370 (100)			
Job with vigorous activity						
Yes	270 (36.1)	174 (47.0)	92 (24.9)			
No	478 (63.9)	196 (53.0)	278 (75.1)	2.7	2.0–3.7	< 0.001
Total	748 (100)	370 (100)	370 (100)			
Exercise regularly						
Yes	194 (26.0)	114 (31.0)	76 (20.5)			
No	552 (74.0)	254 (69.0)	294 (79.5)	1.7	1.2–2.4	0.001
Total	746 (100)	368 (100)	370 (100)			
Late diagnosis of DM						
Yes	732 (98.1)	369 (99.7)	361 (97.6)			
No	14 (1.9)	1 (0.3)	9 (2.4)	9.2	1.2–73.4	0.011
Total	746 (100)	370 (100)	370 (100)			
Taking antidiabetic medicine						
Yes	700 (95.6)	360 (97.3)	338(93.9)			
No	32 (4.4)	10 (2.7)	22 (6.1)	2.3	1.1–5.0	0.025
Total	732 (100)	370 (100)	360 (100)			
Type of antidiabetic medicine						
Oral antidiabetic	666 (95.1)	348 (96.7)	316 (93.5)			
Insulin	34 (4.9)	12 (3.3)	22 (6.5)	2.0	1.0–4.1	0.051
Total	700 (100)	360 (100)	338 (100)			
Co-morbidities present						
Yes	612 (81.8)	304 (82.2)	300 (81.1)			
No	136 (18.2)	66 (17.8)	70 (18.9)	1.1	0.7–1.6	0.704
Total	748 (100)	370 (100)	370 (100)			
Blood pressure						
Normal	400 (53.5)	198 (53.5)	196 (53.0)			
Hypertension	348 (46.5)	172 (46.5)	174 (47.0)	1.0	0.8–1.4	0.883
Total	748 (100)	370 (100)	370 (100)			
BMI						
Normal	180 (24.1)	80 (21.6)	98 (26.6)			
Overweight/Obese	566 (75.9)	290 (78.4)	270 (73.4)	0.8	0.5–1.1	0.112
Total	746 (100)	370 (100)	368 (100)			

BMI — body mass index; DM — diabetes mellitus; T2DM — type 2 diabetes mellitus

Discussion

In this cross-sectional study, we studied 748 T2DM patients to determine the factors in uncontrolled T2DM in Kandahar, Afghanistan. Although DM is prevalent in Afghanistan, until now very few studies have been conducted on this devastating disease [7–9]. To our knowledge, there has never been any study in Afghanistan to find out the factors affecting uncontrolled DM.

In our study, DM was uncontrolled in half (50%) of the patients. This higher prevalence of uncontrolled DM is of great concern, and is also broadly in line with studies from Ethiopia (50%) [11] and Pakistan (38.9%) [12]. Contrary, even higher prevalence of uncontrolled DM have been reported from Ghana (86.4%) [3] and Saudi Arabia (74%) [13]. This differences in prevalence of DM may be due to the differences in care, attitude, and practices among DM patients; different methods of health education, treatment, and counselling or variances in geographical regions [3].

Table 5. Binary logistic regression for estimating the factors affecting uncontrolled T2DM

Variable	AOR	95%CI	P value
Job with vigorous activity	2.2	1.3–3.6	0.003
Gender	2.1	1.3–3.5	0.004
Late diagnosis of DM	9.2	1.2–73.4	0.035
Taking antidiabetic medicine	0.1	0.0–1.1	0.055
Type of antidiabetic medicine	2.2	0.9–5.0	0.067
Age	1.4	0.9–2.2	0.106
Eating fruit	1.4	0.9–2.2	0.173
Occupation	0.7	0.3–1.4	0.279
Exercise regularly	0.9	0.5–1.5	0.683

DM — diabetes mellitus; T2DM — type 2 diabetes mellitus

In our study, uncontrolled DM was more prevalent (61.1%) among females. Similar results have been reported from Jordan (51.9%) [14], Ghana (76.8%) [3] and Pakistan (77.3%) [12].

Sedentary lifestyle and lack of regular exercise increases the risk of T2DM. In our study only 26% of the patients were doing regular exercise. Similarly, studies Saudi Arabia [15], Jordan [14], and USA [16] have also revealed that physical inactivity is the predictor of poor glycemic control. Physical exercise not only improves glycemic control, but also boosts patient's insulin sensitivity and repairs some of the damage due by DM associated complications, for instance impaired cardiovascular health [17].

Comorbidities were present in majority (81.8%) of our patients. Similarly, most of the patients had comorbidities in Ghana (86,4%) [3], Jordan (65.1%) [14], and Saudi Arabia (65.0%) [18]. In our study, main factors associated with uncontrolled T2DM were female gender, job without vigorous activity, and late diagnosis of DM. A study in Jordan revealed that statistically significant factors associated with uncontrolled DM were increased duration of DM, not following dietitians-recommended eating plan, negative attitude towards DM, and increased barriers to adherence scale scores [14]. A study conducted in Pakistan showed that patients aged < 50 years, being diagnosed in a hospital rather than a clinic, diabetes information from a doctor or nurse only rather than multiple sources, higher monthly treatment cost, and higher consumption of tea as the main factors for uncontrolled DM. On the other hand, a study in Saudi Arabia concluded that a family history of DM, having longer diabetic durations, not doing sufficient physical exercise, and being overweight were the statistically significant risk factors [18]. These findings emphasize on the importance of patients at risk of developing complication due to DM and implementation of more effective preventive measure [19, 20].

Main limitations of our study were cross-sectional nature of the study (all risk factors of uncontrolled T2DM could not be studied, especially HbA$_{1c}$), patients were mostly from urban area (we cannot generalize the results to the entire population), and inability to follow up the patients longitudinally.

Conclusion

Diabetes mellitus is prevalent in Kandahar, affecting females more than males. Half of the T2DM patients had uncontrolled DM. Main risk factors for uncontrolled DM were female gender, job without vigorous activity, and late diagnosis of DM. Proper control of these risk factors will help in decreasing the severity and complications of DM. Diabetic services improvement, especially public awareness programs on media, is highly recommended to improve diabetic care in Kandahar. Future studies (especially prospective studies) are needed in Kandahar to find out the different aspects of DM prevalence, clinical features, complications, diagnosis, management, and prognosis.

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Conflict of interests

The authors report no conflicts of interest in this study.

REFERENCES

1. World Health Organization. Global Report on Diabetes. WHO. 2016. https://www.who.int/publications-detail/global-report-on-diabetes (20.02.2019).
2. Trapp CB, Barnard ND. Usefulness of vegetarian and vegan diets for treating type 2 diabetes. Curr Diab Rep. 2010; 10(2): 152–158, doi: 10.1007/s11892-010-0093-7, indexed in Pubmed: 20425575.
3. Fiagbe J, Takramah W, Axame W, et al. Risk factors associated with diabetes mellitus among adults in the Hohoe Municipality of Ghana. Journal of Advances in Medicine and Medical Research. 2017; 23(2): 1–12, doi: 10.9734/jammr/2017/33846.
4. Alberti G, Zimmet P, Shaw J, et al. Consensus Workshop Group. Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. Diabetes Care. 2004; 27(7): 1798–1811, doi: 10.2337/diacare.27.7.1798, indexed in Pubmed: 15220270.
5. Koopman RJ, Mainous AG, Diaz VA, et al. Changes in age at diagnosis of type 2 diabetes mellitus in the United States, 1988 to 2000. Ann Fam Med. 2005; 3(1): 60–63, doi: 10.1370/afm.214, indexed in Pubmed: 15671192.
6. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010; 87(1): 4–14, doi: 10.1016/j.diabres.2009.10.007, indexed in Pubmed: 19896746.

7. Islam Saeed KM. Diabetes Mellitus Among Adults in Herat, Afghanistan: A Cross-Sectional Study. Cent Asian J Glob Health. 2017; 6(1): 271, doi: 10.5195/cajgh.2017.271, indexed in Pubmed: 29138737.

8. Khwaja S, Islam M. Prevalence and Predictors of Diabetes Mellitus in Jalalabad City, Afghanistan-2013. Iran J DIABETES Obes. 2014; 6 (1): 1–8.

9. Saeed K, Asghar R, Sahak M, et al. Prevalence and risk factors associated with diabetes mellitus among Kabul citizens — Afghanistan, 2012. International Journal of Diabetes in Developing Countries. 2015; 35(3): 297–303, doi: 10.1007/s13410-014-0270-3.

10. Mir K, Saeed I. Prevalence of Diabetes and its Risk Factors in Urban Setting of Kandahar City, Afghanistan-2015. IOSR J Pharm. 2016; 6(11): 53 –60.

11. Woldu MA, Wami CD. Factors associated with poor glycemic control among patients with type 2 diabetes mellitus in Ambo Hospital, Ambo; Ethiopia. Endocrinology & Metabolic Syndrome. 2014; 03(04), doi: 10.4172/2161-1017.1000143.

12. Siddiqui FJ, Avan BI, Mahmud S, et al. Uncontrolled diabetes mellitus: prevalence and risk factors among people with type 2 diabetes mellitus in an Urban District of Karachi, Pakistan. Diabetes Res Clin Pract. 2015; 107(1): 148–156, doi: 10.1016/j.diabres.2014.09.025, indexed in Pubmed: 25451895.

13. Almutairi MA, Said SM, Zainuddin H. Predictors of poor glycemic control among type two diabetic patients. Am J Medicine Medical Sci. 2013; 3(2): 17–21, doi: 10.5923/j.ajmms.20130302.01.

14. Khattab M, Khader YS, Al-Khawaldeh A, et al. Factors associated with poor glycemic control among patients with type 2 diabetes. J Diabetes Complications. 2010; 24(2): 84–89, doi: 10.1016/j.jdiacomp.2008.12.008, indexed in Pubmed: 19282203.

15. Almutairi MA, Said SM, Zainuddin H. Predictors of Poor Glycemic Control Among Type Two Diabetic Patients. Am J Med Med Sci. 2013; 3(2): 17–21, doi: 10.5923/j.ajmms.20130302.01.

16. Daly JM, Hartz AJ, Xu Y, et al. An assessment of attitudes, behaviors, and outcomes of patients with type 2 diabetes. J Am Board Fam Med. 2009; 22(3): 280–290, doi: 10.3122/jabfm.2009.03.080114, indexed in Pubmed: 19429734.

17. Thent ZC, Das S, Henry LJ. Role of exercise in the management of diabetes mellitus: the global scenario. PLoS One. 2013; 8(11): e80436, doi: 10.1371/journal.pone.0080436, indexed in Pubmed: 24236181.

18. Alzaheb RA, Altemani AH. The prevalence and determinants of poor glycemic control among adults with type 2 diabetes mellitus in Saudi Arabia. Diabetes Metab Syndr Obes. 2018; 11: 15–21, doi: 10.2147/DMSO.S156214, indexed in Pubmed: 29430192.

19. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000; 321(7258): 405–412, doi: 10.1136/bmj.321.7258.405, indexed in Pubmed: 10938048.

20. Nathan DM, Bayless M, Cleary P, et al. DCCT/EDIC Research Group. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions. Diabetes. 2013; 62(12): 3976–3986, doi: 10.2337/db13-1093, indexed in Pubmed: 24264395.

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Factors associated with control of type 2 diabetes mellitus in North Iran

ABSTRACT

Backround. Diabetes is an important public health problem, one of four priority noncommunicable diseases targeted for action by world leaders. The aim of this study was to investigate the factors affecting diabetes control in patients with type 2 diabetes in the rural areas of northern Iran.

Methods. This study was conducted following a descriptive-analytical cross-sectional study design based on the data of 308 patients with type 2 diabetes in the rural areas of Golestan province. The samples were selected through two-stage stratified random sampling. Data were collected using a questionnaire (completed by the interviewer) and by measuring the blood glucose, blood pressure, and lipid profile of patients and also using data from patients' records. Data were analyzed using descriptive and analytical statistics and SPSS version 19.

Results. The mean age of patients was 57 ± 15 years and 220 patients (71%) were female. Fifty-five percent of patients had a family history of diabetes and 69% had comorbidity. The mean vegetable intake in patients was 3 days a week with 1.5 servings per day and only 20% had exercise at least three times a week. The proportion of patients with adequately controlled glycated hemoglobin (HBA$_{1c}$), blood pressure (BP), triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were 27, 91, 31, 41 and 55.5%, respectively. There was also a significant relationship between the controlled blood glucose with increasing age, absence of comorbidity, the number of nutrition counseling, and lowering blood triglycerides.

Conclusion. The results of this study showed poor blood glucose control in the studied geography. Therefore, considering these data, it seems necessary to review the national plan for the prevention and control of diabetes. (Clin Diabetol 2020; 9; 6: 426–432)

Key words: type 2 diabetes, diabetes control, glycated hemoglobin

Introduction

Diabetes is a serious, chronic disease that occurs when there are raised levels of glucose in the blood because the body cannot produce any or enough of the hormone insulin or use insulin effectively. Raised blood glucose, a common effect of uncontrolled diabetes, may, over time, lead to serious damage to the heart, blood vessels, eyes, kidneys and nerves [1, 2]. The International Diabetes Federation (IDF) estimated the number of people with diabetes increases to 451 million if the age is expanded to 18–99 years, and according to prediction of the World Health Organization (WHO), diabetes is the seventh cause of mortality at 2030 [2, 3].

The prevalence of diabetes worldwide increased from 4.7% in 1998 to 8.5% in 2014 (in people over 18 years), indicating an increasing prevalence of diabetes worldwide. The International Diabetes Federation also

estimated that the prevalence of diabetes in Iran in 2015 was 8.5% (in the population of 20–79 years) and based on the provincial reports, the prevalence of diabetes in the Golestan province was also estimated to be 10% (in the population over 18 years). While the prevalence of diabetes in the middle- and low-income countries is increasing at a faster rate, and if there is no proper action to tackle the disease, it is estimated that by 2040, there will be approximately 642 million people with diabetes [2, 4].

The causes of type 2 diabetes are not completely understood but there is a strong link with overweight and obesity and with increasing age as well as with ethnicity and family history [2]. Some risk factors for type 2 diabetes such as genetics, ethnicity and age — are not modifiable. Others, such as being overweight or obese, unhealthy diet, insufficient physical activity and smoking are modifiable through behavioral and environmental changes [1]. Diabetes is a chronic, progressive disease but people who have diabetes can live long, high quality lives with good diabetes management [2]. According to the report by WHO, diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication and regular screening and treatment for complications [3]. But unfortunately many studies that investigated the control and care of diabetes in different countries, especially in Iran, mostly indicate that the status of care and control of diabetes is not desirable [5–15].

In an effort to address this growing health challenge, since early this decade world leaders have committed to reducing the burden of diabetes as one of four priority noncommunicable diseases (NCDs). In our country, the National Program for Prevention and Control of Type 2 Diabetes, with the main purpose of prevention and control of diabetes and its complications, has been integrated into the family physician program of rural areas in our country at 2004 and is running. Therefor the aim of this study was to investigate the factors affecting diabetes control in patients with type 2 diabetes in the rural areas of northern Iran.

Methods

This study was a descriptive-analytical cross-sectional study conducted between April 2018 and April 2019 based on the data of 340 patients with type 2 diabetes who were selected through two-stage stratified random sampling (stratified proportional allotment). The study population consisted of patients with diabetes with medical records in the rural healthcare centers of Golestan province in north Iran. Inclusion criteria included type 2 diabetes, being older than 20 years, at least one year since the initiation of treatment, and willingness to cooperate.

The study consisted of two consecutive stages. In the first stage, after obtaining the consent of the participants, data on the factors affecting diabetes control were collected from the information recorded in the paper and electronic records of the patients as well as using a questionnaire (completed by the interviewer). In the second stage, all participants were evaluated for glycated hemoglobin (HBA_{1c}), blood pressure (BP), and lipid profile in order to determine the status of diabetes control. In the process of patient evaluation performed by trained experts, blood pressure was measured using a mercury sphygmomanometer in the sitting position. The BT1500 autoanalyzer was also used for the measurement of glycated hemoglobin and lipid profile of patients. The data were finally entered into SPSS software and analyzed using descriptive (such as mean, standard deviation, etc.) and analytical (Pearson correlation coefficient, chi-square, and independent t-test) statistics.

Results

In this study, out of 340 cases studied, 308 patients were included in the final analysis, with a response rate of 91%. Of the participants, 88 (28%) were male and 220 (71%) were female. The mean age was 57 ± 15 years and the youngest and oldest age was 24 and 86 years, respectively. The mean household size in the participants was 4 persons. In terms of education level, the majority of participants (62%) were illiterate. Most of the participants were housewives (72%). The majority of the participants were married (82%). The mean duration of diabetes at the time of diagnosis was 7.8 years. Table 1 shows the frequency distribution of some of the variables studied in patients with type 2 diabetes.

The mean glycated hemoglobin (HBA_{1c}) was 8.1 ± 1.7 and the mean body mass index (BMI) was 29 ± 6 kg/m². The proportion of patients with well controlled HBA^{1c} ($\leq$ 7), blood pressure (BP) ($\leq$ 140/90), triglyceride (TG) ($\leq$ 150), low-density lipoprotein (LDL) ($\leq$ 100), and high-density lipoprotein (HDL) ($\geq$ 50) were 27, 91, 31, 41, and 55.5%, respectively.

According to the results of the independent t-test, the mean age and number of nutrition counseling per month were significantly higher in those who had controlled glycated hemoglobin and the mean blood triglyceride levels were significantly higher in those who had uncontrolled glycated hemoglobin (P < 0.05). Table 2 shows the comparison of mean age, blood triglyceride, and the number of nutrition counseling with glycated hemoglobin control status in the subjects.

Chi-square test results also showed that there was a significant relationship between the glycated hemo-

Table 1. Frequency distribution of some of the variables studied in patients with type 2 diabetes

Variable		Number	Percentage	Descriptions
Education				
	Illiterate	192	62.3	
	Less than a high school diploma	106	4.4	
	Diploma	8	2.6	
	Academic	2	0.6	
Marital status				
	Married	255	82.7	
	Single	3	1	
	Divorced	6	1.9	
	Widowed	44	14.3	
Occupation				
	Housewife	222	72.1	
	Worker	15	4.9	
	Farmer	28	9.1	
	Employee	3	1	
	Self-employed	15	4.9	
	Retired	11	3.6	
	Unemployed	14	4.5	
Income				
	Less than 1 million Tomans	217	70.4	
	Between 1 and 2 million Tomans	86	27.8	
	More than 2 million Tomans	5	1.6	
Family history				
	Yes	169	55	
	No	139	45	
Insurance coverage				
	Yes	303	98.4	68% had rural insurance
	No	5	1.6	
Type of treatment				
	Medication-free treatment (diet, etc.)	4	1	
	Tablet	253	82	
	Insulin	51	17	
Comorbidity				
	Yes	211	68.5	30% had hypertension
	No	97	31.5	
Complications of diabetes				
	Yes	108	35	
	No	200	65	
Attending physician				
	General practitioner (GP)	139	45	
	Specialist	169	55	They were referred to a specialist physician at least once a year to control diabetes
Cigarette smoking, hookah smoking, and drug use	Patients with cigarette smoking	3	0.9	With an average consumption of 16.7 ± 2.9
	Patients with hookah smoking	1	0.3	With an average consumption of 2 times a day
	Patients with drug use	25	8	
Exercise	Exercising at least three times a week (for 150 minutes)	61	20	With a mean of 4.5 ± 2 days a week and 37 ± 16 minutes a day
	Not exercising at least three times a week (for 150 minutes)	247	80	

→

Table 1 (cont.). Frequency distribution of some of the variables studied in patients with type 2 diabetes

Variable		Number	Percentage	Descriptions
Fruit and vegetable intake	Vegetable intake	–	–	The mean vegetable intake was 3 ± 1.9 days per week with 1.5 ± 0.8 servings per day
	Fruit intake	–	–	The mean fruit intake was 4.5 ± 2 days per week and 1.8 ± 1 servings per day
Care taken	Patients who were visited at least seasonally by a physician form healthcare centers	109	35	
	Patients who were visited monthly by a health worker form healthcare centers	62	20	According to medical records data, 92% of patients were seasonally cared for by health workers
Glycated hemoglobin test	Patients who had undergone at least 2 tests per year	95	31	

Table 2. The comparison of mean age, blood triglyceride, and the number of nutrition counseling with glycated hemoglobin control status in the subjects

Variable	Age (Mean ± SD)	Number of nutrition counseling (Mean ± SD)	Triglyceride [mL/dL] (Mean ± SD)
Controlled HBA$_{1c}$ (n = 104)	59.81 ± 10.3	0.85 ± 1.7	175.40 ± 86.1
Uncontrolled HBA$_{1c}$ (n = 204)	55.60 ± 9.6	0.43 ± 1.4	223.52 ± 141.7
P value	P = 0.001	P = 0.048	P = 0.001

Table 3. The comparison of the frequency distribution of glycated hemoglobin status according to the presence of comorbidity in the subjects

Glycated hemoglobin status		Uncontrolled n (%)	Controlled n (%)	Chi-square test results
Comorbidity	No	64 (66)	33 (34)	
	Hypertension	52 (56.5)	40 (43.5)	P = 0.044
	Dyslipidemia (blood lipid disorder)	44 (78.6)	12 (21.4)	X^2 = 8.1
	Hypertension and dyslipidemia	42 (70)	18 (30)	df = 3

globin status and the presence of comorbidity (P = 0.044). The comparison of the frequency distribution of glycated hemoglobin status according to the presence of comorbidity in the subjects is shown in Table 3.

Discussion

In the present study, 71% of patients were female. In domestic studies, this percentage ranged from 62 to 81% [6, 16, 17]. In the Middle East, women are more likely to have diabetes than men [2]. It can be said that a sedentary lifestyle in women is one of the causes. Also according to our findings, there was no significant relationship between gender and blood glucose control status, which is in line with the findings of a study conducted in Malaysia [14] and with other findings from domestic studies and Asian and African studies [6, 18, 19].

In the present study, the control rates of glycated hemoglobin (HBA$_{1c}$), blood pressure (BP), low-density lipoprotein (LDL), and triglyceride (TG) in patients covered by the National Diabetes Control Program were 27, 91, 41 and 31%, respectively. Control rate of glycated hemoglobin level as one of the most important therapeutic targets of diabetes ranged from 21 to 27% in the similar domestic studies [6, 7, 20] and 29.3 to 46% in the Arabic countries on the periphery of the Persian

Gulf (Saudi Arabia, United Arab Emirates, and Oman) [21]. This index was reported to be 50, 40, and 88% in the studies conducted in China, the United States, and Sweden, respectively [12, 22, 23]. It can be said that the level and quality of blood glucose control in the rural areas of Golestan province, like in other studies in the rural areas of our country, is not favorable and is far from the American Diabetes Association's (ADA's) standards of medical care and our national standards.

The International Diabetes Federation (IDF) has also cited ethnicity, genetics, and age as non-modifiable risk factors for type 2 diabetes [5]. Although many of the diabetes-predisposing genes have not yet been identified, it is known that the disease is polygenic and multifactorial. Various genetic loci have been implicated in susceptibility to the disease. Environmental factors (such as nutrition and physical activity) also influence its phenotypic expression [16]. In this study, 55.2% of patients had a history of diabetes in their first-degree relatives. The data of the present study, like other domestic studies and international resources, indicated the important role of genetic factors in the development of type 2 diabetes [4, 5, 17, 18].

The mean age of the patients was 57.1 (57 years for men and 56 years for women). Also, 75% of the patients were over 50 years old, which is consistent with the results of the country studies [6, 17, 24]. It is natural that the prevalence of diabetes increases with age. This is because as the person ages, he or she may lose physical activity and gain weight, and this increase in fat deposits around the abdomen and upper body, especially in women after menopause. Low activity and weight gain decrease insulin activity and develop insulin resistance [6]. Also, there was a significant relationship between an increase in the mean age of patients and a more favorable blood glucose control status in our study (P = 0.001). Some studies have also cited age as a positive predictor (but not a strong factor) in controlling blood glucose. These data are in line with the findings of studies conducted in Asia and Africa [14, 18, 25, 26].

Various studies have shown that obesity plays a role in the pathogenesis of type 2 diabetes. It is generally accepted that obesity is responsible for disease emergence in those who are genetically susceptible. The World Health Organization (WHO) stated in 1980 that obesity is one of the most important risk factors for type 2 diabetes [1], and the International Diabetes Federation (IDF) also lists obesity as a risk factor for diabetes [2]. Our findings showed that the mean patients' BMI was 29 kg/m^2 and about 78.6% of patients were in the overweight or obesity range. This is in line with the results of domestic studies, indicating an undesirable prevalence of overweight and obesity

among type 2 diabetic patients in the country [6, 16]. Also, our findings showed a significant relationship between the mean high triglyceride levels and poor blood glucose control in patients (P = 0.001). This finding is consistent with the studies conducted in Malaysia, Japan, and Australia that found a significant association between dyslipidemia and poor blood glucose control [14, 26, 27].

For many people with diabetes, the challenging part of the treatment plan is to determine how to eat and following a diet. Every person with diabetes must actively participate in training, self-management, and treatment planning with their health care team, including in the development of their individual diet plan [28]. In the present study, the mean vegetable intake was 3 days a week with 1.5 servings a day, and the mean fruit intake was 4.5 days a week with the mean intake of 1.8 servings a day. Our study data are consistent with the mean fruit and vegetable intake reported in the domestic studies. However, it is far from the recommendations of the food pyramid which are based on a daily intake of 2–4 fruit units and 5–3 vegetable units [7] and the recommendations of the International Diabetes Federation (IDF) which are based on the daily use of at least three units of fruit and vegetables in individuals [2]. Also, in our study, there was a significant relationship between the mean number of nutrition counseling services provided and blood glucose control (P = 0.048), such that patients who had experienced more nutrition counseling had more favorable blood glucose control status.

Proper and regular physical activity reduces insulin resistance in people with diabetes. Therefore, the American Diabetes Association (ADA) has recommended that adults with both type 1 and type 2 diabetes should exercise for at least 150 minutes of moderate-to-vigorous-intensity aerobic activity per week (at least 3 days per week, without interruption, more than 2 consecutive days) [28]. In our study, 247 (80.2%) of the participants did not exercise normally during the week, but 61 (19.8%) reported a mean exercise of 4.56 ± 1.8 days per week and 0.37 ± 0.16 minutes per day, which indicates an undesirable level of proper physical activity in the rural areas of the province under study.

Comorbidity is common in diabetic patients. These conditions have a significant impact on the treatment and management of type 2 diabetes, such that hypertension has also been reported in a significant proportion of adults with diabetes, and patients with hypertension alone have often shown evidence of insulin resistance [29, 30]. Our study showed that there was a significant relationship between having comorbidity (hypertension, dyslipidemia) and glycated hemoglobin

levels, such that those with controlled diabetes had less comorbidity than those with uncontrolled one (based on the chi-square test, P = 0.044). These findings are in line with studies conducted in Asia and Australia [14, 18, 26, 27].

In our study, no significant relationship was found between other variables including income level, occupation, education level, marital status, etc. and blood glucose control status. These findings are consistent with some of the findings from domestic and Arabic studies, respectively indicating that there was no significant relationship between (cigarette) smoking and occupation with blood glucose control levels [6, 25], but are inconsistent with other studies in Japan and Ethiopia, which respectively indicated a significant relationship between (cigarette) smoking and occupation with blood glucose control levels [19, 26]. The reason for this lack of correlation between some variables and glucose control levels can be attributed to the homogeneity of some variables in the rural statistical population followed by the homogeneity of variables among the patients under study, such that, in our study, 83% of participants were married, 97% had education level less than a high school diploma, 98% had an income of less than 2 million Tomans, 72% of women were housewives, and 2% were cigarette and hookah smoker. Such homogeneity among participants may affect the above-mentioned variables.

Limitations of the study

This study faced some difficulties and limitations that attempted to be adjusted by the following strategies. The first limitation was the lack of proper cooperation of patients during the study stages due to the parallelization of the project implementation time with the agricultural season in the rural areas of the province. It was attempted to attract cooperation by providing patients with proper justification for the importance of the plan and properly encouraging them to participate in the plan as well as by using flexible scheduling to invite patients. The second limitation was the illegibility of some medical records. The solution adopted for this limitation was to obtain consultative and technical advice from the medical staff of the study center and to randomly replace the illegible medical records with the new ones.

Conclusion

The findings of our study showed the frequency and relevance of some of the factors affecting blood glucose control as well as poor blood glucose control status in patients with type 2 diabetes in rural areas (patients were treated under the supervision of government healthcare centers).

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Ethical considerations

This research has a code of ethics No. 1396.276 and date of approval: 18.2.2018. All participants were given the necessary information regarding the purposes of the project and the confidentiality of the information. The participants voluntarily participated in the project after completing the informed consent form.

Conflict of interest

The authors report no conflicts of interest in this study.

REFERENCES

1. World Health Organization. Global report on diabetes. 2016. https://www.who.int/publications-detail-redirect/9789241565257.
2. IDF DIABETES ATLAS Eighth edition 2017. International Diabetes Federation 2017.
3. World Health Organization. Facts Sheets. http://who.int/mediacentre/factsheets/fs312/en/.
4. Ministry of Health and Medical Education. Golestan University of Medical Sciences. prevalence of diabet in golestan province. 2017 May 29.
5. Fallah S, Rostamzadeh S. Success of the family practice plan in diabetes control. Journal of Health. 2016; 7(4): 417–24.
6. Khazaei S, Saatchi A, Mirmoeini R, et al. Assessing treatment and care in patients with type 2 diabetes in rural regions of Hamadan Province in 2013. Scientific Journal of Hamadan University of Medical Sciences. 2015; 21(4): 318.
7. Delpisheh A, Azizi H, Dantalab Es, et al. Quality of care and blood sugar control in type II diabetic patients of rural areas under the care by family physicians. Iranian Journal of Diabetes and Metabolism. 2016; 14(3): 189–198.
8. Al-Kaabi J, Al-Maskari F, Saadi H, et al. Physical activity and reported barriers to activity among type 2 diabetic patients in the United arab emirates. Rev Diabet Stud. 2009; 6(4): 271–278, doi: 10.1900/RDS.2009.6.271, indexed in Pubmed: 20043039.
9. Al Balushi KA, Al-Haddabi M, Al-Zakwani I, et al. Glycemic control among patients with type 2 diabetes at a primary health care center in Oman. Prim Care Diabetes. 2014; 8(3): 239–243, doi: 10.1016/j.pcd.2014.01.003, indexed in Pubmed: 24472420.
10. Alsulaiman TA, Al-Ajmi HA, Al-Qahtani SM, et al. Control of type 2 diabetes in King Abdulaziz Housing City (Iskan) population, Saudi Arabia. J Family Community Med. 2016; 23(1): 1–5, doi: 10.4103/2230-8229.172221, indexed in Pubmed: 26929722.
11. Yue J, Mao X, Xu K, et al. Prevalence, Awareness, Treatment and Control of Diabetes Mellitus in a Chinese Population. PLoS One. 2016; 11(4): e0153791, doi: 10.1371/journal.pone.0153791, indexed in Pubmed: 27096738.
12. Ding L, Xu Yu, Wang L, et al. 2010 China Non-communicable Disease Surveillance Group. Prevalence and control of diabetes in Chinese adults. JAMA. 2013; 310(9): 948–959, doi: 10.1001/jama.2013.168118, indexed in Pubmed: 24002281.
13. Ghorbani Be, Yazdanbood A, Amini Sa, et al. Quality of care in 100 diabetic patients in a diabetes clinic in Ardabil. Journal of Ardabil University of Medical Sciences. 2012; 12(3): 239–247.

14. Mahmood MI, Daud F, Ismail A. Glycaemic control and associated factors among patients with diabetes at public health clinics in Johor, Malaysia. Public Health. 2016; 135: 56–65, doi: 10.1016/j.puhe.2015.07.043, indexed in Pubmed: 26976488.

15. Heidari S, Shirazi F, Sanjari M, et al. Factors influencing glycemic control in type 2 diabetic patients referred to the Institute of Endocrinology and Metabolism, University of Iran Medical Sciences. Iranian Journal of Diabetes and Lipid. 2010; 9(4): 365–375.

16. Amini M, Mehdigoya M, Delavaei A, et al. Quality of diabetic management in Iran in 2004-2006. Journal of Medical Council of Islamic Republic of IRAN. 2008: 20–29.

17. Montazem SH, Soleimani A, Hosseini SH, et al. Care quality of patients with diabetes type 2 in the rural areas of Malekan, Iran. Journal of North Khorasan University of Medical Sciences. 2011; 3(3): 75–82, doi: 10.29252/jnkums.3.3.75.

18. Al Mansari A, Obeid Y, Islam N, et al. GOAL study: clinical and non-clinical predictive factors for achieving glycemic control in people with type 2 diabetes in real clinical practice. BMJ Open Diabetes Res Care. 2018; 6(1): e000519, doi: 10.1136/bmjdrc-2018-000519, indexed in Pubmed: 30023075.

19. Kassahun T, Eshetie T, Gesesew H. Factors associated with glycemic control among adult patients with type 2 diabetes mellitus: a cross-sectional survey in Ethiopia. BMC Res Notes. 2016; 9: 78, doi: 10.1186/s13104-016-1896-7, indexed in Pubmed: 26861243.

20. Hashemi Nazari S, Bigdelli MA, Khodakarim S, et al. Estimating the effect of direct and indirect factors on glycemic control in type II diabetic patients by path analysis. Iranian Journal of Diabetes and Metabolism. 2018; 2(1), doi: 10.31031/gjem.2018.02.000528.

21. Alramadan MJ, Afroz A, Hussain SM, et al. Patient-related determinants of glycaemic control in people with type 2 diabetes in the gulf cooperation council countries: A Systematic Review. J Diabetes Res. 2018; 2018: 9389265, doi: 10.1155/2018/9389265, indexed in Pubmed: 29682584.

22. Takahashi PY, St Sauver JL, Finney Rutten LJ, et al. Health outcomes in diabetics measured with Minnesota Community Measurement quality metrics. Diabetes Metab Syndr Obes. 2015; 8: 1–8, doi: 10.2147/DMSO.S71726, indexed in Pubmed: 25565873.

23. Husdal R, Thors Adolfsson E, Leksell J, et al. Associations between quality of work features in primary health care and glycaemic control in people with Type 2 diabetes mellitus: A nationwide survey. Prim Care Diabetes. 2019; 13(2): 176–186, doi: 10.1016/j.pcd.2018.11.005, indexed in Pubmed: 30545793.

24. Iranparvar Alamdari M, Yazdanbood A, Islam Panah S. Quality of care in100diabetic patients in a diabetes clinic in Ardabil. Ardabil J Med Sci. 2012; 12(3): 239–247.

25. Badedi M, Solan Y, Darraj H, et al. Factors Associated with Long-Term Control of Type 2 Diabetes Mellitus. J Diabetes Res. 2016; 2016: 2109542, doi: 10.1155/2016/2109542, indexed in Pubmed: 28090538.

26. Hu H, Hori Ai, Nishiura C, et al. Japan Epidemiology Collaboration on Occupational Health Study Group. Hba1c, Blood Pressure, and Lipid Control in People with Diabetes: Japan Epidemiology Collaboration on Occupational Health Study. PLoS One. 2016; 11(7): e0159071, doi: 10.1371/journal.pone.0159071, indexed in Pubmed: 27437997.

27. Nanayakkara N, Ranasinha S, Gadowski AM, et al. Age-related differences in glycaemic control, cardiovascular disease risk factors and treatment in patients with type 2 diabetes: a cross-sectional study from the Australian National Diabetes Audit. BMJ Open. 2018; 8(8): e020677, doi: 10.1136/bmjopen-2017-020677, indexed in Pubmed: 30121593.

28. Care D. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes — 2019. Diabetes Care. 2018; 42(Supplement 1): S13–S28, doi: 10.2337/dc19-s002.

29. Long AN, Dagogo-Jack S. Comorbidities of diabetes and hypertension: mechanisms and approach to target organ protection. J Clin Hypertens (Greenwich). 2011; 13(4): 244–251, doi: 10.1111/j.1751-7176.2011.00434.x, indexed in Pubmed: 21466619.

30. Nowakowska M, Zghebi SS, Ashcroft DM, et al. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. BMC Med. 2019; 17(1): 145, doi: 10.1186/s12916-019-1373-y, indexed in Pubmed: 31345214.

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Optimization of type 2 diabetes mellitus control in Egyptian patients

ABSTRACT

Background. Optimum management for a patient with type 2 diabetes mellitus (T2DM) requires periodic evaluation and monitoring of the patient's risk factors to measure its impact on different classes of treatment. Also the diabetes complications must be evaluated and initial review of drug history. This study aims to analyze clinical characteristics, risk factors, and contributions of each variable on predictive performances of each protocol used in the treatment of T2DM patients.

Methods. A comparative description, a study of 2000 Egyptian patients. Patients were categorized into eight groups according to the treatment protocol used. Multivariate logistic regression was applied to assess the probability of each protocol to reach target glycated hemoglobin A_{1c} (HbA_{1c}) in comparison to the standard protocol metformin + SU (protocol A)

Results. The proportion of patients in our study reaching $HbA_{1c} \leq 7\%$ ranged between 48.9% in dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) group (protocol H), and 59.2% in metformin + DPP-4 inhibitors group (protocol B). In subgroup analysis according to disease duration (≤ 8 years duration), mean HbA_{1c} spanned from 7.4 ± 0.49% in SU monotherapy (protocol D) to 8.6 ± 0.5% in metformin + SU; the likelihood of reaching $HbA_{1c} > 7$ was lower in the protocol A and protocol B.

Conclusion. Patients not controlled on metformin alone with lifestyle modification should be switched to either protocol A or protocol B based on the preferential clinical outcome if there is no contraindication, as these two protocols are associated with the best result and a high percentage of patients reaching target HbA_{1c}. (Clin Diabetol 2020; 9; 6: 433–441)

Introduction

Type 2 diabetes mellitus (T2DM) is considered one of the major worldwide public health problems. It is mainly a consequence of the currently observed bad lifestyle behavior such as sedentary life, fast food and obesity, which is considered an essential contributor to T2DM worldwide [1]. By 2030, it is expected that around half of the adult population in the world will be overweight (BMI 25–29.9 kg/m^2) or obese (BMI > 30 kg/m^2) [2]. Thus, diabetes prevalence is predicted to rise to 693 million worldwide by 2045 [3]. T2DM is associated with a large number of complications and increased mortality [4, 5], as it is the main cause of renal failure [6–8], blindness, and leg amputations [9]. Also, diabetes mellitus has of cardiovascular complications, the major cause of death in patients with diabetes [10]. So, patient quality of life reduces significantly with this disease, especially if uncontrolled, and life expectancy is decreased by, on average, eight years compared with healthy people [3].

The American Diabetes Association's Standards of Medical Care in Diabetes [11] focuses on diet and other non-pharmacological measures for the management of T2DM, but the concept of these measures is not applicable in many of primary health care systems [12, 13]. Optimum management for a patient with diabetes requires an initial evaluation of the patient's

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risk factors for careful selection of different classes of treatment. Additionally, diabetes complications, as well as medical history should be evaluated [14]. So far metformin is the first-line treatment for T2DM unless there are contraindications, either metformin alone or with lifestyle modifications or in combination with other agents [15]. In comparison with sulfonylureas (SUs), metformin as first-line therapy has a good impact on target HbA_{1c}, weight, and cardiovascular mortality [16]. However, choosing a second-line therapy is challenging, because it differs according to patient characteristics and risk factors.

A lot of studies suggests that each new class of treatment if added to metformin generally lowers HbA_{1c} by approximately 0.7–1.0% [17]. If the HbA_{1c} target is not achieved after approximately 3 months, a combination of metformin and any one of the preferred six treatment options should be considered: SU, thiazolidinedione, dipeptidyl peptidase 4 (DPP-4) inhibitor, sodium glucose cotransporter 2 (SGLT2) inhibitor, glucagon like peptide (GLP-1) receptor agonist, or basal insulin; the choice of agent to add is based mainly on the drug effects, side effects and patient factors. Nowadays, the choice of a second agent to add to metformin is controversial. Rather, drug choice is based on avoidance of side effects, particularly risk of hypoglycemia and weight gain, cost, and patient preference [18].

A study including 2677 adult American patients with self-reported T2DM called National Health and Nutrition Examination Survey showed that mean HbA_{1c} was reduced with treatment with different classes, but still didn't reach the recommended treatment target [19]. Additionally, the actual effectiveness in clinical practice is mostly unknown.

Aim of the study

Our study was designed to identify clinical characteristics, risk factors affecting target goal control and likelihood of each protocol to achieve target HbA_{1c} in unselected T2DM patients.

Methods

A comparative descriptive, observational study. Representative sample of adult T2DM patients who received treatment at several diabetes outpatient clinics were assessed to evaluate different treatments' effects on HbA_{1c}, the relationship between different treatments and patient characteristics, risk factors and proportion of diabetes complication in outpatient clinics of the following hospitals (Ahmed Maher Hospital, National Diabetes Center, Alasr Elainy Hospital, Eldemerdash Hospital and Elsalam Hospital) in the period from January 2017 to February 2019.

Patients received metformin (Glucophage, 500 and 850 mg tablets, Bristol Myers Squibb, NY) as monotherapy (protocol C). During the 4-week run-in period, patients were treated with 500 to 2550 mg/day of metformin divided into one to three doses. The dose was adjusted during the first 3 weeks of the run-in to (1) achieve and maintain target fasting blood glucose (FBG) levels of 90–126 mg/dL, or (2) the maximally tolerated dose, or (3) a maximum daily dose of 2550 mg. The patient's metformin dose was not changed after the fourth week of the run-in period, unless a dose reduction was necessary for clinical reasons. At the end of the run-in period, patients who were not able to achieve the FBG target of 90–126 mg/dL on metformin only were randomized to one of four treatment regimens: (1) metformin and biphasic insulin aspart (protocol E) (70% protaminated insulin aspart, 30% soluble insulin aspart, NovoLog Mix 70/30) administered within 10 min before the start of dinner; (2) metformin and Glibenclamide 10 mg twice daily (protocol A) or (3) metformin and sitagliptin (protocol B) 100 mg daily dose or (4) metformin + SU + insulin NPH (protocol F). The dose adjustments were based on twice-weekly self-monitored blood glucose (SMBG) assessments. SU monotherapy (Glibenclamide) 10 mg twice daily (protocol D). DPP-4 inhibitors monotherapy (sitagliptin) 100 mg daily dose (protocol H). SU (Glibenclamide 10 mg twice daily) + insulin NPH (protocol G). The starting insulin dose was 0.16 U/kg. During the first 4 weeks of treatment, the insulin dosage was adjusted by 2–6 U to achieve FBG levels of 90–126 mg/dL.

For all subjects in groups, patient education programs, and counseling with oral and printed material about types of food suitable for type 2 diabetes, lifestyle modifications, any potential dietary factors that may be harmful to patients, and the importance of adherence to medication and home self-measurement.

A total of 2000 Egyptian patients, who were categorized into eight groups according to the protocol used, were recruited.

Patient data collection included standardized medical examinations, patient interviews, blood sample collection and medical history review. We analyzed age, sex, diabetes duration (DD), HbA_{1c}, low-density lipoprotein (LDL), lipid-lowering medication (LW), systolic and diastolic blood pressure (BP), antihypertensive medication, estimated glomerular filtration rate (eGFR), cumulative microalbuminuria, body mass index (BMI), smoking, physical activity (PA), and a history of cardiovascular disease (CVD) for each protocol group.

We used cut-off $\leq 7\%$ instead of $< 7\%$ as HbA_{1c} goal in Egyptian outpatient clinics standard, since to most clinicians, 7% is the treatment goal (according to hospitals protocols). A smoker was defined as

smoking one or more cigarettes per day, or who had stopped smoking within the past 3 months. Estimated GFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation: $175 \times$ serum creatinine/88.4 $1.154 \times$ age-0.203 for men, and: $175 \times$ serum creatinine/88.4$-1.154 \times$ age-0.203×0.742 for women [20]. Cumulative microalbuminuria was defined as urine albumin excretion > 20 mcg/min in two of three consecutive tests. History of CVD and CHD was defined as history of at least one CVD or CHD. Physical activity was defined according to the Center for Disease Control and Prevention (CDC): moderate physical activity — walking at a moderate or brisk pace of 3 to 4.5 mph on a level surface inside or outside; mild — walking at a pace of less than 3 to 4.5 mph; severe — race-walking and aerobic walking at a pace of 5 mph or faster [21]. The definition of T2DM used in this study was a patient treated with oral hypoglycemic agents (OHAs) only, or onset age of diabetes at the age of $\geq$ 40 years and treated with insulin combined with oral hypoglycemic agent. To ensure at least six months of continuous medication, enrolled were only patients treated in Egypt outpatient clinics who had filled at least six-monthly prescriptions.. One prescription generally corresponds to one-month continuous treatment. Thus, six filled prescriptions correspond to at least six months of medication.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and ranges, and as medians when the data were nonparametric. Comparisons between two parallel groups with continuous data were performed using an independent t test, while similar non-parametric categorical data were compared using the chi-square test and non-parametric continuous data were compared using the Mann Whitney test. Univariate and multivariate analyses were used to predict influence of clinical characteristics and protocol type on the likelihood of reaching HbA_{1c} > 7.0% using metformin and SU as a reference. The confidence interval was set at 95%. Thus, the P value was considered significant at P < 0.05. Statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS® 25), and R program software version 9.2.

Results
Treatment regimens

Of the 2000 patients treated with the most common prescribed treatment, 9.8% were treated with metformin monotherapy (protocol C), 9.2% SU monotherapy (protocol D), 25.7% metformin + SU (protocol A), 14.2% metformin + DPP-4 inhibitors (protocol B),

10.6% metformin + insulin NPH (protocol E), 10.5% metformin + SU + insulin NPH (protocol F), 11.3% SU + insulin NPH (protocol G), 8.7% DPP-4 inhibitors monotherapy (protocol H).

Clinical characteristics

Age varied between 53.1 ± 7.1 and 57.2 ± 6.3 years in the treatment groups; diabetes duration 7.2 ± 2.1–10.3 ± 2.1 years; BMI 26.9 ± 3.9–30.3 ± 5.8 kg/m^2; eGFR 52.1 ± 7.01–55.1 ± 9.3 ml/min/1.73 m^2; proportion with cumulative microalbuminuria 23–33%; history of CVD 24.3–28.8% (Table 1). Patients on metformin + SU had the highest duration of diabetes, baseline HbA_{1c} and proportion of smokers; patients on metformin monotherapy had a shorter duration of diabetes, a lower proportion of patients with microalbuminuria, and a lower proportion of patients with CVD than the other protocols. Patients on metformin + SU + insulin NPH were older, had higher eGFR, and more frequent antihypertensive treatment; there were a higher proportion of women on all treatments.

Treatment results

Comparing glycated hemoglobin A_{1c} (HbA_{1c}) between the groups, there were significant differences, as it ranged from 7.6 ± 0.49 in metformin + SU + insulin NPH (lowest) to 8.6 ± 5.3% in metformin + SU (highest), P < 0.0001. The proportion of patients reaching $HbA_{1c} \leq 7\%$ ranged between 48.9% in DPP-4 inhibitors monotherapy, and 59.2% in metformin + DPP-4 inhibitors. In a subgroup of newly diagnosed patients (≤ 8 years duration), mean HbA_{1c} spanned from 7.4 ± 0.49% in SU monotherapy, to 8.6 ± 0.5 in metformin + SU. Patient with diabetes duration > 8 years has HbA_{1c} range from 7.57 ± 0.51 SU monotherapy to 8.65 ± 0.53 in metformin + SU (Table 2).

The percent of patients reaching targets for blood pressure and LDL ranged between 41.2% to 49.3% and 23.5% to 36.1%, respectively (Table 2). Comparisons between men and women (Table 3) showed significant differences in the odds of obtaining $HbA_{1c} \leq 7$ in only two treatment groups (protocol A and B). There were slightly higher proportions of men among those who reached $HbA_{1c} \leq 7\%$ in all treatment groups. Differential impact of different variables on the likelihood of having HbA_{1c} such as age, sex, use of lipid-lowering agents (lowest impact), physical activity, disease duration, body mass index, and estimated glomerular filtration rate (highest impact) is presented in Figures 1 and 2.

Data in Table 4 and Figure 3 give the likelihood of having HbA_{1c} >7% in each group and the impact of each variable compared to patients on metformin + SU (reference). Patients on all other pharmacological

Table 1. Clinical characteristics of T2DM patients on most commonly prescribed treatment, 2017

Protocol		A n = 514	B n = 284	C n = 196	D n = 184	E n = 211	F n = 211	G n = 226	H n = 174
Age (years)	Mean ± SD	54.53 ± 6.9	54.51 ± 6.8	55.7 ± 6.5	55.3 ± 7.1	53.5 ± 7.2	56.1 ± 7.5	53.1 ± 7.1	57.2 ± 6.3
Gender Male/female	%	40.7/59.3	39.1/60.9	34.2/65.8	42.4/57.6	40.8/59.2	31.8/68.2	43.4/56.6	36.2/63.8
Diabetes duration	Mean ± SD	10.3 ± 2.1	8.7 ± 2.0	7.2 ± 2.1	7.6 ± 1.9	7.5 ± 2.7	7.3 ± 1.8	7.5 ± 2.4	7.5 ± 2.0
Smokers	%	24.7	21.8	23	17.9	20.4	16.8	16	22.5
BMI [kg/m^2]	Mean ± SD	27.9 ± 5.1	28.3 ± 4.9	28.8 ± 4.4	26.9 ± 3.89	30.3 ± 5.8	28.8 ± 5.4	28.2 ± 4.7	29.1 ± 5.1
HbA$_{1c}$ [mmol/mol]	Mean ± SD	9.27 ± 0.18	8.6 ± .17	7.8 ± .15	7.9 ± 0.53	7.6 ± 0.2	7.8 ± 0.19	8.2 ± 0.18	8.1 ± 0.17
BP [mm Hg]	%	43	37.7	35	44	46	42	40	42.5
Use of lipid-lowering agents	%	57.8	63.7	61.2	58.2	62	60.2	46.9	56.5
eGFR	Mean ± SD	52.6 ± 7.7	53.3 ± 8.1	53.5 ± 7.3	52.8 ± 7.91	55.1 ± 9.33	53.4 ± 8.7	52.1 ± 7.01	54.2 ± 6.88
Microalbuminuria	%	30	23	26	32	28	29.9	33	27
History of CVD	%	28.8	26.1	25.5	25	28	28.4	24.3	26.4
Physical activity (low)	%	49.6	49	53	43.5	27.5	49.3	50	47.1
Physical activity (moderate)	%	29.6	29.9	27	32.6	27.5	32.7	30.5	29.9
Physical activity (high)	%	20.8	21	19	23.9	27.5	18	19.5	23
Vaccinated with influenza/pnemococcal	%	4.5/4.5	4.2/3.2	2.6/2.6	6.5/6	5.7/5.3	3.3/3.3	4/4	3.4/3.4

Means ± standard deviation (Mean ± SD) and proportions (%); BMI — body mass index; HbA$_{1c}$ — hemoglobin A$_{1c}$; BP — blood pressure; eGFR — estimated glomerular filtration rate; CVD — cardiovascular disease; T2DM — type 2 diabetes mellitus

Table 2. Risk factor control

		A n = 514	B n = 284	C n = 196	D n = 184	E n = 211	F n = 211	G n = 226	H n = 174
HbA$_{1c}$	Mean ± SD	8.6 ± 0.53	8.2 ± 0.51	7.5 ± 0.6	7.6 ± 0.52	7.7 ± 0.61	7.6 ± 0.49	7.7 ± 0.51	7.7 ± 0.55
HbA$_{1c}$ ≤ 7	%	56.6	59.2	51.5	50	53.6	57.3	51.8	48.9
HbA$_{1c}$ for diabetes duration (> 8 years)	Mean ± SD	8.65 ± 0..53	8.31 ± 0.54	7.61 ± 0.5	7.57 ± .51	7.64 ± 0.51	7.7 ± 0.53	7.6 ± .52	7.8 ± 0.46
HbA$_{1c}$ for diabetes duration (≤ 8 years)	Mean ± SD	8.6 ± 0.5	8.2 ± .52	7.6 ± .53	7.4 ± 0.4	7.6 ± 0.53	7.5 ± 0.54	7.7 ± 0.5	7.6 ± 0.55
Diastolic	Mean ± SD	82.3 ± 8.8	81.1 ± 8.9	81.5 ± 9.3	82 ± 9.2	81.5 ± 9.5	80.1 ± 9.1	82 ± 9.6	81 ± 8.7
Systolic	Mean ± SD	132.5 ± 14.2	130.6 ± 14.5	131.1 ± 15	132 ± 14.7	131 ± 15	132 ± 14.8	131 ± 15.5	132.7 ± 13.8
BP < 130/80	%	44	45.4	44.9	44.6	47.9	49.3	41.2	45
LDL	Mean ± SD	118.5 ± 25	117 ± 24	120 ± 25	121 ± 25.6	119 ± 23.6	120.6 ± 24	118.7 ± 25.3	119.5 ± 26
LDL < 100	%	26.8	27.8	23.5	27.7	23.7	36.1	28.3	27
HDL	Mean ± SD	35 ± 5.6	34.8 ± 5.2	34 ± 6.1	36.1 ± 5.7	35 ± 5.4	36 ± 6	35.5 ± 5.3	35 ± 5.3

HbA$_{1c}$ — hemoglobin A$_{1c}$; LDL — low-density lipoprotein; HDL — high-density lipoprotein

Table 3. Glycemic control in men and women

		A	B	C	D	E	F	G	H
		n = 514	n = 284	n = 196	n = 184	n = 211	n = 211	n = 226	n = 174
HbA$_{1c}$ mean M	n	209	111	67	78	86	67	98	63
	Mean ± SD	8.66 ± 0.53	8.2 ± 0.6	7.7 ± 0.51	7.6 ± 0.52	7.6 ± 0.54	7.7 ± 0.53	7.7 ± 0.52	7.6 ± 0.51
	n	305	173	129	106	125	144	128	111
HbA$_{1c}$ mean W	Mean ± SD	8.63 ± 0.5	8.4 ± 0.52	7.6 ± 0.53	7.7 ± 0.53	7.6 ± 0.53	7.5 ± 0.53	7.85 ± 0.6	7.7 ± 0.5
P value*		0.539	0.033	0.143	0.662	0.834	0.664	0.727	0.707
HbA$_{1c}$ ≤ 7 M	%	63	67	53	56	60	58	52	57
HbA$_{1c}$ ≤ 7 W	%	52	54	50	45	49	57	51.5	44
P value*		0.008	0.026	0.385	0.090	0.063	0.492	0.525	0.068

*P value of categorical data were performed using the chi-square test; M — men; W — women
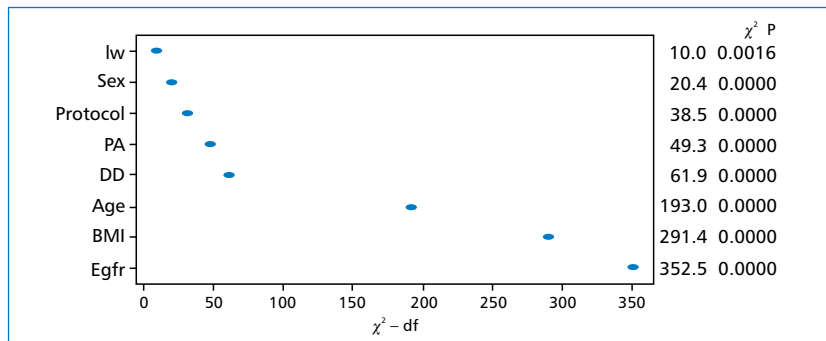
Figure 1. Contribution of each individual variable on predictive performance of the final multivariate model. Lw — lipid-lowering medication; PA — physical activity; DD — disease duration; BMI — body mass index; eGFR — estimated glomerular filtration rate

treatment regimens had a significantly higher likelihood of having HbA$_{1c}$ > 7%, ranging from) OR 2.89; 95% CI 1.41–5.92(in metformin + SU + insulin NPH group to (OR 5.22; 95% CI 2.58–10.56(in DPP-4 inhibitors group, except for patients on metformin + DPP-4 inhibitors (OR 1.71; 95% CI 0.94–3.12) where the difference versus metformin + SU regimen was insignificant. Patients on metformin + DPP-4 inhibitors, in general, had the lowest likelihood of having HbA$_{1c}$ > 7%. Patients on SU monotherapy and DPP-4 inhibitors monotherapy had the lowest likelihood of reaching the target HbA$_{1c}$ ≤ 7. The agreement between predicted data with real observation data is demonstrated in figure 3, indicating the internal validity of the developed regression model. Moreover, area under ROC curve was significantly higher (P < 0.0001), confirming the internal validity.

Table 5 shows that our model had good predictability and there is high concordance (0.96) between observed and predicted data.

Discussion

The results of the present study proved that outpatient clinics in Egypt apply world treatment guidelines in routine clinical care, as high percent of patients with T2DM (70.8%) were treated with metformin alone or in combination with other agents [22].

Fewer studies describing different treatment protocols according to different patient characteristics in real practice in Egypt are available, but there are many studies evaluating treatment effects of different T2DM medications. This study is a nation-wide cross sectional study analyzing clinical characteristics and impact or risk factors among T2DM patients with standard protocol (metformin and SU), as well as the most commonly used treatment regimens.

Most patients (> 25%) were prescribed sulfonylureas add on to first-line metformin. This result matched to a population-based study that assessed which class of drugs was most commonly prescribed as second-line treatment added to metformin in the period between 2011 and 2015 where the results showed that these drugs are sulfonylureas [23]. Similarly, the study of Zekarias et al. [24] found that more than 50% of patients were prescribed sulfonylureas.

When comparing male and female sexes between each protocol, we found that almost all protocols
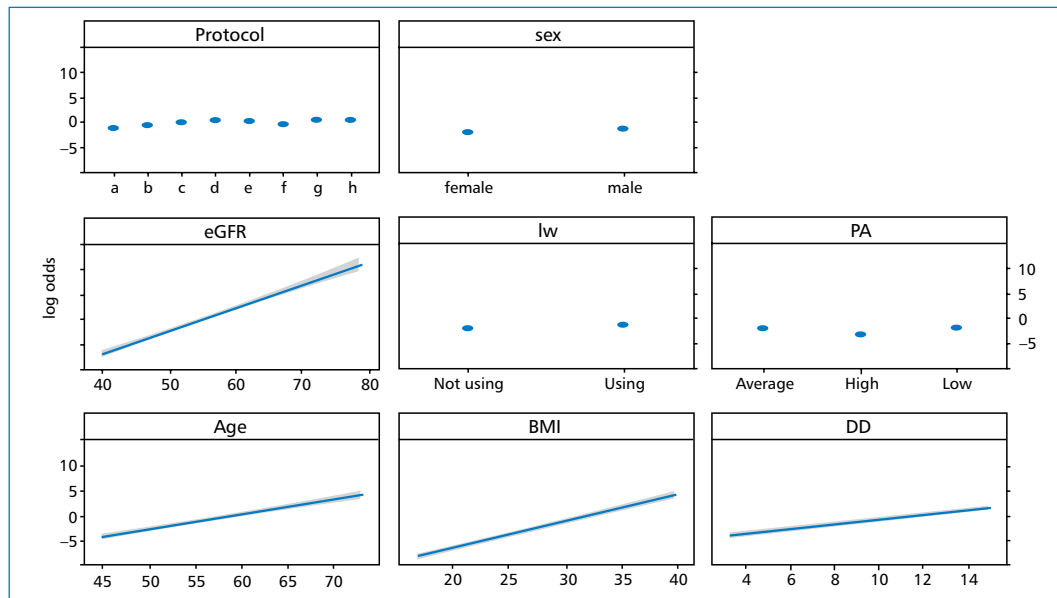
Figure 2. Change in log (odds ratio) by changing each independent variable. Lw — lipid-lowering medication; PA — physical activity; DD — disease duration; BMI — body mass index; eGFR — estimated glomerular filtration rate

Table 4. Multivariate regression for significant variables and each protocol to estimate likelihood [(OR) with 95% CI] of having HbA$_{1c}$ > 7%

Clinical variable	Univariate analysis			Multivariate analysis		
	Regression coefficient	SE	P value	Adjusted OR	95%CI	P value
Age (years)	0.133	0.008	< 0.001	1.35	1.29–1.41	< 0.0001 (S)
BMI [kg/m^2]	0.178	0.012	< 0.001	1.71	1.61–1.82	< 0.0001 (S)
eGFR [mL/min]	0.173	0.009	< 0.001	1.58	1.5–1.65	< 0.0001 (S)
Protocol						
B	−0.104	0.15	0.49	1.71	0.94–3.12	0.081 (NS)
C	0.205	0.17	0.22	3.92	1.96–7.81	0.0001 (S)
D	0.266	0.17	0.12	5.18	2.52–10.66	< 0.0001 (S)
E	0.124	0.16	0.45	4.41	2.17–8.96	< 0.0001 (S)
F	-0.03	0.17	0.86	2.89	1.41–5.92	0.0038 (S)
G	0.195	0.16	0.22	5.8	2.91–11.54	< 0.0001 (S)
H	0.312	0.176	0.08	5.22	2.58–10.56	< 0.0001 (S)
Sex	0.34	0.093	< 0.0001	2.23	1.58–3.17	< 0.0001 (S)
PA level						
High (PA)	−0.32	0.13	0.013	0.37	0.23–0.6	< 0.0001 (S)
Low (PA)	0.23	0.1	0.028	1.93	1.32–2.83	0.0007 (S)
Disease duration (years)	0.24	0.021	< 0.0001	1.6	1.42–1.8	< 0.0001 (S)
Lipid-lowering agent use	0.0021	0.092	0.98	0.58	0.41–0.81	0.0016 (S)

OR — odd ratio; CI — confidence interval; HbA$_{1c}$ — hemoglobin A1c; eGFR — estimated glomerular filtration rate; BMI — body mass index; PA — physical activity

showed marginally higher proportions of men reaching HbA$_{1c}$ ≤ 7%, unlike a study of Ekström et al. [25] that found a proportion of women marginally higher with non-pharmacological treatment and metformin monotherapy. And there was a higher proportion of men reaching treatment goal on metformin + pre-mixed analogues containing rapid-acting insulin and metformin + SU only. However, these differences were no statistically significant, except in only two protocols (metformin and SU) and (metformin and DPP-4 inhibi-

AUC	SE	P value	95% Confidence interval	
			Lower bound	Upper bound
.963	.004	< 0.0001	.955	.970
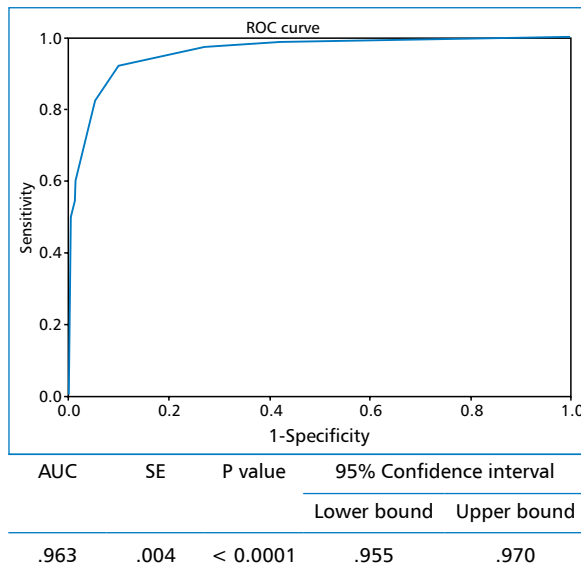
Figure 3. ROC curve of the final multivariate model

tors). Thus, the clinical significance of these minor differences is controversial.

In GRADE study [26] on 5000 patients categorized on the following medications: sulfonylureas, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists, and insulin as the second-line added to metformin found 64% of all participants reporting statin use but in our study, 58% of all participants reported statin use although new guidelines recommend statin for all patients with diabetes who are > 40 years of age, although without other cardiovascular risk. Unfortunately, this percent indicates poor compliance with the guidelines [27].

According to ADA and the European Association for the Study of Diabetes, guidelines recommend starting basal insulin when HbA_{1c} is > 9% [22]. Our findings from real practice does not support this recommendation, as there is high percent of patients with baseline HbA_{1c} > 9 treated effectively with metformin and sulfonylurea protocol and metformin and DPP-4 inhibitors protocols; this finding is similar to that of Wilding et al. [28]. This result may not be consistent with guidelines because a high proportion of patient have HbA_{1c} > 9 not because of treatment resistance but due to poor adherence to treatment regimen. On other hand, mean reduction in HbA_{1c} from baseline for those on metformin and sulfonylurea was significantly larger than all other protocols, so we conclude that treatment options for those with HbA_{1c} > 9% might not need to be limited only to insulin.

In comparison to study of Ekström et al. [25], insulin-based protocol achieved a higher proportion

of patient $HbA_{1c} \leq 7\%$, as clinician in Egypt use insulin as add on to metformin early in management. So, patient respond better than those who start insulin late. Also percent of patients achieving target LDL was significantly lower in our study, but our result matched with Ekström et al. [29], ADA, IDF and AACE guidelines that patient with metformin protocol had less history of CVD, microalbuminuria and percent of people achieving blood pressure goals as all groups ranged from 41.2–49.3%.

Yurgin et al. [30] found on German patients that around 50% of patients did not achieve target HbA_{1c} < 6.5. However, this ratio is not applicable in our study as we reached in some protocols more than 55% (metformin + SU, metformin + DPP-4 inhibitors and metformin + SU + insulin NPH. Although German study included higher number of participant, our study addressed risk factors and patient characteristics not studied in German study, such as diabetes duration, blood pressure, eGFR, LDL and body mass index.

According to ADA and EASD, Swedish and international guidelines based on trials [31, 32], metformin is the first-line treatment when lifestyle and non-pharmacological interventions are insufficient, and also a higher proportion of patient is treated with metformin monotherapy or in combination, so our real practice is consistent with this guidelines. But there are fewer studies which compare between different protocols and determine which protocol has the likelihood that patient achieve or not achieve the target; therefore, we in Table 4 found that only one protocol (metformin and DPP-4 inhibitors) was nonsignificant with standard protocol (metformin and SU) in likelihood of patient reaching HbA_{1c} > 7 and all other protocols are significant and odd ratio of patient reaching HbA_{1c} > 7 ranges from 2.89–5.8. So, we strongly recommend metformin + SU and metformin + DPP-4 inhibitors protocols, but we did not address cost, consequences, CVD exacerbation, and incidence of hypoglycemia of these protocols to make a complete judgment.

This study discusses the determinants of adequate glycemic control in T2DM population, explaining their underlying relative weights, and how they may affect the clinical decision regarding the choice of the antihyperglycemic protocol on an individual basis. The main strength point in the current study is comparative analysis of eight different and commonly used protocols in patients with diabetes as we study the effect of significant variables and how each variable, such as age, BMI, sex, physical activity, disease duration, lipid-lowering agents and eGFR, can predict the outcome (Figs 1, 2). Thus, we conclude that good outcome does not dependent only on which protocol patient will be

treated but also these variables must be evaluated first and monitored.

The major strengths of this observational study are that patients were treated at hospital outpatient clinics nation-wide, representing the real-life situation in clinical practice; also HbA$_{1c}$ analyses were quality assured.

Conclusion

The likelihood of reaching HbA$_{1c}$ > 7 is lower in the protocol A and protocol B, and other protocols are associated with a significantly higher likelihood of reaching target HbA$_{1c}$ in comparison to protocol A. Significant variables, age, BMI, sex, physical activity, disease duration, lipid-lowering agents and eGFR if controlled, can improve treatment outcome significantly.

Study limitations

There are also some limitations. Data from participating outpatient clinics may vary slightly in accuracy, although increased use of electronic dataset for data transfer can mitigate this problem. Also, around 20% of patients were excluded because of missing data. Controlling diet in this number of participants in each group is difficult and may cause slight changes in the response of each group to their medication. Blood lipid values were not measured at baseline. Instead, we used lipid-lowering medication (mostly statins) as a marker of the presence of dyslipidemia. Information regarding doses of drugs in protocols was not available, but the aim was to analyze the effect of clinical characteristics and risk factors on treatment outcome of each protocol with simulating in real practice.

Recommendations

Large, multicenter, observational studies in similar patient populations are needed to validate our conclusion.

Compliance with ethical standards

Informed consent was obtained from each patient included in the study, and the study protocol was conducted in compliance with the 1975 Declaration of Helsinki and approved by Faculty of Pharmacy, Helwan University Ethical Committee.

Conflicts of interest

None of the authors have a conflict of interest.

REFERENCES

1. Afshin A, Forouzanfar MH, Reitsma MB, et al. GBD 2015 Obesity Collaborators. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017; 377(1): 13–27, doi: 10.1056/NEJMoa1614362, indexed in Pubmed: 28604169.
2. Menke A, Casagrande S, Geiss L, et al. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. JAMA. 2015; 314(10): 1021–1029, doi: 10.1001/jama.2015.10029, indexed in Pubmed: 26348752.
3. International Diabetes Federation (2017) IDF Atlas 8th edition. International Diabetes Federation, Brussels. http://www.diabetesatlas.org (26.11.2019).
4. Park J, Peters PA. Mortality from diabetes mellitus, 2004–2008: a multiple-causeof-death analysis. Health Rep. 2014; 25(3): 12–16.
5. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation. 2009; 119(13): 1728–1735, doi: 10.1161/CIRCULATIONAHA.108.829176, indexed in Pubmed: 19307472.
6. Pugliese G, Solini A, Bonora E, et al. RIACE Study Group. Chronic kidney disease in type 2 diabetes: lessons from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study. Nutr Metab Cardiovasc Dis. 2014; 24(8): 815–822, doi: 10.1016/j.numecd.2014.02.013, indexed in Pubmed: 24780515.
7. Rao C, Adair T, Bain C, et al. Mortality from diabetic renal disease: a hidden epidemic. Eur J Public Health. 2012; 22(2): 280–284, doi: 10.1093/eurpub/ckq205, indexed in Pubmed: 21245077.
8. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007; 298(17): 2038–2047, doi: 10.1001/jama.298.17.2038, indexed in Pubmed: 17986697 **7. Bunce C, Wormald R (2008) Causes of blind certifcations in England and Wales: April 1999–March 2000. Eye. 2007; 22(7):905–9118.**
9. Vamos EP, Bottle A, Edmonds ME, et al. Changes in the incidence of lower extremity amputations in individuals with and without diabetes in England between 2004 and 2008. Diabetes Care. 2010; 33(12): 2592–2597, doi: 10.2337/dc10-0989, indexed in Pubmed: 20833865.
10. Jansson SPO, Andersson DKG, Svärdsudd K. Mortality trends in subjects with and without diabetes during 33 years of follow-up. Diabetes Care. 2010; 33(3): 551–556, doi: 10.2337/dc09-0680, indexed in Pubmed: 20009100.
11. American Diabetes Association (2019) Standards of medical care in Diabetes. Diabetes Care. 2019; 42(13): 28.
12. Orozco-Beltrán D, Gil-Guillen VF, Quirce F, et al. Collaborative Diabetes Study Investigators. Control of diabetes and cardiovascular risk factors in patients with type 2 diabetes in primary care. The gap between guidelines and reality in Spain. Int J Clin Pract. 2007; 61(6): 909–915, doi: 10.1111/j.1742-1241.2007.01367.x, indexed in Pubmed: 17504353.
13. Hermans MP, Brotons C, Elisaf M, et al. (for the OPTIMISE (OPtimal Type 2 dIabetes Management Including benchmarking and Standard trEatment) International Steering Committee). Optimal type 2 diabetes mellitus management: the randomised controlled OPTIMISE benchmarking study: baseline results from six European countries. Eur J Prev Cardiol. 2013; 20(6): 1095–1105, doi: 10.1177/2047487312449414, indexed in Pubmed: 22605788.
14. Standards of Medical Care in Diabetes-2016: Summary of Revisions. Diabetes Care. 2016; 39 Suppl 1: S4–S5, doi: 10.2337/dc16-S003, indexed in Pubmed: 26696680.
15. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359(15): 1577–1589, doi: 10.1056/NEJMoa0806470, indexed in Pubmed: 18784090.
16. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2016; 164(11): 740–751, doi: 10.7326/M15-2650, indexed in Pubmed: 27088241.
17. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011; 154(9): 602–613, doi: 10.7326/0003-4819-154-9-201105030-00336, indexed in Pubmed: 21403054.
18. Vijan S, Sussman JB, Yudkin JS, et al. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med. 2014; 174(8):

1227–1234, doi: 10.1001/jamainternmed.2014.2894, indexed in Pubmed: 24979148.

19. Ford ES. Trends in the control of risk factors for cardiovascular disease among adults with diagnosed diabetes: findings from the National Health and Nutrition Examination Survey 1999-2008*. J Diabetes. 2011; 3(4): 337–347, doi: 10.1111/j.1753-0407.2011.00148.x, indexed in Pubmed: 21767347.

20. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 130(6): 461–470, doi: 10.7326/0003-4819-130-6-199903160-00002, indexed in Pubmed: 10075613.

21. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc. 1993; 25(1): 71–80, doi: 10.1249/00005768-199301000-00011, indexed in Pubmed: 8292105.

22. Srivastava A. Bringing ADA 2019 and EASD 2018 Guidelines in Clinical Practice. Int J Diab. 2019; 22: 29.

23. Ackermann RT, Wallia A, O'Brien MJ. Correlates of second-line type 2 diabetes medication selection in the USA. BMJ Open Diabetes Res Care. 2017; 5: e000421.

24. Zekarias K, Davey C, Seaquist E. Intensification of medical management in type 2 diabetes: A real-world look at primary care practice. J Diabetes Complications. 2020; 34(1): 107477, doi: 10.1016/j.jdiacomp.2019.107477, indexed in Pubmed: 31711841.

25. Ekström N, Miftaraj M, Svensson AM, et al. Glucose-lowering treatment and clinical results in 163 121 patients with type 2 diabetes: an observational study from the Swedish national diabetes register. Diabetes Obes Metab. 2012; 14(8): 717–726, doi: 10.1111/j.1463-1326.2012.01591.x, indexed in Pubmed: 22364580.

26. Nathan DM, Buse JB, Davidson MB. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009; 32(193): 203.

27. Chamberlain JJ, Herman WH, Leal S, et al. Pharmacologic Therapy for Type 2 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med. 2017; 166(8): 572–578, doi: 10.7326/M16-2937, indexed in Pubmed: 28288484.

28. Wilding J, Godec T, Khunti K. Changes in HbA1c and weight, and treatment persistence, over the 18 months following initiation of second-line therapy in patients with type 2 diabetes: results from the United Kingdom. Clinical Practice Research Datalink BMC Med. 2018; 16: 116.

29. Handelsman Y, Mechanick JI, Blonde L, et al. AACE Task Force for Developing Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract. 2011; 17 Suppl 2: 1–53, doi: 10.4158/ep.17.s2.1, indexed in Pubmed: 21474420.

30. Yurgin N, Secnik K, Lage MJ. Antidiabetic prescriptions and glycemic control in German patients with type 2 diabetes mellitus: a retrospective database study. Clin Ther. 2007; 29(2): 316–325, doi: 10.1016/j.clinthera.2007.02.012, indexed in Pubmed: 17472823.

31. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UK-PDS 34). The Lancet. 1998; 352(9131): 854–865, doi: 10.1016/s0140-6736(98)07037-8.

32. Bolen SD, Bricker E, Samuels TA, et al. Factors associated with intensification of oral diabetes medications in primary care provider-patient dyads: a cohort study. Diabetes Care. 2009; 32(1): 25–31, doi: 10.2337/dc08-1297, indexed in Pubmed: 18931096.

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Glycaemic and weight-loss outcomes of graded doses of canagliflozin in type 2 diabetes — a real-world study

ABSTRACT

Background. Costs are the most important cause of therapeutic non-compliance. Half canagliflozin (CANA)–300 tablet has lowest cost/mg among all CANA preparations; data are unavailable on efficacy of half CANA-300. This study evaluated weight loss and glycaemic outcomes of 100 mg versus 150 mg versus 300 mg of canagliflozin as part of standard therapy.
Methods. Data, retrospectively captured from medical records of two centres in Delhi for patients > 35 years with type-2 diabetes (T2DM), and on canagliflozin, having > 6 months follow-up, were analysed. Patients were in 3-groups depending on canagliflozin dosage: Group 1 on canagliflozin 100 mg/day (1 tablet CANA--100), Group-2 on canagliflozin 150 mg/day (half tablet CANA-300), and Group 3 on canagliflozin 300 mg/day (1 tablet CANA-300). Primary endpoints were glycaemic efficacy and weight-loss.
Results. From 3,569 records evaluated, 1,232 people with T2DM on canagliflozin were screened; data from 528 individuals analysed (257, 138 and 133 in Groups: 1, 2 and 3 respectively). People in all three groups were comparable with regards to sex, T2DM duration, glycated haemoglobin (HbA$_{1c}$), haemoglobin, creatinine, lipids, albuminuria and medications. Group-2 patients were youngest and had highest BMI. Following 6-months, both absolute and percent weight-loss was significantly higher in Group-2 (–3.5 kg [–6.60–0.00]; –3.62%), followed by Group-3 (–3.0 kg [–5.3 to –0.8]; –3.33%), and lowest in Group-1 (–1.05 kg [–2.85 to –0.17]; –1.31%) (P = 0.002 and 0.014, respectively). Glycaemic efficacy was comparable among groups.
Conclusion. Half CANA-300 tablet has comparable glycaemic efficacy and weight-loss compared to single CANA-300 tablet, but superior weight-loss compared to CANA-100. (Clin Diabetol 2020; 9; 6: 442–453)

Key words: obesity canagliflozin, weight loss, diabetes reversal, euglycaemia, type 2 diabetes, cost analysis

Introduction

Diabetes and obesity, or diabesity, has become a global pandemic. Recent studies have suggested an alarming burden of diabetes and obesity in the Indian population. India currently has an overall 9% and 14–18% prevalence of diabetes and prediabetes, respectively [1, 2]. Indians are metabolically challenged, as is evidenced by nearly two decades earlier onset of diabetes coupled with one of the highest global annual rates of prediabetes progression to diabetes (14.0–18.0%, 11.0%, 6.0% and 2.5% per annum in India, China, Finland and USA, respectively) [3]. The

problem is especially acute in urban areas. The CARRS study, a population screening of 5,365 individuals from New Delhi, revealed a very high prevalence of prediabetes/diabetes of 72.7% [4]. Two studies from New Delhi reported very high rates of obesity in the general population (71.50% and 69.29% in a cohort of 1,473 and 5,336 patients, respectively) [5, 6]. Hence, it is the high prevalence of obesity which is driving this diabetes epidemic, especially in the urban areas.

Recent studies have demonstrated the importance of weight loss in not only ensuring better glycaemic control in type 2 diabetes mellitus (T2DM), but also in diabetes remission [7]. Sodium-glucose co-transporter-2 (SGLT2) inhibitors have become popular agents for managing diabetes especially in the setting of diabesity. This is due to their good glycaemic efficacy, glycaemic durability, beneficial impact on cardiovascular outcomes, low risk of hypoglycaemia, along with their mild weight-loss properties [8].

There are currently four SGLT2 inhibitors available for clinical practice in India: canagliflozin, dapagliflozin, empagliflozin and remogliflozin. In terms of selectivity for the inhibition of SGLT2, SGLT1 transporter, empagliflozin, is the most selective, whereas canagliflozin is the least selective [8]. Hence canagliflozin is believed to have some additional therapeutic potential in view of its inhibiting SGLT1 transporters present in the intestines [9]. No significant impact of canagliflozin on SGLT1 transporter in heart and kidneys has been documented [10]. The intestinal SGLT1 transporter inhibition by canagliflozin is believed to result in an additional post–prandial glucose reduction, which is not seen with other SGLT2 inhibitors [10].

One of the major limitations with long-term use of SGLT2 inhibitors in clinical practice, is the significantly increased monthly costs of treatment. Since most of the healthcare expenditure is out of pocket in India, increased monthly treatment costs have been linked to poor medication compliance, resulting in impaired glycaemic control [11, 12]. Canagliflozin is currently available in 100 mg and 300 mg tablets for clinical use in India, costing INR 54.5 (INR 0.55/mg; INR 1,635 per month) and INR 120 (INR 0.4/mg; INR 3,600 per month) per tablet, respectively [13, 14]. Treatments costs for sulfonylurea glipizide 5 mg, metformin sustained release preparation 1 g, and pioglitazone 15 mg are: INR 0.53 per tablet (monthly cost INR 63.6 for 20 mg therapy per day), INR 3 per tablet (monthly cost INR 180 for 2 g therapy per day) and INR 2 per tablet (monthly cost INR 120 for 30 mg therapy per day), respectively, highlighting nearly 10–60–times increased cost burden with SGLT2 inhibitor use in India [15]. The cost per unit of human regular insulin, human neutral protamine

Hagedorn (NPH) insulin, lispro insulin, aspart insulin and glargine insulin is INR 0.96, 0.96, 2.26 and 2.19, respectively, when used in the form of cartridges for pen fill [16–19]. The monthly cost of therapy of above 4 insulins when taken at doses of 20U/d would be INR 580, 580, 1,356 and 1,314 respectively [16–19]. Hence monthly costs of human insulin analogous (both short- and long-acting) is almost similar to that of SGLT2 inhibitors.

From costing point of view, half tablet of canagliflozin 300 mg (CANA-300) would provide 150 mg of canagliflozin at INR 60, which would be much more cost effective than taking 1.5 tablets of canagliflozin 100 mg (CANA-100) tablet at INR 81.75. However, no data are available on the glycaemic and weight-loss properties of half tablet of CANA-300 taken once a day as compared to 1 tablet of CANA-100 per day and 1 tablet of CANA-300 per day in clinical practice. Half CANA-300 tablet has the lowest cost per mg as well as the lowest monthly cost of therapy among all the different doses of canagliflozin available for clinical use. Hence, this study aimed to evaluate the glycaemic efficacy and weight loss properties of graded doses of canagliflozin (100 mg, 150 mg, 300 mg), as a part of multi–drug therapy for managing type-2 diabetes in India.

Methods

Data were retrospectively captured from the electronic medical record (EMR) database of two different centres in New Delhi. Patients with T2DM, aged > 35 years and on canagliflozin were considered for the study. T2DM onset in Indians is nearly 2 decades earlier than the western world, and the peak age of T2DM onset in Indians is in 30s and 40s [1, 20]. People > 35 years–age were considered for this study to rule out those who were likely to have latent onset autoimmune diabetes of adults and late onset T1DM [1, 20].

Patients with associated severe chronic co-morbid states like chronic liver disease (Child's B or C), renal disease (glomerular filtration rate < 60 mL/min as calculated by CKD–EPI formula), cardiac disease (including coronary artery disease and heart failure), malignancies, active infection (tuberculosis, HIV, viral hepatitis), post organ transplant, patients on psychiatry medications, and those with chronic autoimmune disorders (lupus, scleroderma), were excluded. Also, patients with history of hospital admission in the last 6 months were excluded [6]. Patients with prior use of SGLT2 inhibitors were excluded. Incomplete records were excluded from the analysis. Details of other medications being used as per standard care were noted [6]. Patients on any other medications which can cause weight loss apart
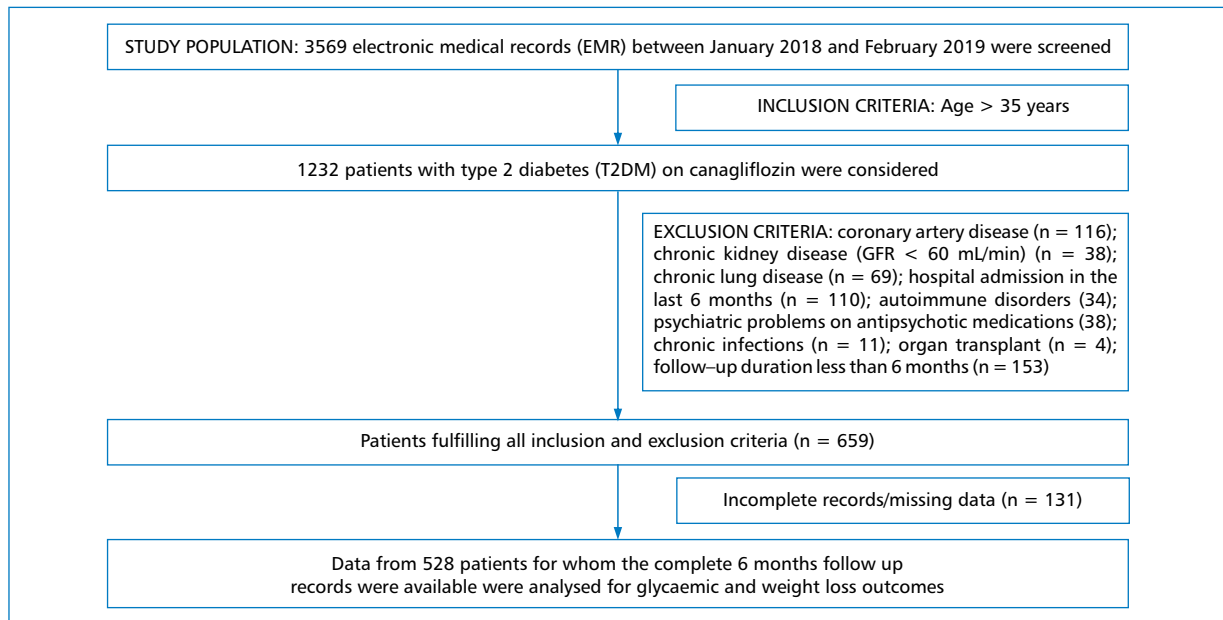
Figure 1. Flowchart of study protocol and flow of patients. GFR — glomerular filtration rate

Figure 2. A — appearance of an intact canagliflozin 300 mg tablet; **B** — appearance of split canagliflozin 300 mg tablet; **C** — storage of one-half of the split canagliflozin 300 mg tablet of use on the subsequent day

from the medications considered in this study (canagliflozin, metformin, glucagon like peptide 1 receptor agonists and orlistat) were excluded. Patients with at least 6 months follow-up data available were included in the study. The duration of this study was from January 2018 to February 2019. The entire flow of patient recruitment has been elaborated in Figure 1.

Patients were put into one of three groups depending on their canagliflozin dose: Group 1 were on canagliflozin 100 mg/day (1 tablet of CANA-100),

Group 2 were on canagliflozin 150 mg/day (half tablet of CANA-300), and Group 3 were on canagliflozin 300 mg/day (1 tablet of CANA-300).

Patients in Group-2 (canagliflozin 150 mg/d) were given a demonstration how to split the CANA-300 tablet. CANA-300 tablet is relatively a big tablet making splitting easier. Using preferably a pill-cutter, the patients were shown how to cut the CANA-300 tablet (Fig. 2A) into 2 halves (Fig. 2B). In case a pill-cutter was not available, the patients were explained that

a small kitchen knife can also be used to cut the tablet into 2 equal halves. The patients were asked to keep one of the halves in the tablet package carefully to be used the next day (Fig. 2C). They were reassured that sometimes the halves may not be exactly from the middle, but since the patient himself/herself will only be taking the other half of the tablet the subsequent day, it would average out and result in an overall intake of 15 CANA-300 tablets over a period of 30 days.

Data for the following variables were collected at baseline and after 6 months follow-up (height, weight, fasting glucose, 2-hour post prandial glucose and HbA$_{1c}$). Additionally, data were collected on haemoglobin, renal function status (creatinine), lipid-parameters (low-density lipoprotein cholesterol (LDL-C) and triglycerides) and spot urine albumin creatinine ratio (ACR) as a measure of microvascular complication. Information was noted with regards to occurrence of different adverse drug reactions, specifically, hypogly-caemia, genital infections, complicated upper urinary tract infections, fractures, euglycaemic ketosis and any other event reported by the patients.

Statistical analysis

Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 20.0 (IBM, USA). Kolmogrov-Smirnov test was used to check the normality of the variable distribution. Normally distributed variables were expressed as mean ± standard deviation. Skewed variables were expressed as median (25th–75th percentile). ANOVA was used for comparing three or more study groups. Chi-square test was used for categorical variables. An *a priori* alpha of $P < 0.05$ was considered statistically significant.

Results

A total of 3,569 medical records were screened between January 2018 and February 2019, of which 1,232 patients with T2DM were on canagliflozin. Data from 528 patients, who fulfilled all inclusion criteria and for whom at least 6-month follow-up data were available, were analysed. Out of the 528 patients, 257 patients were on canagliflozin 100 mg/day (Group 1; 1 tablet of CANA-100), 138 were on canagliflozin 150 mg/ /day (Group 2; half tablet of CANA-300) and 133 were on canagliflozin 300 mg/day (Group 3: 1 tablet of CANA--300). Demographic details, anthropometric, glycaemic, metabolic and medication profiles of the patients in the three groups have been elaborated in Table 1.

The patients in all three groups were comparable with regards to sex distribution, duration of T2DM, baseline HbA$_{1c}$, haemoglobin, renal function (creatinine), lipid parameters and microvasculature damage

(ACR), as per a direct ANOVA of the 3 groups (Table 1) as well as by a post-hoc pair wise analysis between each of the groups (Tables 2–4). The groups were also comparable with regards to use of all the other different anti-diabetes medications (metformin, sulfonylureas, dipeptidyl-peptidase-4 inhibitors, alpha glucosidase inhibitors, pioglitazone, glucagon like peptide-1 receptor agonists and insulins; as per a direct ANOVA of the 3 groups (Table 1) as well as by a post-hoc pair wise analysis between each of the groups (Tables 2–4). However, the patients in Group 2 were significantly younger as compared to patients in Groups 1 and 3 (Tables 1–4). Additionally, BMI was significantly higher in patients in Group 2 as compared to Groups 1 and 3 (Tables 1–4). Patients in Group-3 had significantly higher systolic and diastolic blood pressure (Table 3). Patients in Group-2 had a significantly higher diastolic blood pressure, but comparable systolic blood pressure as compared to Group-1 (Table 4).

Following 6 months of treatment, the absolute weight loss was highest in patients receiving canagli-flozin 150 mg/day (Group 2; –3.5 kg [–6.60 to 0.00]) as compared to those receiving 100 mg/day (Group 1; –1.05 kg [–2.85 to –0.17]) and 300 mg/day (Group 3; –3.0 kg [–5.3 to –0.8]), which was statistically sig-nificant (P = 0.002) (Table 1). The percent weight loss after 6 months of therapy (which is not effected by the higher baseline BMI) was also significantly higher in Group 2 (–3.62%) as compared to –3.33% and –1.31% in Groups 3 and Group 1 respectively, which was statistically significant (P = 0.014) (Table 1). Post-hoc analysis between each of the 3 groups re-confirmed this observation. A significantly higher absolute and percent weight loss among patients in Group-3 vs Group-1 (Table 3), Group-2 vs Group-1 (Table 4) with comparable absolute and percent weight loss among patients in Group-3 vs Group-2 (Table 2) highlights the superiority of canagliflozin 150 mg/day and 300 mg/day over canagliflozin 100 mg/day with regards to weight loss.

In terms of glycaemic efficacy, the fall in HbA$_{1c}$ after 6 months of therapy, and the final HbA$_{1c}$ were not statistically different among the three groups (P = 0.083) (Table 1). Post-hoc analysis between each of the 3 groups re-confirmed this observation (Tables 2–4). The baseline HbA$_{1c}$, the fall in HbA$_{1c}$ after 6 months of therapy and the final HbA$_{1c}$ were comparable when Group-3 was compared to Group-1 (Table 3), Group-2 was compared to Group-1 (Table 4), and when Group-3 was compared to Group-2 (Table 2) Groups 2 and 3 were significantly different only with regards to age and in their baseline BMI (Table 2), hence a separate, post-hoc analysis of the study outcomes was done

Table 1. Baseline demographics, treatment parameters and outcomes after 6 months of follow-up in patients receiving different graded doses of canagliflozin

Parameter	Canagliflozin study groups			P value
	Group 1 Canagliflozin 100 mg/day n = 257	Group 2 Canagliflozin 150 mg/day n = 138	Group 3 Canagliflozin 300 mg/day n = 133	
Age, years	54.26 ± 10.58	45.31 ± 13.86	54.62 ± 10.08	< 0.001
Sex, male:female	139:118	78:61	71:62	0.891
Duration of diagnosis, years (range)*	4.5 (2.0–8.0)	4.0 (2.0–5.0)	4.0 (2.07–7.0)	0.275
BMI at baseline, kg/m^2	27.96 ± 5.29	34.95 ± 5.76	32.92 ± 5.78	< 0.001
SBP, mm Hg	131.12 ± 19.70	134.92 ± 21.31	135.89 ± 19.42	0.057
DBP, mm Hg	79.19 ± 10.32	84.05 ± 10.61	82.25 ± 10.41	< 0.001
Weight, kg (range) [†]	72.95 (65.08–82.38)	93.9 (80.03–105.98)	84.6 (76.6–95.51)	< 0.001
Absolute weight loss at 6 months, kg (range)[†]	–1.05 (–2.85 to –0.17)	–3.5 (–6.60 to 0.00)	–3.0 (–5.3 to –0.81)	0.002
Percent weight loss at 6 months, % (range)[†]	–1.31 (–3.28 to –0.22)	–3.62 (–6.64 to 0.00)	–3.33 (–6.00 to –0.99)	0.014
HbA$_{1c}$, % (range)	8.1 (7.0–9.6)	8.1 (6.8–9.2)	8.8 (7.5–9.6)	0.153
HbA$_{1c}$, mmol/mol (range)[†]	65 (53–81)	65 (51–77)	73 (58–81)	
HbA$_{1c}$ at 6 months, % (range)	7.70 (6.4–8.6)	7.0 (6.1–8.0)	7.2 (6.1–8.4)	0.303
HbA$_{1c}$ at 6 months, mmol/mol (range)[†]	61 (46–70)	53 (43–64)	55 (43–68)	
Δ HbA$_{1c}$, % (range)[†]	–0.75 (–2.25 to 0.15)	–0.90 (–1.83 to –0.05)	–0.95 (–1.92 to –0.38)	0.833
HbA$_{1c}$ < 5.7% at 6 months, n (%)	6 (2.33%)	14 (10.14%)	6 (4.51%)	0.119
Creatinine, μmol/L	78.68 ± 20.33	69.84 ± 0.22.10	78.68 ± 30.94	0.159
Haemoglobin, gm/dL	12.08 ± 1.91	3.23 ± 1.99	12.51 ± 2.22	
LDL-C, mmol/L[†] (range)	2.56 (1.74–3.42)	2.85 (2.01–3.94)	2.46 (2.06–3.45)	0.070
Triglycerides, mmol/L[†] (range)	1.93 (1.30–2.94)	1.81 (1.46–2.59)	2.31 (1.38–3.27)	0.339
Hypothyroidism, n (%)	26 (10.12%)	30 (21.74%)	11 (8.27%)	0.347
Metformin, n (%)	229 (89.11%)	128 (92.75%)	127 (95.49%)	0.097
GLP1a, n (%)	28 (10.89%)	25 (18.12%)	14 (10.53%)	0.089
DPP4i, n (%)	195 (75.88%)	98 (71.01%)	102 (76.69%)	0.415
Orlistat, n (%)	45 (17.51%)	30 (21.74%)	27 (20.30%)	0.587
Pioglitazone, n (%)	112 (43.58%)	49 (35.51%)	50 (37.59%)	0.223
Alpha-glucosidase inhibitors, n (%)	29 (11.28%)	21 (15.22%)	24 (18.05%)	0.179
Sulfonylureas, n (%)	219 (85.21%)	108 (78.26%)	111 (83.46%)	0.163
Basal insulin, n (%)	50 (19.46%)	28 (20.29%)	37 (27.82%)	0.148
Short acting insulin, n (%)	28 (10.89%)	20 (14.49%)	22 (16.54%)	0.273
ACR, mg/gm (range)	64.12 (32.42–187.14)	63.11 (32.24–212.13)	72.11 (16.14–331.43)	0.195
Severe hypoglycaemia, n	2	1	2	0.743
Non-severe hypoglycaemia, n	15	11	12	0.476
Genital infections, n	10	5	7	0.725

Normality of the variable distribution calculated using Kolmogorov-Smirov test; all normally distributed variables expressed as mean ± standard deviation; discreet variables have been expressed as absolute numbers and percentages; P < 0.05 considered statistically significant. ANOVA was used for analysis. *As reported by the patient. †all non-normally distributed variables expressed as median (25th–75th percentile). Δ HbA$_{1c}$ — difference in glycated haemoglobin; ACR — spot urine albumin creatinine ratio; BMI — body mass index; DBP — diastolic blood pressure; DPP4i — dipeptidyl peptidase 4 inhibitor; GLP1a — glucagon like peptide receptor-1 antagonists; HbA$_{1c}$ — glycated haemoglobin; LDL-C — low density lipoprotein cholesterol; SBP — systolic blood pressure

for patients receiving canagliflozin 100 mg/day versus those receiving canagliflozin 150 mg/day or 300 mg//day (Table 5).

Patients in the post-hoc analysis group (receiving canagliflozin 150 mg/day or 300 mg/day) were signifi-cantly younger, had significantly higher baseline BMI, and had more severe hypertension, but were comparable with regards to use of all the other different anti-diabetes medications (metformin, sulfonylureas, dipeptidyl-peptidase-4 inhibitors, alpha glucosidase

Table 2. Baseline clinical and treatment parameters and outcomes after 6 months of follow-up in patients receiving canagliflozin 150 mg per day as compared to those receiving 300 mg per day

Parameter	Canagliflozin study groups		P value
	Group 2 Canagliflozin 150 mg/d n = 138	Group 3 Canagliflozin 300 mg/d n = 133	
Age (years)	45.31 ± 13.86	54.62 ± 10.08	**0.001**
Sex (Male:Female)	78:61	71: 62	0.651
Duration of diagnosis (years)*	4.0 [2.0–5.0]	4.0 [2.07–7.0]	0.163
BMI [kg/m^2]	34.95 ± 5.76	32.92 ± 5.78	**0.005**
SBP [mm Hg]	134.92 ± 21.3	135.89 ± 19.4	0.707
DBP [mm Hg]	84.05 ± 10.61	82.25 ± 10.4	0.181
Weight [kg]†	93.9 [80.03 – 105.98]	84.6 [76.6–95.5]	**0.001**
Weight loss [kg]†	–3.5 [–6.60–0.00]	–3.0 [–5.3 to –0.8]	0.813
Percent weight loss at 6 months (%)†	–3.62 [–6.64–0.00]	–3.33 [–6.00 to –0.99]	0.734
HbA$_{1c}$ (%)	8.1 [6.8–9.2]	8.8 [7.5–9.6]	0.117
[mmol/mol]†	65 [51–77]	73 [58–81]	0.335
HbA$_{1c}$ at 6 months (%)	7.0 [6.1–8.0]	7.2 [6.1–8.4]	
[mmol/mol]†	53 [43– 64]	55 [43–68]	
Δ HbA$_{1c}$ (%)†	–0.90 [–1.8 to –0.05]	–0.95 [–1.92 to –0.38]	0.589
HbA$_{1c}$ < 5.7% at 6 months	14 (10.14%)	6 (4.5%)	0.066
Creatinine [μmol/L]	69.84 ± 0.22.10	78.68 ± 30.94	0.113
Haemoglobin [gm/dL]	13.23 ± 1.99	12.51 ± 2.22	0.166
LDL-C [mmol/L]†	2.85 [2.01–3.94]	2.46 [2.06–3.45]	0.315
Triglycerides [mmol/L]†	1.81 [1.46–2.59]	2.31 [1.38–3.27]	0.054
Hypothyroidism	30 (21.73%)	11 (8.27%)	0.246
Metformin	128 (92.75%)	127 (95.48%)	0.247
GLP1a	25 (18.11%)	14 (10.52%)	0.079
DPP4i	98 (71.01%)	102 (76.69%)	0.248
Orlistat	35 (25.36%)	27 (20.30%)	0.338
Pioglitazone	49 (35.50%)	50 (37.59%)	0.688
Alpha-glucosidase inhibitors	21 (15.21%)	24 (8.04%)	0.532
Sulfonylureas	108 (78.26%)	111(83.45%)	0.231
Basal insulin	28 (20.28%)	37 (27.81%)	0.138
Short acting insulin	20 (14.49%)	22 (16.5%)	0.623
ACR [mg/gm]	63 [32.2–212]	72 [16–331]	0.483

Normality of the variable distribution calculated using Kolmogorov Smirov test; All normally distributed variables expressed as mean ± standard deviation; †all non-normally distributed variables expressed as median [25th–75th percentile]; discreet variables have been expressed as absolute numbers and percents; P < 0.05 considered statistically significant; Δ HbA$_{1c}$: HbA$_{1c}$ at 6 months — HbA$_{1c}$ at baseline; GLP1a: glucagon like peptide receptor-1 antagonists; BMI: body mass index; DPP4i: dipeptidyl peptidase 4 inhibitor; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACR: spot urine albumin creatinine ratio; LDL-C — low density lipoprotein cholesterol; HbA$_{1c}$ — glycated haemoglobin; *duration of diagnosis (in years) as told by the patient

inhibitors, pioglitazone, glucagon like peptide-1 receptor agonists and insulins) (Table 5). Both absolute and percent weight loss was significantly higher among patients in the post-hoc analysis group (canagliflozin 150 or 300 mg/day) as compared to those receiving 100 mg/day (Table 5). Both basal and final HbA$_{1c}$ after 6 months of therapy were comparable among the groups (Table 5). A greater percent of patients in the post-hoc analysis group (canagliflozin 150 or 300 mg//day) achieved HbA$_{1c}$ < 5.7% as compared to those on canagliflozin 100 mg/day but not statistically significant (20 vs 6; P = 0.428) (Table 5).

There were five reports (0.009%) of severe hypoglycaemia, necessitating a visit to the hospital emergency department, 38 (7.20%) reports of mild self-limiting hypoglycaemia, 22 reports (4.17%) of mild lower

Table 3. Baseline clinical and treatment parameters and outcomes after 6 months of follow-up in patients receiving canagliflozin 100 mg per day as compared to those receiving 300 mg per day

Parameter	Canagliflozin study groups		P value
	Group 1 Canagliflozin 100 mg/d n = 257	Group 3 Canagliflozin 300 mg/d n = 133	
Age (years)	54.26 ± 10.58	54.62 ± 10.08	0.771
Sex (Male: Female)	139: 118	71: 62	0.895
Duration of diagnosis (years)*	4.5 [2.0–8.0]	4.0 [2.07–7.0]	0.923
BMI [kg/m^2]	27.96 ± 5.29	32.92 ± 5.78	**< 0.001**
SBP [mm Hg]	131.12 ± 19.7	135.89 ± 19.4	**0.027**
DBP [mm Hg]	79.19 ± 10.32	82.25 ± 10.4	**0.007**
Weight [kg]†	72.95 [65.08–82.38]	84.6 [76.6–95.5]	**< 0.001**
Weight loss [kg]†	−1.05 [−2.85 to −0.17]	−3.0 [−5.3 to −0.8]	**< 0.001**
Percent weight loss at 6 months (%)†	−1.31 [−3.28 to −0.22]	−3.33 [−6.00 to −0.99]	**0.002**
HbA$_{1c}$ (%)	8.1 [7.0–9.6]	8.8 [7.5–9.6]	0.983
[mmol/mol]†	65 [53–81]	73 [58–81]	
HbA$_{1c}$ at 6 months (%)	7.70 [6.4–8.6]	7.2 [6.1–8.4]	0.576
[mmol/mol]†	61 [46–70]	55 [43–68]	
Δ HbA$_{1c}$ (%)†	−0.75 [−2.25–0.15]	−0.95 [−1.92 to −0.38]	0.627
HbA$_{1c}$ < 5.7% at 6 months	6 (2.33%)	6 (4.5%)	0.785
Creatinine [μmol/L]	78.68 ± 20.33	78.68 ± 30.94	0.953
Haemoglobin [gm/dL]	12.08 ± 1.91	12.51 ± 2.22	0.614
LDL-C [mmol/L]†	2.56 [1.74–3.42]	2.46 [2.06–3.45]	0.304
Triglycerides [mmol/L]†	1.93 [1.30–2.94]	2.31 [1.38–3.27]	0.629
Hypothyroidism	26 (10.11%)	11 (8.27%)	0.987
Metformin	229 (89.10%)	127 (95.48%)	0.054
GLP1a	28 (10.89%)	14 (10.52%)	0.911
DPP4i	195 (75.87%)	102 (76.69%)	0.858
Orlistat	45 (17.50%)	27 (20.30%)	0.501
Pioglitazone	112 (43.57%)	50 (37.59%)	0.255
Alpha-glucosidase inhibitors	29 (11.28%)	24 (8.04%)	0.067
Sulfonylureas	219 (85.21%)	111(83.45%)	0.649
Basal insulin	50 (19.45%)	37 (27.81%)	0.063
Short acting insulin	28 (10.89%)	22 (16.5%)	.1170
ACR [mg/gm]	64 [32–187]	72 [16–331]	0.606

Normality of the variable distribution calculated using Kolmogorov Smirov test; All normally distributed variables expressed as mean ± standard deviation; †all non-normally distributed variables expressed as median [25th–75th percentile]; discreet variables have been expressed as absolute numbers and percents; P < 0.05 considered statistically significant; Δ HbA$_{1c}$ — HbA$_{1c}$ at 6 months–HbA$_{1c}$ at baseline; GLP1a — glucagon like peptide receptor-1 antagonists; BMI — body mass index; DPP4i — dipeptidyl peptidase 4 inhibitor; SBP — systolic blood pressure; DBP — diastolic blood pressure; ACR — spot urine albumin creatinine ratio; LDL-C — low density lipoprotein cholesterol; HbA$_{1c}$ — glycated haemoglobin; *duration of diagnosis (in years) as told by the patient

genital infection and one report of upper urinary tract infection involving the kidneys. There were no reports of fractures, amputations, euglycaemic ketosis or any hypersensitivity reactions. The occurrence of adverse drug reactions was comparable across the three different dose groups of canagliflozin (Table 1). Monthly cost of canagliflozin 100 mg/d, 150 mg/d and 300 mg/d was INR 1,635, INR 1,800 and INR 3,600, respectively.

Discussion

Literature is available to suggest that the function and efficacy of canagliflozin changes with increases in its doses. Polidori et al. [21] reported that the transient intestinal inhibition of SGLT1 was observed with canagliflozin primarily at doses > 200 mg/day. Studies have also suggested that higher doses of canagliflozin have a more sustained 24-hour inhibition of renal glucose

Table 4. Baseline clinical and treatment parameters and outcomes after 6 months of follow-up in patients receiving canagliflozin 100 mg per day as compared to those receiving 150 mg per day

Parameter	Canagliflozin study groups		P value
	Group 1 Canagliflozin 100 mg/d n = 257	Group 2 Canagliflozin 150 mg/d n = 138	
Age (years)	54.26 ± 10.58	45.31 ± 13.86	**< 0.001**
Sex (Male: Female)	139: 118	78:61	0.699
Duration of diagnosis (years)*	4.5 [2.0–8.0]	4.0 [2.0–5.0]	0.133
BMI [kg/m^2]	27.96 ± 5.29	34.95 ± 5.76	**< 0.001**
SBP [mm Hg]	131.12 ± 19.7	134.92 ± 21.3	0.096
DBP [mm Hg]	79.19 ± 10.32	84.05 ± 10.61	**< 0.001**
Weight [kg]†	72.95 [65.08–82.38]	93.9 [80.03–105.98]	**< 0.001**
Weight loss [kg]†	−1.05 [−2.85 to −0.17]	−3.5 [−6.60–0.00]	**0.002**
Percent weight loss at 6 months (%)†	−1.31 [−3.28 to −0.22]	−3.62 [−6.64–0.00]	**0.021**
HbA$_{1c}$ (%)	8.1 [7.0–9.6]	8.1 [6.8–9.2]	0.118
[mmol/mol]†	65 [53–81]	65 [51–77]	0.071
HbA$_{1c}$ at 6 months (%)	7.70 [6.4–8.6]	7.0 [6.1–8.0]	
[mmol/mol]†	61 [46–70]	53 [43–64]	
Δ HbA$_{1c}$ (%)†	−0.75 [−2.25–0.15]	−0.90 [−1.8 to −0.05]	0.990
HbA$_{1c}$ < 5.7% at 6 months	6 (2.33%)	14 (10.14%)	0.135
Creatinine [μmol/L]	78.68 ± 20.33	69.84 ± 0.22.10	0.060
Haemoglobin [gm/dL]	12.08 ± 1.91	13.23 ± 1.99	0.011
LDL-C [mmol/L]†	2.56 [1.74–3.42]	2.85 [2.01–3.94]	0.026
Triglycerides [mmol/L]†	1.93 [1.30–2.94]	1.81 [1.46–2.59]	0.310
Hypothyroidism	26 (10.11%)	30 (21.73%)	0.170
Metformin	229 (89.10%)	128 (92.75%)	0.342
GLP1a	28 (10.89%)	25 (18.11%)	0.063
DPP4i	195 (75.87%)	98 (71.01%)	0.245
Orlistat	45 (17.50%)	35 (25.36%)	0.323
Pioglitazone	112 (43.57%)	49 (35.50%)	0.107
Alpha-glucosidase inhibitors	29 (11.28%)	21 (15.21%)	0.269
Sulfonylureas	219 (85.21%)	108 (78.26%)	0.060
Basal insulin	50 (19.45%)	28 (20.28%)	0.884
Short acting insulin	28 (10.89%)	20 (14.49%)	0.316
ACR [mg/gm]	64 [32–187]	63 [32.2–212]	0.132

Normality of the variable distribution calculated using Kolmogorov Smirov test; All normally distributed variables expressed as mean ± standard deviation; †all non-normally distributed variables expressed as median [25th–75th percentile]; discreet variables have been expressed as absolute numbers and percents; P < 0.05 considered statistically significant; Δ HbA$_{1c}$ — HbA$_{1c}$ at 6 months–HbA$_{1c}$ at baseline; GLP1a — glucagon like peptide receptor-1 antagonists; BMI — body mass index; DPP4i — dipeptidyl peptidase 4 inhibitor; SBP — systolic blood pressure; DBP — diastolic blood pressure; ACR — spot urine albumin creatinine ratio; LDL-C — low density lipoprotein cholesterol; HbA$_{1c}$ — glycated haemoglobin; *duration of diagnosis (in years) as told by the patient

resorption [22]. A head-to-head pharmacokinetic-pharmacodynamic study of canagliflozin 300 mg versus dapagliflozin 10 mg demonstrated an additional about 25% lowering of 2-hour prandial glucose with canagliflozin [22, 23]. Phase III studies of CANA-300 have demonstrated an additional 5–20% patients achieving HbA$_{1c}$ < 7% over CANA-100 [23]. Also, CANA-300 was shown to have greater blood-pressure and body-weight lowering trends over CANA-100 in some of the study groups [23]. In a Bayesian network meta-analysis of 13 trials, Shyangdan et al. [24] reported a statistically significant lowering of HbA$_{1c}$ with CANA-300 in monotherapy (Δ −0.2%; 95% confidence interval [CI] −0.05 to −0.36) and dual therapy as add on to metformin (Δ −0.15%; 95% CI, −0.04 to −0.26), compared to CANA-100. In another larger network meta-analysis

Table 5. Baseline clinical and treatment parameters and outcomes after 6 months of follow-up in patients receiving canagliflozin 100 mg per day as compared to those receiving 150 mg or 300 mg per day

Parameter	Canagliflozin study groups		P value
	Group 1 Canagliflozin 100 mg/d n = 257	Group 2+3 Canagliflozin 150 mg/d or 300 mg/d n = 271	
Age (years)	54.26 ± 10.58	49.89 ± 13.00	**< 0.001**
Sex (Male:Female)	139: 118	149:123	0.873
Duration of diagnosis (years)*	4.5 [2.0–8.0]	4.0 [2.0–6.0]	0.381
BMI [kg/m^2]	27.96 ± 5.29	33.91 ± 5.84	**< 0.001**
SBP [mm Hg]	131.12 ± 19.7	135.4 ± 20.3	**0.018**
DBP [mm Hg]	79.19 ± 10.32	83.11 ± 10.52	**< 0.001**
Weight [kg]†	72.95 [65.08–82.38]	89.95 [79.5–100.07]	**< 0.001**
Weight loss [kg]†	–1.05 [–2.85 to –0.17]	–3.0 [–5.60 to –0.60]	**< 0.001**
Percent weight loss at 6 months (%)†	–1.31 [–3.28 to –0.22]	–3.39 [–6.34 to –0.71]	**0.004**
HbA$_{1c}$ (%)	8.1 [7.0–9.6]	8.4 [6.7–9.4]	0.242
[mmol/mol]†	65 [53–81]	68 [50–79]	
HbA$_{1c}$ at 6 months (%)	7.70 [6.4–8.6]	7.1 [6.1–8.0]	0.230
[mmol/mol]†	61 [46–70]	54 [43–64]	
Δ HbA$_{1c}$ (%)†	–0.75 [–2.25–0.15]	–0.9 [–1.9 to –0.3]	0.769
HbA$_{1c}$ < 5.7% at 6 months	6 (2.33%)	20 (7.38%)	0.429
Creatinine [μmol/L]	78.68 ± 20.33	74.26 ± 26.52	0.258
Haemoglobin [gm/dL]	12.08 ± 1.91	12.86 ± 2.3	0.069
LDL-C [mmol/L]†	2.56 [1.74–3.42]	2.67 [2.05–3.73]	0.101
Triglycerides [mmol/L]†	1.93 [1.30–2.94]	178 [129–249.5]	0.756
Hypothyroidism	26 (10.11%)	41 (15.12%)	0.313
Metformin	229 (89.10%)	255 (94.09%)	0.079
GLP1a	28 (10.89%)	39 (14.39%)	0.234
DPP4i	195 (75.87%)	200 (73.8%)	0.535
Orlistat	45 (17.50%)	57 (21.031%)	0.186
Pioglitazone	112 (43.57%)	99 (36.53%)	0.098
Alpha-glucosidase inhibitors	29 (11.28%)	45 (16.61%)	0.081
Sulfonylureas	219 (85.21%)	219 (80.81%)	0.152
Basal insulin	50 (19.45%)	65 (23.98%)	0.224
Short acting insulin	28 (10.89%)	42 (15.49%)	0.127
ACR [mg/gm]	64 [32–187]	64 [32–415]	0.204

Normality of the variable distribution calculated using Kolmogorov Smirov test; All normally distributed variables expressed as mean ± standard deviation; †all non–normally distributed variables expressed as median [25th–75th percentile]; discreet variables have been expressed as absolute numbers and percents; P < 0.05 considered statistically significant; Δ HbA$_{1c}$ — HbA$_{1c}$ at 6 months–HbA$_{1c}$ at baseline; GLP1a — glucagon like peptide receptor-1 antagonists; BMI — body mass index; DPP4i — dipeptidyl peptidase 4 inhibitor; SBP — systolic blood pressure; DBP — diastolic blood pressure; ACR — spot urine albumin creatinine ratio; LDL-C — low density lipoprotein cholesterol; HbA$_{1c}$ — glycated haemoglobin; *duration of diagnosis (in years) as told by the patient

of 38 trials involving 23,997 patients, a statistically significant reduction of HbA$_{1c}$ (Δ –0.1%; 95% CI, 0.00 to –0.20), fasting glucose (Δ –0.33 mmol/L; 95% CI, –0.07 to –0.90), body weight (Δ –0.61 kg; 95% CI, –0.23 to –0.99) and SBP (Δ –0.98 mm Hg; 95% CI, 0.00 to –1.96) was noted with CANA-300 as compared to CANA-100 [25].

Although there are no head-to-head comparison studies on the efficacy of different SGLT2 inhibitors, Singh et al. [23], through indirect comparison of results of different clinical trials, noted that canagliflozin 300 mg gave the highest reduction in HbA$_{1c}$ (either monotherapy or as a part of multidrug therapy), noting an additional HbA$_{1c}$ lowering of 0.11–0.33%, in

the background of similar baseline HbA_{1c} and duration of the studies. With regards to weight loss, weight reduction appeared larger with CANA-300 in clinical trials, except when CANA-300 was a part of triple-drug therapy with sulfonylureas and metformin [23]. However, baseline body weights were also different to start with in these patients [23]. In the Bayesian network meta-analysis from 13 trials by Shyangdan et al. (vide supra) CANA-300 was shown to have a greater glycaemic efficacy than other SGLT2 inhibitors as monotherapy (additional HbA_{1c} reduction of Δ −0.37%; 95% CI −0.16 to −0.58 w.r.t empagliflozin 25 mg/day and Δ −0.64%; 95% CI −0.45 to −0.83 with regards to dapagliflozin 10 mg/day) [24]. With regards to weight reduction CANA-300 was associated with a statistically significant reduction of weight as compared to empagliflozin 10 mg/day [24]. These results were replicated in a network meta-analysis by Zaccardi et al. (vide supra) [25]. CANA-300 was associated with an additional 0.21% and 0.20% lowering of HbA_{1c} w.r.t dapagliflozin 10 mg/day and empagliflozin 25 mg/day, respectively, without any statistically significant difference in body weight reduction. The differences were blunted when SGLT2 inhibitors were used as a part of dual- or multi-drug therapy [23–25]. Hence, preclinical data as well as data from clinical trials suggest that not only canagliflozin may be the most potent SGLT2 inhibitor, because of its additional SGLT1 inhibiting properties, but also that higher doses of canagliflozin may have increased therapeutic benefits.

Our study demonstrated, for the first time in a real-world setting, that higher doses of canagliflozin, 150 mg/day and 300 mg/day, were superior in terms of causing both absolute and percent weight loss as compared to canagliflozin 100 mg/day when used as a part of standard of care for managing diabesity. The highlight of this study is the comparable use of all the different anti-diabetes medications across all the three study groups, especially medications which are linked with mild weight gain like sulfonylureas, pioglitazone and insulin, thus negating any potential impact of these medications on the study outcomes (glycaemic efficacy and weight loss).

It is important to highlight here that the differences in the baseline BMI may have impacted the absolute weight loss, but has no impact on percent weight loss. Following 6 months of treatment, the absolute weight loss was significantly higher in patients receiving canagliflozin 150 mg/day as compared to those receiving 100 mg/day and 300 mg/day (P = 0.002) (Table 1). The highest baseline BMI in canagliflozin 150 mg/d group may have contributed to the greater absolute weight loss in that group. However, it must be realised that the percent weight loss after 6 months of therapy (which is not effected by the higher baseline BMI) was also significantly higher in canagliflozin 150 mg/d group as compared to canagliflozin 300 mg/d and canagliflozin 100 mg/d group (P = 0.014). Post-hoc analysis confirmed that in terms of both absolute and percent weight loss, canagliflozin 150 mg/day and 300 mg/day performed similarly.

The glycaemic efficacy was comparable across the three different doses of canagliflozin used in this study. Since canagliflozin was used as a part of multi drug therapy in this real-world study, this may explain the lack of difference in HbA_{1c} reduction across the different doses of canagliflozin. This study provided reassuring data, for the first time, that the glycaemic and the weight-loss benefits of CANA-300 tablet is retained, even when it is broken into half and taken over 2 different days. "Tablet splitting" not something new, and has been in practice for a long time in India, USA and many other countries across the globe. Freeman et al in a review of PubMed (1966–June 2011) and International Pharmaceutical Abstract (1975–June 2011) found 17 studies dealing with different clinical outcomes, patient acceptance or economic benefits of "tablet splitting" [26]. Patients with chronic disorders, which often needed life-long therapy were most commonly doing "tablet-splitting" viz those on statins, anti-hypertensive medications and anti-psychotics. Their main conclusion was "tablet splitting" did not seem to effect clinical outcomes related to hypertension, cholesterol, or psychiatric disorders [26]. The authors' personal observation are that tablet splitting is commonly practiced in India with regards to diabetes medications, as especially with relatively costlier medications like SGLT2 inhibitors.

Canagliflozin 150 mg/day (half tablet of CANA-300) is significantly cheaper, having a monthly cost of therapy INR 1,800, as compared to INR 3,600 for CANA-300 [13, 14]. The monthly cost of canagliflozin 150 mg/day is only marginally higher than canagliflozin 100 mg/day (INR 1,800 versus INR 1,635, respectively) [13, 14], but the therapeutic benefits of canagliflozin 150 mg/day is superior to 100 mg/day.

The limitations of this study include the lack of matching of study groups at baseline, especially with regards to age and body weight. These are limitations intrinsic to real-world studies, where matching and randomisation is not possible. Hence, we have focussed on percent weight loss and not absolute weight loss, which would not be affected by the baseline weight//BMI. Other limitations include the short study period of 6 months, making it difficult to assess long-term weight loss, and the lack of robust data on adherence.

However, as a department policy we always encourage our patients to carry medicines with them whenever they come for visits to the outpatient department (for checking and verification), and collect back empty packs of medicines from patients during these follow-up visits to ensure a good compliance of medication intake. This study highlights the significant cost benefits of using half tablet of CANA-300 in clinical practice, without any compromise in the glycaemic efficacy and weight loss properties of this molecule.

To summarise, this is the first study, to date, that documents the glycaemic efficacy, durability and weight-loss potential of half tablet of CANA-300 taken once a day over a period of 6 months. Half tablet of CANA-300 (150 mg/day) is associated with a significantly greater weight loss and comparable glycaemic efficacy as compared to 1 tablet of CANA-100 with similar costing. Half tablet of CANA-300 (150 mg/day) has glycaemic and weight-loss efficacy equivalent to that of 1 tablet of CANA-300 when used as a part of multi-drug therapy for managing diabesity in India.

Disclosures

DD, MS, AD, SA and DK have no conflicts of interest, and nothing to declare in relation to this article.

REFERENCES

1. Dutta D, Mukhopadhyay S. Intervening at prediabetes stage is critical to controlling the diabetes epidemic among Asian Indians. Indian J Med Res. 2016; 143(4): 401–404, doi: 10.4103/0971-5916.184281, indexed in Pubmed: 27377494.
2. Dutta D, Choudhuri S, Mondal SA, et al. Urinary albumin : creatinine ratio predicts prediabetes progression to diabetes and reversal to normoglycemia: role of associated insulin resistance, inflammatory cytokines and low vitamin D. J Diabetes. 2014; 6(4): 316–322, doi: 10.1111/1753-0407.12112, indexed in Pubmed: 24251376.
3. Mondal SA, Dutta D, Kumar M, et al. Neck circumference to height ratio is a reliable predictor of liver stiffness and nonalcoholic fatty liver disease in prediabetes. Indian J Endocrinol Metab. 2018; 22(3): 347–354, doi: 10.4103/ijem.IJEM_31_18, indexed in Pubmed: 30090726.
4. Deepa M, Grace M, Binukumar B, et al. CARRS Surveillance Research Group. High burden of prediabetes and diabetes in three large cities in South Asia: The Center for cArdio-metabolic Risk Reduction in South Asia (CARRS) Study. Diabetes Res Clin Pract. 2015; 110(2): 172–182, doi: 10.1016/j.diabres.2015.09.005, indexed in Pubmed: 26432412.
5. Singla R, Garg A, Singla S, et al. Temporal change in profile of association between diabetes, obesity, and age of onset in urban India: a brief report and review of literature. Indian J Endocrinol Metab. 2018; 22(3): 429–432, doi: 10.4103/ijem.IJEM_601_17, indexed in Pubmed: 30090739.
6. Dutta D, Jaisani R, Khandelwal D, et al. Role of metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and orlistat based multidrug therapy in glycemic control, weight loss, and euglycemia in diabesity: a real-world experience. Indian J Endocrinol Metab. 2019; 23(4): 460–467, doi: 10.4103/ijem.IJEM_185_19, indexed in Pubmed: 31741907.
7. Lean MEJ, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018; 391(10120): 541–551, doi: 10.1016/S0140-6736(17)33102-1, indexed in Pubmed: 29221645.
8. Singh AK, Unnikrishnan AG, Zargar AH, et al. Evidence-based consensus on positioning of SGLT2i in type 2 diabetes mellitus in Indians. Diabetes Ther. 2019; 10(2): 393–428, doi: 10.1007/s13300-019-0562-1, indexed in Pubmed: 30706366.
9. Devineni D, Murphy J, Wang SS, et al. Absolute oral bioavailability and pharmacokinetics of canagliflozin: A microdose study in healthy participants. Clin Pharmacol Drug Dev. 2015; 4(4): 295–304, doi: 10.1002/cpdd.162, indexed in Pubmed: 27136910.
10. Singh AK, Singh R. Spotlight on Canagliflozin 300: review of its efficacy and an indirect comparison to other SGLT-2 inhibitors and long-acting GLP-1 receptor agonists. Expert Rev Clin Pharmacol. 2017; 10(6): 633–647, doi: 10.1080/17512433.2017.1318061, indexed in Pubmed: 28393583.
11. Mentock SM, Ng VY, Narayana R, et al. Treatment-seeking behavior and obstacles to treatment compliance in diabetic patients in Mangaluru, India. Diabetes Metab Syndr. 2017; 11 Suppl 2: S617–S622, doi: 10.1016/j.dsx.2017.04.014, indexed in Pubmed: 28465150.
12. Dalvi V, Mekoth N. Patient non-adherence: an interpretative phenomenological analysis. Int J Health Care Qual Assur. 2017; 30(3): 274–284, doi: 10.1108/IJHCQA-03-2016-0033, indexed in Pubmed: 28350217.
13. 1mg. Canagliflozin 100mg tablet online purchase. https://www.1mg.com/drugs/invokana-100mg-tablet-173290 (12.01.2020).
14. 1mg. Canagliflozin 300mg tablet online purchase. https://www.1mg.com/drugs/motivyst-tablet-332650 (12.01.2020).
15. Sharma M, Kumar M, Dutta D. Hydroxychloroquine in diabetes and dyslipidaemia: primum non nocere. Diabet Med. 2020; 37(8): 1404––1405, doi: 10.1111/dme.14144, indexed in Pubmed: 31557353.
16. 1mg. Actrapid online purchase with a valid prescription. https://www.1mg.com/drugs/actrapid-hm-100iu-ml-penfill-248417 (12.01.2020).
17. 1mg. Insulatard online purchase with a valid prescription. https://www.1mg.com/drugs/insulatard-hm-100iu-ml-penfill-372998 (12.01.2020).
18. 1mg. Humalog online purchase with a valid prescription. https://www.1mg.com/drugs/humalog-100iu-ml-solution-for-injection-341834 (12.01.2020).
19. 1mg. Lantus online purchase with a valid prescription. https://www.1mg.com/drugs/lantus-100iu-ml-solution-for-injection-113528 (12.01.2020).
20. Dutta D, Ghosh S. Young-onset diabetes: An Indian perspective. Indian J Med Res. 2019; 149(4): 441–442, doi: 10.4103/ijmr.IJMR_1938_18, indexed in Pubmed: 31411167.
21. Polidori D, Sha S, Mudaliar S, et al. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: results of a randomized, placebo-controlled study. Diabetes Care. 2013; 36(8): 2154–2161, doi: 10.2337/dc12-2391, indexed in Pubmed: 23412078.
22. Sha S, Devineni D, Ghosh A, et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. Diabetes Obes Metab. 2011; 13(7): 669–672, doi: 10.1111/j.1463-1326.2011.01406.x, indexed in Pubmed: 21457428.
23. Singh AK, Singh R. Spotlight on Canagliflozin 300: review of its efficacy and an indirect comparison to other SGLT-2 inhibitors and long-acting GLP-1 receptor agonists. Expert Rev Clin Pharmacol. 2017; 10(6): 633–647, doi: 10.1080/17512433.2017.1318061, indexed in Pubmed: 28393583.
24. Shyangdan DS, Uthman OA, Waugh N. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. BMJ Open. 2016; 6(2): e009417, doi: 10.1136/bmjopen-2015-009417, indexed in Pubmed: 26911584.

25. Zaccardi F, Webb DR, Htike ZZ, et al. Efficacy and safety of sodium-
    -glucose co-transporter-2 inhibitors in type 2 diabetes mellitus:
    systematic review and network meta-analysis. Diabetes Obes
    Metab. 2016; 18(8): 783–794, doi: 10.1111/dom.12670, indexed
    in Pubmed: 27059700.

26. Freeman MK, White W, Iranikhah M. Tablet splitting: a review
    of the clinical and economic outcomes and patient acceptance.
    Second of a 2-part series. Part 1 was published in May 2012 (Con-
    sult Pharm 2012;27:239-53). Consult Pharm. 2012; 27(6): 421–430,
    doi: 10.4140/TCP.n.2012.421, indexed in Pubmed: 22698549.

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Plasma microRNA-192 expression as a potential biomarker of diabetic kidney disease in patients with type 2 diabetes mellitus

ABSTRACT

Background. Albuminuria is an early clinical indicator of diabetic kidney disease (DKD). However, it has several limitations. The aim of this study was to evaluate the plasma microRNA-192 (miRNA-192) expression and its diagnostic performance in patients with type 2 diabetes mellitus (T2DM) and DKD.
Methods. In this case-control study, 75 subjects were included into 3 groups: group (1): 20 patients with T2DM and UACR (urinary albumin creatinine ratio) < 30 mg/gm, group (2): 30 patients with T2DM and ACR ≥ 30 mg/gm, and group (3): 25 healthy controls. Patients were recruited from the outpatient clinic of the Diabetes unit at our institution. Real-Time Quantitative Reverse Transcription PCR was used to assess plasma miRNA-192 expression.
Results. Plasma miRNA-192 was significantly higher in T2DM patients with DKD compared to those with normal UAE. Additionally, in patients with T2DM, plasma miRNA-192 was positively correlated with UACR. The ROC curve analysis for miRNA-192 plasma expression in patients with T2DM, revealed that miRNA-192 had a good diagnostic performance (AUC = 0.778) to define T2DM patients with DKD.

Conclusion. Plasma expression of miRNA-192 was able to discriminate increased UAE among patients with T2DM; suggesting a promising role for miRNA-192 as a potential biomarker for DKD. (Clin Diabetol 2020; 9; 6: 454–460)

Key words: type 2 diabetes, diabetic kidney disease, albuminuria, microRNA, microRNA-192

Introduction

Diabetes mellitus (DM) is an expanding universal health problem; according to the International Diabetes Federation (IDF), the prevalence of DM worldwide is 8.3% expected to reach 9.8% by 2045 [1]. This continuously growing prevalence, is mainly attributed to the increase in type 2 diabetes mellitus (T2DM), the most common type of DM representing 90% of cases [2]. In Egypt, the prevalence of T2DM is around 15.6% among adults; thus Egypt is ranked the ninth country worldwide regarding the number of patients with T2DM [1].

Diabetic kidney disease (DKD) is not only the most frequent microvascular complication of DM, but also, it is the leading cause of end-stage renal disease (ESRD), accounting for 50% of cases [2].

Despite being an early clinical indicator of DKD, albuminuria, detected by urinary albumin creatinine ratio (UACR), has some limitations [3]. Diabetic patients may present with impaired renal function without significant increases in albuminuria [4]. Moreover, albuminuria is not a perfect prognostic indicator for DKD progression, as the degree of albuminuria does not closely correlate with the decrease in glomerular

filtration rate (GFR) [5]. In addition, some structural alterations associated with DKD may precede albuminuria [6, 7]. Furthermore, 30% only of patients with moderately increased albuminuria (30–300 mg/gm) progress to overt nephropathy [8]. Accordingly, there is a call for identifying a biomarker which efficiently allows early diagnosis for more effective therapeutic interventions, and acts as a reasonable prognostic indicator for disease progression.

MicroRNAs (miRNAs) are highly conserved noncoding RNAs, consisting of 18–24 nucleotides and exerting their role in controlling human gene expression through post-transcriptional gene regulation or silencing [9]. Circulating miRNAs are characterized by high stability [10], reproducibility [11] and available detection by sensitive and specific quantitative real-time polymerase chain reaction (qRT-PCR) [12], therefore they are appealing biomarkers for a variety of diseases.

MicroRNA-192 is one of the most commonly expressed miRNAs in the renal cortex [13]. Several studies have reported an important role for miRNA-192 in the fibrogenesis process in DKD induced by transforming growth factor-β1 (TGF-β1). However, the results of these studies are conflicting. Owing to these contradicting reports about the role of miRNA-192 in identifying DKD, together with the need for an efficient diagnostic marker; we were directed to carry out the present study.

Subjects

In this case-control study 75 subjects were included and divided into 3 groups: group (1): 20 patients with T2DM without DKD, group (2): 30 patients with T2DM and DKD, and group (3): 25 healthy subjects of matched age and sex as a control group. T2DM and DKD were defined according to the diagnostic criteria of American Diabetes Association (ADA) [14, 15].

Patients were recruited from the outpatient clinic of the Diabetes and metabolism unit at Alexandria Main University hospital, in the period between December 2018 and August 2019. Patients with acute illness at time of the study, hepatic disease, cardiovascular disease, hematological disorders, malignancy, systemic chronic inflammation, history of hemodialysis or renal transplantation and patients using nephrotoxic drugs or corticosteroids were excluded.

An informed consent was obtained from each patient after explaining the nature and the aim of the study. The current study was done according to the Ethical Principles for Medical Research Involving Human Subjects defined in the Helsinki Declaration in 1975 (revised in 2008). The approval of the ethics committee of Faculty of Medicine, Alexandria University was obtained in 2018.

Methods
Laboratory investigations

Fasting plasma glucose (FPG), fasting insulin, glycated haemoglobin (HbA$_{1c}$) and UACR were determined by commercial enzymatic methods. Insulin resistance was calculated on the basis of the homeostasis model assessment of insulin resistance (HOMA-IR), using the following formula: [HOMA-IR = (fasting insulin in uIU/L × fasting glucose in mg/dL)/405] [16].

Molecular analysis: Relative quantification of miRNA-192 expression using Real-Time qRT-PCR [17] was done through 3 steps:

I.   Total RNA extraction: Purification of cell-free total RNA from plasma, which includes small RNAs as miRNAs, was done using the miRNeasy Serum/Plasma Kit (Qiagen, Germany). Exogenous oligonucleotide (cel-miR-39) was added in order to monitor miRNA analysis (RNA extraction and reverse-transcription real time PCR).

II. Real-time qRT-PCR, in 2 steps:
1. Reverse transcription (RT): complementary DNA was synthesized from purified RNA samples using the miScript II RT Kit (Qiagen, Germany) according to the manufacturer's protocol.
2. Real-time PCR quantification of mature miRNA-192: using target-specific miScript Primer Assays (forward primers) (Qiagen, Germany) and the miScript SYBR Green PCR Kit (Qiagen, Germany), which contains the miScript Universal Primer (reverse primer) and QuantiTect SYBR Green PCR Master Mix.

III. Calculation relative quantification of miRNA-192 was determined using comparative CT method (2$^{-\Delta\Delta CT}$) normalized to RNU6B as an endogenous control.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Chi-square test for categorical variables, to compare between different groups. Mann-Whitney test for abnormally distributed quantitative variables, to compare between two studied groups. F-test (ANOVA) for normally distributed quantitative variables, to compare between more than two groups, and post hoc test (Tukey) for pairwise comparisons. Kruskal Wallis test for abnormally distributed quantitative variables, to compare between more than two studied groups, and post hoc (Dunn's multiple com-

Table 1. Comparison between the studied groups according to demographic data

	uACR [mg/gm]		Control (n = 25)	Test of sig.	P
	< 30 (n = 20)	≥ 30 (n = 30)			
Sex					
Male	11 (55%)	16 (53.3%)	12 (48%)	$\chi^2 = 0.254$	0.881
Female	9 (45%)	14 (46.7%)	13 (52%)		
Age (years)	48.75 ± 2.94	47.43 ± 3.24	46.48 ± 3.93	F = 2.458	0.093
Diabetes duration (years)	5.50 (1–12)	7.0 (1–16)	–	U = 237.0	0.211

χ^2 — Chi square test; F — F for ANOVA; test U — Mann Whitney test; P — P value for comparing between the studied groups
Qualitative data were described using number and percentage
Normally Quantitative data was expressed using Mean ± SD
Abnormally Quantitative data was expressed using Median (Min–Max)

Table 2. Comparison between the study groups according to the studied parameters

	uACR [mg/gm]			Test of sig.	P
	< 30 (n = 20)	≥ 30 (n = 30)	Control (n = 25)		
FPG [mg/dL]	156 (72–263)	210.50 (105–325)	87 (75–99)	H = 46.43*	< 0.001*
		$P_1 = 0.039^*, P_2 < 0.001^*, P_3 < 0.001^*$			
F insulin [uIU/mL]	14.7 (2.3–23.4)	17.8 (7.27–42)	7.90 (1.20–41.50)	H = 11.025*	0.004*
		$P_1 = 0.122, P_2 = 0.132, P_3 = 0.001^*$			
HOMA-IR	4.14 (1.39–12.96)	9.91 (3.46–22.6)	1.70 (0.20–9.80)	H = 34.14*	< 0.001*
		$P_1 = 0.008^*, P_2 = 0.007^*, P_3 < 0.001^*$			
HbA_{1c} (%)	9.98 ± 2.30	9.56 ± 2.41	5.29 ± 0.14	F = 44.004*	< 0.001*
		$P_1 = 0.452, P_2 < 0.001^*, P_3 < 0.001^*$			
MicroRNA 192	2.08 (1.0–2.99)	3.12 (1.36–4.80)	0.82 (0.23–1.05)	H = 53.74*	< 0.001*
		$P_1 = 0.025^*, P_2 < 0.001^*, P_3 < 0.001^*$			

F — F for ANOVA test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Tukey); H — H for Kruskal Wallis test, Pairwise comparison bet. each 2 groups was done using Post Hoc Test (Dunn's for multiple comparisons test); P — P value for comparing between the studied groups; P_1 — P value for comparing between < 30 and ≥ 30; P_2 — P value for comparing between < 30 and control; P_3 — P value for comparing between ≥ 30 and control; *Statistically significant at P ≤ 0.05
Normally Quantitative data was expressed using Mean ± SD
Abnormally Quantitative data was expressed using Median (Min–Max)

parisons test) for pairwise comparisons. Spearman coefficient to correlate between two distributed abnormally quantitative variables. Receiver operating characteristic curve (ROC) It is generated by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the ROC curve (AUC) denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two tests. Significance of the obtained results was judged at the 5% level.

Results

The 3 study groups were age- and sex-matched and there was no statistically significant difference between the 2 groups of diabetic patients regarding diabetes duration (Table 1).

The FPG and HOMA-IR were significantly lower in T2DM patients with normal UAE compared to those with increased UAE (P = 0.039 and P = 0.008 respectively). On the contrary, there was no significant difference between both groups regarding HbA_{1c} (P = 0.452).

Regarding the plasma expression of miRNA-192 was significantly higher in diabetic patients with normal and increased UAE compared to the controls (P < 0.001). Moreover, plasma miRNA-192 expression was significantly higher in T2DM patients with DKD (UACR ≥ 30) compared to T2DM patients with normal UAE (P = 0.025). (Table 2, Fig. 1).

Additionally, in patients with T2DM, the plasma expression of miRNA-192 was positively correlated with FPG (r = 0.598, P < 0.001), HOMA-IR (r = 0.565, P < 0.001), diabetes duration (r = 0.450, P < 0.001) and UACR (r = 0.506, P < 0.001) (Table 3).
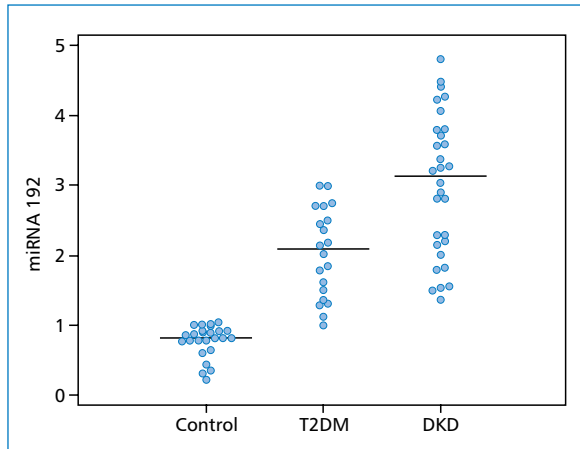
Figure 1. Comparison between the studied groups according to microRNA-192

Figure 2. ROC curve for microRNA-192 to predict T2DM patients with uACR ≥ 30 mg/gm

Furthermore, the ROC curve analysis for miRNA-192 plasma expression in patients with T2DM, revealed that miRNA-192 had a good diagnostic performance (AUC 0.778, 95% C.I 0.652–0.904) to discriminate T2DM patients with DKD from those with normal UAE. Also, according to the ROC curve, at a cutoff value > 2.7549, plasma miRNA-192 expression had 63.33% sensitivity and specificity was 90% (Fig. 2).

Discussion

DKD is the most frequent diabetic microvascular complication and the most common cause of chronic kidney disease worldwide [18]. Despite being the most widely used test for early detection of DKD, albuminuria has multiple drawbacks [5]. This triggers exploring new biomarkers for the identifying early diagnosis and prognosis of DKD.

MicroRNA- 192 is among miRNAs which are highly expressed in the human kidneys, and it has an important role in normal kidney function [19]. An important role for miRNA-192 in the fibrogenesis process in DKD

has been suggested in several studies. However, the results of these studies are inconsistent.

Kato et al. [20], in 2007, provided the first landmark report about the role of miRNA in DKD, as they found that miRNA-192 levels significantly increased in glomeruli of diabetic mice parallel to the increased TGF-β1 and collagen 1a2 levels.

In 2010, Kato and colleagues [21] found that in mouse mesangial cells, TGF-β1 was upregulated by miRNA-192. In addition, inhibition of miRNA-192 decreased the expression of miR-200b/c, collagen 1a2, collagen 4a1 and TGF-β1 in mouse mesangial cells, and in mouse kidney cortex.

In line with these results, Putta et al. [22] reported that in in cultured glomerular mesangial cells and in glomeruli from diabetic mice, TGF-β1 upregulated miRNA-192. Furthermore, they found that miRNA-192

Table 3. Correlation between miRNA 192 and different studied parameters

	miRNA 192					
	ACR < 30 mg/gm (n = 20)		ACR ≥ 30 mg/gm (n = 30)		Total cases with T2DM (n = 50)	
	r_s	P	r_s	P	r_s	P
FPG [mg/dL]	0.598*	0.005*	0.535*	0.002*	0.598*	< 0.001*
HbA$_{1c}$ (%)	−0.154	0.518	−0.328	0.077	−0.244	0.087
DM duration (years)	0.542*	0.013*	0.339	0.067	0.450*	0.001*
uACR [mg/gm]	0.189	0.426	0.247	0.189	0.506*	< 0.001*
HOMA-IR	0.293	0.210	0.608*	< 0.001*	0.565*	< 0.001*

r_s — Spearman coefficient; *Statistically significant at P ≤ 0.05

increased collagen expression through targeting the E-box repressors Zeb1/2. Additionally, locked nucleic acid, an inhibitor of miRNA-192, significantly increased Zeb1/2 and decreased expression of collagen, TGF-β1 and fibronectin in the kidneys of diabetic mice. Moreover, inhibition of miRNA-192 decreased proteinuria in these mice.

Contrariwise, Krupa and colleagues [23] reported that decreased miRNA-192 expression was associated with tubulointerstitial fibrosis and low GFR in tissues of renal biopsies from patients with DKD. Moreover, reduced miRNA-192 expression in proximal tubular cells was observed after treatment with TGF-β1.

The observed contradictory between the results of the aforementioned studies may be attributed to the different models, cell lines and time points that were used. It also can be suggested that these discrepancies may indicate a cell-type-specific regulation; such that upregulated glomerular miRNA-192 enhances matrix deposition, whereas miRNA-192 downregulation in renal tubules, facilitates epithelial to mesenchymal transition [24].

Conflicting results regarding the role miRNA-192 in DKD were not only reported in studies of cultured tissues and mice, but also studies involving patients with DKD revealed similar contradiction.

In the current work, the results showed that plasma miRNA-192 was significantly higher in T2DM patients with DKD compared to those with normal UAE. Moreover, in patients with T2DM, plasma miRNA-192 was positively correlated with UACR. The ROC curve analysis for miRNA-192 plasma expression in patients with T2DM, revealed that miRNA-192 had a good diagnostic performance to define T2DM patients with DKD.

In line with our results, Saadi et al. [25], demonstrated that serum miRNA-192 was significantly higher in diabetic patients with lower GFR and higher UACR.

Chien et al. [26] reported that there was no significant difference in serum miRNA-192 between T2DM subjects with and without DKD. However, serum miRNA-192 was significantly higher in patients with markedly increased UAE than in patients with moderately increased UAE.

Conversely, in a study of patients with T2DM with different levels of UAE, Jia et al. [27] reported that miRNA-192 levels were significantly higher in urine extracellular vesicles of patients with moderately increased UAE compared to normoalbuminuric and control subjects. Moreover, miRNA was positively correlated with albuminuria and TGF-β1 in patients with normal and moderately increased UAE. Additionally, the ROC curve analysis showed AUC of 0.802 for miRNA-192 in discriminating T2DM patients with normal UAE

from those with moderately increased UAE. However, miRNA-192 levels in urine extracellular vesicles was decreased in patients with markedly increased UAE.

On the other hand, in disagreement with the results of the current study, Ma et al. [13] found that miRNA-192 in patients with markedly increased UAE was significantly lower than those with moderately increased UAE. Additionally, miRNA-192 was in patients with moderately increased UAE compared to those with normal UAE. Furthermore, the expression of miR-192 was negatively correlated with TGF-β1.

Comparably, in study by Al-Kafaji and colleagues, miRNA-192 expression was 2.4-fold lower in the microalbuminuric patients compared to the normoalbuminuric group. Moreover, it was significantly lower by 19-folds in patients with macroalbuminuria compared to the normoalbuminuric patients. Additionally, the AUC of the ROC curve for miRNA was 0.70 regarding detection of increased UAE [28].

Similarly, A. El-Monem et al. [29] found that miRNA-192 expression was significantly lower in T2DM patients with microalbuminuria than those with normoalbuminuria. Microalbuminuria in patients with T2DM was accompanied by significantly higher serum level of IL-18 and TGF-β. Moreover, the ROC curve of miRNA-192 in patients with microalbuminuria showed very good performance with AUC of 0.946.

Despite their conflicting results, the current work together with the aforementioned studies suggest a significant importance for miRNA-192 in identifying DKD. Nevertheless, further research should be carried out on larger number of patients with different ethnicities and different stages of DKD in order to define clearly the role of miRNA-192 in pathogenesis of DKD and its ability to diagnose and predict the clinical course of DKD.

The current work proved a high specificity for miRNA-192. Different methods have been endorsed by international guidelines to screen for DKD. Spot urine sample UACR is a simple easy method for screening, but many limitations are there. In addition to the intraday variability and the need for repeated measures for conformation, false-positive rates were found to increase with age approaching 30%, so it is considered a poor predictor of quantitative AER, and so, should not be used as a diagnostic test [30].

Again, Although GFR is commonly accepted as the best overall index of kidney function, it is generally reduced after widespread structural damage, so its sensitivity to early detect renal damage is questionable. it has been reported to underestimate the renal function in some populations, especially in patients with near-normal renal function [31].

Conclusion

In this case-control study, the plasma expression of miRNA-192 was significantly higher in T2DM patients with DKD compared to those with normal UAE. Additionally, in patients with T2DM, the plasma expression of miRNA-192 was positively correlated with albuminuria and displayed good diagnostic performance in discriminating patients with DKD in T2DM. Thus, the plasma expression of miRNA-192 was able to discriminate increased UAE among patients with T2DM; suggesting a promising role for miRNA-192 as a potential biomarker for DKD.

Acknowledgement

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Saeedi P, Petersohn I, Salpea P, et al. IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9 edition. Diabetes Res Clin Pract. 2019; 157: 107843, doi: 10.1016/j.diabres.2019.107843, indexed in Pubmed: 31518657.
2. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care. 2014; 37(10): 2864–2883, doi: 10.2337/dc14-1296, indexed in Pubmed: 25249672.
3. Krolewski AS, Niewczas MA, Skupien J, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. Diabetes Care. 2014; 37(1): 226–234, doi: 10.2337/dc13-0985, indexed in Pubmed: 23939543.
4. MacIsaac RJ, Panagiotopoulos S, McNeil KJ, et al. Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes Care. 2004; 27(1): 195–200, doi: 10.2337/diacare.27.1.195, indexed in Pubmed: 14693989.
5. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015; 313(8): 837–846, doi: 10.1001/jama.2015.0602, indexed in Pubmed: 25710660.
6. Caramori ML, Kim Y, Huang C, et al. Cellular basis of diabetic nephropathy: 1. Study design and renal structural-functional relationships in patients with long-standing type 1 diabetes. Diabetes. 2002; 51(2): 506–513, doi: 10.2337/diabetes.51.2.506, indexed in Pubmed: 11812762.
7. Najafian B, Crosson JT, Kim Y, et al. Glomerulotubular junction abnormalities are associated with proteinuria in type 1 diabetes. J Am Soc Nephrol. 2006; 17(4 Suppl 2): S53–S60, doi: 10.1681/ASN.2005121342, indexed in Pubmed: 16565248.
8. Rossing P, Hougaard P, Parving HH. Progression of microalbuminuria in type 1 diabetes: ten-year prospective observational study. Kidney Int. 2005; 68(4): 1446–1450, doi: 10.1111/j.1523-1755.2005.00556.x, indexed in Pubmed: 16164620.
9. Dave VP, Ngo TA, Pernestig AK, et al. MicroRNA amplification and detection technologies: opportunities and challenges for point of care diagnostics. Lab Invest. 2019; 99(4): 452–469, doi: 10.1038/s41374-018-0143-3, indexed in Pubmed: 30542067.
10. Mitchell PS, Parkin RK, Kroh EM, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci U S A. 2008; 105(30): 10513–10518, doi: 10.1073/pnas.0804549105, indexed in Pubmed: 18663219.
11. Chen Xi, Ba Yi, Ma L, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res. 2008; 18(10): 997–1006, doi: 10.1038/cr.2008.282, indexed in Pubmed: 18766170.
12. Guay C, Regazzi R. Circulating microRNAs as novel biomarkers for diabetes mellitus. Nat Rev Endocrinol. 2013; 9(9): 513–521, doi: 10.1038/nrendo.2013.86, indexed in Pubmed: 23629540.
13. Ma X, Lu C, Lv C, et al. The Expression of miR-192 and its significance in diabetic nephropathy patients with different urine albumin creatinine ratio. J Diabetes Res. 2016; 2016: 6789402, doi: 10.1155/2016/6789402, indexed in Pubmed: 26881255.
14. American Diabetes Association, American Diabetes Association, American Diabetes Association. 2. Classification and Diagnosis of Diabetes: . Diabetes Care. 2019; 42(Suppl 1): S13–S28, doi: 10.2337/dc19-S002, indexed in Pubmed: 30559228.
15. American Diabetes Association. 11. Microvascular Complications and Foot Care: . Diabetes Care. 2019; 42(Suppl 1): S124–S138, doi: 10.2337/dc19-S011, indexed in Pubmed: 30559237.
16. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004; 27(6): 1487–1495, doi: 10.2337/diacare.27.6.1487, indexed in Pubmed: 15161807.
17. Kantharidis P, Hagiwara S, Brennan E, et al. Study of microRNA in diabetic nephropathy: isolation, quantification and biological function. Nephrology (Carlton). 2015; 20(3): 132–139, doi: 10.1111/nep.12374, indexed in Pubmed: 25487691.
18. Hu C, Sun L, Xiao L, et al. Insights into the Mechanisms Involved in the Expression and Regulation of Extracellular Matrix Proteins in Diabetic Nephropathy. Curr Med Chem. 2015; 22(24): 2858–2870, doi: 10.2174/0929867322666150625095407, indexed in Pubmed: 26119175.
19. Sun Y, Koo S, White N, et al. Development of a micro-array to detect human and mouse microRNAs and characterization of expression in human organs. Nucleic Acids Res. 2004; 32(22): e188, doi: 10.1093/nar/gnh186, indexed in Pubmed: 15616155.
20. Kato M, Zhang J, Wang M, et al. MicroRNA-192 in diabetic kidney glomeruli and its function in TGF-beta-induced collagen expression via inhibition of E-box repressors. Proc Natl Acad Sci U S A. 2007; 104(9): 3432–3437, doi: 10.1073/pnas.0611192104, indexed in Pubmed: 17360662.
21. Kato M, Arce L, Wang M, et al. A microRNA circuit mediates transforming growth factor- 1 autoregulation in renal glomerular mesangial cells. Kidney Int. 2011; 80(4): 358–368, doi: 10.1038/ki.2011.43, indexed in Pubmed: 21389977.
22. Putta S, Lanting L, Sun G, et al. Inhibiting microRNA-192 ameliorates renal fibrosis in diabetic nephropathy. J Am Soc Nephrol. 2012; 23(3): 458–469, doi: 10.1681/ASN.2011050485, indexed in Pubmed: 22223877.
23. Krupa A, Jenkins R, Luo DD, et al. Loss of MicroRNA-192 promotes fibrogenesis in diabetic nephropathy. J Am Soc Nephrol. 2010; 21(3): 438–447, doi: 10.1681/ASN.2009050530, indexed in Pubmed: 20056746.
24. Ruiz MA, Chakrabarti S. MicroRNAs: the underlying mediators of pathogenetic processes in vascular complications of diabetes. Can J Diabetes. 2013; 37(5): 339–344, doi: 10.1016/j.jcjd.2013.07.003, indexed in Pubmed: 24500562.
25. Ahmed G, Saadi G, Meligi AEl, et al. Evaluation of microRNA-192 in patients with diabetic nephropathy. Egypt J Intern Med. 2019; 31(2): 122, doi: 10.4103/ejim.ejim_89_18.
26. Chien HY, Chen CY, Chiu YH, et al. Differential microRNA Profiles Predict Diabetic Nephropathy Progression in Taiwan. Int J Med Sci. 2016; 13(6): 457–465, doi: 10.7150/ijms.15548, indexed in Pubmed: 27279796.

27. Jia Y, Guan M, Zheng Z, et al. miRNAs in urine extracellular vesicles as predictors of early-stage diabetic nephropathy. J Diabetes Res. 2016; 2016: 7932765, doi: 10.1155/2016/7932765, indexed in Pubmed: 26942205.

28. Al-Kafaji G, Al-Muhtaresh HA. Expression of microRNA-377 and microRNA-192 and their potential as blood-based biomarkers for early detection of type 2 diabetic nephropathy. Mol Med Rep. 2018; 18(1): 1171–1180, doi: 10.3892/mmr.2018.9040, indexed in Pubmed: 29845236.

29. El-Monem A, Mahfouz M, Mohamed M. Microrna 192 gene expression in type II diabetic nephropathy. The Egyptian Journal of Hospital Medicine. 2017; 68(1): 885–893, doi: 10.12816/0038187.

30. Houlihan CA, Tsalamandris C, Akdeniz A, et al. Albumin to creatinine ratio: a screening test with limitations. Am J Kidney Dis. 2002; 39(6): 1183–1189, doi: 10.1053/ajkd.2002.33388, indexed in Pubmed: 12046029.

31. Chudleigh RA, Dunseath G, Evans W, et al. How reliable is estimation of glomerular filtration rate at diagnosis of type 2 diabetes? Diabetes Care. 2007; 30(2): 300–305, doi: 10.2337/dc06-1688, indexed in Pubmed: 17259498.

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Prevalence and factors associated with cutaneous manifestations of type 2 diabetes mellitus

ABSTRACT

Background. Type 2 diabetes mellitus (T2DM) is known to cause multiple systemic manifestations. However, there are limited studies describing cutaneous manifestation among T2DM in Malaysia. The objective of this study was to determine the prevalence of cutaneous manifestation among T2DM patients, types of lesions and its associated factors.

Methods. A cross-sectional study was conducted among 271 T2DM patients at a primary care clinic in Kuala Lumpur.

Results. More than one third (63.5%) of patients were found to have cutaneous manifestations of T2DM. The most common manifestation was infections (34.7%) followed by Skin Diseases with Weak to Strong Association with Diabetes (SDWSAD) (31.7%), Skin Manifestation of Diabetic Complication (SMDC) (2.2%) and others cutaneous lesions (22.1%). Among the infections, onychomycosis was the commonest type of infection (27.7%) while diabetic dermopathy was the commonest lesion of SDWSAD (29.7%). Males had almost two times the odds of developing cutaneous manifestations of T2DM, compared to females (adjusted odds ratio [AOR]: 1.871, 95% CI: 1.108–3.160; P = 0.019). There was no association between glycemic control and cutaneous manifestations. However, males and those with T2DM duration of five years and more had 2.6 times the odds of developing SDWSAD (AOR: 2.646, 95% CI: 1.506–4.648 P = 0.001) and (AOR: 2.635, 95% CI: 1.107–6.268, P = 0.028) respectively. Those with diabetic neuropathy and peripheral vascular disease (PVD) had very high odds of developing SMDC such as diabetic foot and trophic ulcers (AOR: 23.259, 95% CI: 1.191–454.2, P = 0.038) and (AOR: 102.36, 95% CI: 4.013–2610, P = 0.005), respectively.

Conclusion. The knowledge of these cutaneous manifestations increases physician's awareness and prompts early screening to reduce morbidity improve quality of life. (Clin Diabetol 2020; 9; 6: 461–468)

Key word: diabetes mellitus, skin manifestations, glycated hemoglobin A, prevalence

Introduction

South-East Asia accounts for more than 60% of the world's diabetes population [1]. The rapid rise in type 2 diabetes mellitus (T2DM) prevalence in Malaysia is alarming with 70 to 80% of patients having poor glycemic control [2]. Cutaneous manifestations of diabetes mellitus appear at disease onset, after the disease is established or precede diabetes by many years. A cutaneous condition is defined as any medical condition that affects the system enclosing the body, including the skin, hair, nails, and related muscle and glands [3]. Cutaneous disorders due to T2DM are attributed to hyperglycemia which affects skin homeostasis resulting in altered keratinocytes metabolism and collagen properties [4, 5]. Relative insulin deficiency in T2DM causes poor growth and differentiation of keratinocyte [4, 5]. Certain conditions such as skin tags and acanthosis nigricans are linked to hyperinsulinemia in the prediabetic state while bullous diabeticorum, diabetic dermopathy and scleroderma are more often see in long stand-

ing T2DM [6]. Microvascular complications, impaired wound healing and other undetermined mechanisms further contribute to cutaneous disease [7].

Prevalence of dermatological disorders due to T2DM ranges from 36% to as high as 88.3% [8, 9]. Factors associated with cutaneous manifestations are poor glycemic control (HbA_{1c} > 7%) [10, 11] and duration of diabetes [8]. Longer disease duration have higher incidence of diabetic dermopathy [8]. Profiling characteristics of T2DM and cutaneous manifestations may help in early diagnosis of diabetes, used as a surrogate marker for poor glycemic control and microvascular complications in other organs. Hence the aim of this study is to determine the prevalence of cutaneous manifestation among patients with T2DM and to determine its associated factors.

Methods

A cross-sectional study was performed between June and September 2019 at the primary care clinic of a university in Kuala Lumpur. Sample size of 246 was calculated using Kish formula, 80% was taken as the highest prevalence cutaneous manifestation of T2DM [8] with 95% confidence interval and 5% absolute precision. The final sample size was 271 as 10% was added to overcome possible incomplete data. Participants were selected using systematic random sampling (sampling interval of 2) from the list of T2DM patients who registered for consultation. Type 1 diabetes mellitus (T1DM), pregnancy and patients with dermatoses due to physical factors such as burns, and trauma were excluded. Written consent was obtained. A thorough physical examination from head to toe including genitalia was performed to evaluate the cutaneous manifestations.

A data collection form was designed to record the intended data, based on a literature search and expert opinion. Section A consists of socio-demographic information such as age, gender, ethnicity and clinical profile such as duration of diabetes, diabetic complication (neuropathy, nephropathy, retinopathy, and peripheral vascular disease), body mass index (BMI) and HbA_{1c} level. Information on HbA_{1c}, diabetic retinopathy, nephropathy and lipid levels was extracted from participant's electronic database. For the purpose of this study, HbA_{1c} level of > 6.5% was considered as poor glycemic control while ≤ 6.5% was considered as a good glycemic control [12]. Peripheral neuropathy was screened using 10-g monofilament, vibration sense using a 128-Hz tuning fork and ankle reflex [12]. Peripheral vascular disease (PVD) was objectively screened based on examination of distal pulses, capillary return time and skin color.

Section B recorded cutaneous manifestation of T2DM that was diagnosed on the consultation day. A list of skin manifestations associated with T2DM was derived from literature search and expert panel input [13, 14]. Cutaneous manifestations of diabetes mellitus were classified into 4 types which are skin diseases with weak to strong associations with diabetes (SDWSAD), skin infections (SI), skin manifestations due to diabetes complication (SMDC) and skin reaction to diabetic treatment [13, 14]. Skin reaction to diabetic treatment was excluded as the objective of this study was to determine the cutaneous manifestations purely due to T2DM and not due to effect of treatment or other secondary causes. Hence lesions which fulfilled these three categories were included:
— Skin Diseases with Weak to Strong Associations with Diabetes (SDWSAD): diabetic dermopathy, acanthosis nigricans, yellow skin, eruptive xanthoma, oral leukoplakia, lichen planus, necrobiosis lipoidica, granuloma annulare and diabetic bullae. Diabetic dermopathy is described as asymptomatic well circumscribed pinkish or brownish atrophic (depressed) lesion on shin, thigh, forearm, scalp or trunk. Lesion may arise in crops gradually resolve, reappear and sometimes ulcerate;
— Skin infections (SI): impetigo, ecthyma, cellulitis, folliculitis, furunculosis, carbuncles, erysipelas, viral warts, tinea capitis, tinea pedis, tinea corporis, tinea cruris, tinea versicolor, tinea manuum, paronychia, onychomycosis, candidiasis. Infections of both dermal and mucosa surfaces were taken into consideration encompassing all types of bacterial and viral infections. All four clinical types of onychomycosis i.e. total dystrophic, white superficial, candida, proximal and distal subungual onychomycosis were all included under the broad term of onychomycosis;
— Skin manifestation of diabetic complication (SMDC): microangiopathy, macroangiopathy, neuropathy e.g. diabetic foot and trophic ulcers.

Patients presenting with of any of the cutaneous disorders related to T2DM was labelled as having cutaneous manifestations of T2DM. Other cutaneous lesions were recorded if found to be present. The primary researcher received hands-on training from a qualified dermatologist and a family medicine specialist with qualification in family practice dermatology prior to the commencement of this study. Clinical diagnosis was made by the primary investigator. Inter-rater reliability for the clinical diagnosis between the 3 investigators was performed using images of the lesions and measured using Cohen's Kappa to ensure the reliability of the diagnosis.

The data collected was analyzed using SPSS (version 25). Descriptive analysis was performed using frequencies and percentage. Simple and multiple logistic regression analyses were used to determine the association between type of cutaneous manifestation with sociodemographic characteristics and clinical profile. Cohen's Kappa was used to determine the agreement between the researchers' diagnoses of the skin condition. This research was approved by the Research and Ethics Committee of University Kebangsaan Malaysia Medical Centre (FF-2018-088) and registered with the National Medical Research Registry (NMRR-17-2555-38622).

Results

A total of 271 patients participated in this study. The median age was 66 (SD 13) years, ranging from 28 to 91 years. Almost half of the participants belonged to the Malay ethnic group 131 (48.3%) and 128 (47.2%) were obese. Female to male ration was almost equal (1:1.08). A large majority of participants 223 (82.3%) had T2DM for more than 5 years. The median HbA1c was 7.7 (2.4) and most 211 (77.9%) had poor glucose control (HbA1c >6.5). About half of them 142 (52.4%) had diabetes complication with nephropathy being the commonest 24 (27.3%) (Table 1).

The interrater agreement between the three investigators on the clinical diagnosis of the cutaneous lesions was good with a Cohen's Kappa value 0.91 (95% confidence interval). More than half of the participants (58.2%) presented with one type of lesion while the rest had two or more types of lesions. The prevalence of cutaneous disorders related to T2DM was 172 (63.5%) with infections being the commonest presentation 94 (34.7%). Fungal infection was commonest (39.9%) (Fig. 1A–E) presenting as onychomycosis (27.7%) (Fig. 1A–C). The most common SDWSADs were diabetic dermopathy (29.9%) (Fig. 1F) and necrobiosis lipoidica (2.6%). Only 0.4% had acanthosis nigricans (Table 2). Other cutaneous lesions observed were eczema 39 (14.4%) (Fig. 1C, G), xerosis 12 (4.4%) (Fig. 1A, H) and callus 5 (1.8%) (Fig. 1I).

Multivariate analysis using independent variables with P values of less than 0.25 and variables considered clinically important showed significant association between cutaneous manifestation and gender. Males were almost two times more likely to have cutaneous manifestation (1.89 [95%CI; 1.12–3.20], P = 0.02) compared to females (Table 3). Males (2.55 [95%CI: 1.46–4.43]) and those with duration of T2DM of more than 5 years (2.42 [95%CI: 1.03–5.70]) have 2 times the odds of having SDWSAD (Table 4).

Table 1. Sociodemographic and clinical characteristics of the study participants

Variables	n (%)	Median (IQR)
Age (years)		66 (13.0)
Gender		
Male	141 (52)	
Female	130 (48)	
Ethnicity		
Malay	131 (48.3)	
Chinese	116 (42.8)	
Indian	24 (8.9)	
Duration of DM in years		10 (10)
BMI [kg/m²]		27 (6)
HBA$_{1c}$ (%)		7.7 (2.4)
LDL level [mmol/L]		2.4 (1.1)
Duration of DM		
< 5 years	48 (17.7)	
≥ 5 years	223 (82.3)	
Glycemic control		
Good control (HbA$_{1c}$ ≤ 6.5%)	60 (22.1)	
Poor control (HbA$_{1c}$ > 6.5%)	211 (77.9)	
BMI		
Underweight/normal (BMI < 22.9)	40 (14.8)	
Overweight (BMI 23–27.4)	103 (38.0)	
Obese (BMI ≥ 27.5)	128 (47.2)	
Diabetic complications		
Yes	142 (52.4)	
No	129 (47.6)	
Type of diabetic complications		
Retinopathy	71 (26.2)	
Neuropathy	47 (17.3)	
Nephropathy	24 (27.3)	
Peripheral vascular disease	6 (2.2)	

Regression analysis demonstrated significant associations between skin manifestations with SMDC such as diabetic neuropathy (P = 0.038) and peripheral vascular disease (P = 0.005). The presence of diabetic neuropathy has 23 times the odds of having SMDC (95% CI: 1.191–454.20, P = 0.038), while peripheral vascular diseases (PVD) 102 times the odds of having SMDC (95% CI: 4.013–2610, P = 0.005) (Table 5). However, these findings need to be interpreted cautiously in view of small number of cases with SMDC. There was no association between skin infection and other cutaneous lesions with the sociodemographic and clinical profile.

Figure 1. Cutaneous lesion in T2DM: **A** — amputated little toe with onychomycosis and xerosis; **B** — onychomycosis with chronic paronychia; **C** — onychomycosis of the big toe due to Aspergillus niger with eczema craquele over the dorsum of the foot; **D** — extensive tinea cruris over the gluteal regions extending to the upper thighs; **E** — maceration of the interdigital space due to fungal infection; **F** — diabetic dermopathy characterized by multiple discrete, hyperpigmented and atrophic macules and patches with thin scales; **G** — ichthyosis over the lower limb; **H** — xerosis with generalized thin scales over the lower limb; **I** — callosities over the first metatarsophalangeal and proximal interphalangeal joints

Discussion

Skin manifestations of T2DM vary in different parts of the world. An outline of common conditions and their etiology would help physicians manage T2DM patients in a holistic manner. We found a high prevalence of cutaneous manifestation of T2DM. The prevalence was similar to that in India, Pakistan and Hong Kong which is between 58 to 67% [10, 15, 16]. Skin infection was the most common cutaneous manifestation of T2DM in our patients, followed by SDWSAD with diabetic dermopathy. Infections and diabetic dermopa-

thy are common cutaneous disorders associated with diabetes [8, 15, 16]. Diabetic foot and trophic ulcer were the most common manifestations of SMDC. Skin infection is common among T2DM patients due to lower immunity and defect in carbohydrate metabolism compared to the normal population [17]. Fungal infection presenting with onychomycosis was the most common pathogen among the infective conditions in our patients. The hot and humid local climate environment is favorable for fungal growth. Fungal infection alters skin barrier and predispose to complications such

Table 2. Prevalence and types of cutaneous manifestations

Variables	n (%)
Presence of cutaneous disorders related to T2DM	
Yes	172 (63.5)
No	99 (36.5)
Types of cutaneous manifestation	
Infections (fungal, bacterial or viral)	94 (34.7)
Skin diseases with weak to strong association with diabetes (SDWSAD)	86 (31.7)
Other cutaneous lesions	60 (22.1)
Skin Manifestation of Diabetic Complications (SMDC)	6 (2.2)
Types of skin diseases with weak to strong association with diabetes (SDWSAD)	
Diabetic dermopathy	81 (29.9)
Necrobiosis lipoidica	7 (2.6)
Acanthosis nigricans	1 (0.4)
Organisms causing skin infection	
Fungal	107 (39.6)
Bacterial	13 (4.7)
Viral	6 (2.2)
Types of infections	
Onychomycosis	75 (27.7)
Paronychia	10 (3.7)
Tinea pedis	8 (3)
Viral wart	6 (2.2)
Candidiasis	5 (1.8)
Tinea corporis	5 (1.8)
Folliculitis	5 (1.8)
Tinea cruris	3 (1.1)
Furunculosis	3 (1.1)
Cellulitis	2 (0.7)
Ecthyma	2 (0.7)
Impetigo	1 (0.4)
Tinea manuum	1 (0.4)
Skin manifestation of diabetic complication	
Diabetic foot	6 (2.2)
Trophic ulcers	1 (0.4)
Other cutaneous lesions	
Eczema*	39 (14.4)
Xerosis	12 (4.4)
Callus	5 (1.8)
Skin Tag	5 (1.8)
Corn	3 (1.1)
Lipoma	2 (0.7)
Psoriasis	2 (0.7)
Xanthelasma	1 (0.4)
Tophi	(0.4)

*The term eczema here is inclusive of both endogenous and exogenous types of eczema

as cellulitis. Fungal infections should be identified early and treated.

We did not determine the onset of lesions in relation to diabetes duration. Skin manifestation like acanthosis nigricans precede diabetes, screening for diabetes at regular intervals for early diagnosis would be beneficial [6]. Although acanthosis nigricans is popularly described as a common association with T2DM, only 0.4 % of our study participants had this manifestation. Prevalence acanthosis nigricans ranged from 1.88% to 4% [8, 18].

We identified the male gender and duration of T2DM of $\geq$ 5 years as risk factors for SDWSA. Diabetic dermopathy was significantly more frequent in males and those with longer duration of DM [19, 20]. Skin lesions were also more common among diabetic men [16]. Skin diseases affect men and women differently and this is attributed differences in skin thickness, pH, effect of sex hormone and immune system [21]. Our study did not show an association between BMI and risk for cutaneous manifestations of T2DM or SDWSA. This may be attributed to the cross-sectional nature of this study where at the point of data collection, cutaneous signs were not elicited as it may have resolved after treatment or yet to manifest in the future, which may be identified in a longitudinal study.

Although an association was expected between the presence of cutaneous manifestations of T2DM and poor glycemic control, this was not evident in our study. There are inconsistent observations on the association between cutaneous manifestations of T2DM with glycemic control with some showing positive association while some did not show any association [22–24]. The cause for cutaneous manifestations of T2DM is multifactorial and not purely due to hyperglycemia. The lack of standardization in the cut off values for good and poor glycemic control based on HbA_{1c} in earlier studies makes the comparison of outcome difficult. HbA_{1c} of more than 6.5% is considered as poor control while some consider 7% as poor control. HbA_{1c} test is performed 6 monthly for our local diabetic population. An average HbA_{1c} level over a longer duration would give a better evaluation of control compared to a single reading to assess the association.

As expected, patients with diabetic neuropathy and PVD have very high odds of having SMDC, such as diabetic foot and trophic ulcers in our study. These associations are well described [25, 26]. Peripheral vascular disease and diabetic neuropathy are indeed risks for developing diabetic foot and trophic ulcers due to poor sensation and blood circulation of the lower limbs. Diabetic foot ulcer is a strong predictor for major limb amputation [27]. Regular foot assess-

Table 3. Risk factors for cutaneous manifestation of T2DM

Variables	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Gender				
Male	1.97 (1.19–3.27)	**0.01***	1.89 (1.12–3.20)	**0.02***
Female	(1)		(1)	
Ethnicity				
Malay	(1)		(1)	
Non-Malay	0.64 (0.39–1.06)	0.08	0.65 (0.39–1.10)	0.10
BMI				
Underweight/normal	(1)		(1)	
Overweight	1.07 (0.51–2.25)	0.85	0.86 (0.40–1.87)	0.71
Obese	1.63 (0.78–3.37)	0.19	1.352 (0.63–2.90)	0.44
Duration of DM				
< 5 years	(1)		(1)	
≥ 5 years	1.05 (0.55–2.01)	0.88	0.93 (0.47–1.85)	0.84
Glycemic control				
Good (HbA$_{1c}$ ≤ 6.5%)	(1)		(1)	
Poor (HbA$_{1c}$ > 6.5%)	1.21 (0.67–2.18)	0.53	1.09 (0.58–2.03)	0.79
Diabetic complication				
Yes	1.53 (0.93–2.51)	0.10	1.40 (0.82–2.38)	0.22
No	(1)		(1)	

*Indicate significant P < 0.05, (1) reference group, adjusted for gender, ethnicity, BMI group, duration of DM, glycemic control, nephropathy, retinopathy

Table 4. Risk factors for SDWSAD type of cutaneous manifestation of T2DM

Variables	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Gender				
Male	2.60 (1.53–4.42)	**0.00***	2.55 (1.46–4.43)	**0.00***
Female	(1)		(1)	
Ethnicity				
Malay	(1)		(1)	
Non-Malay	0.85 (0.51–1.41)	0.53	0.86 (0.49–1.48)	0.52
BMI				
Underweight/normal	(1)		(1)	
Overweight	1.68(0.74–3.82)	0.22	1.51(0.64–3.60)	0.35
Obese	1.32 (0.59–2.95)	0.51	1.14 (0.49–2.69)	0.76
Duration of DM				
< 5 years	(1)		(1)	
≥ 5 years	2.69 (1.20–6.03)	**0.02***	2.42 (1.03–5.70)	**0.04***
Glycemic control				
Good (HbA$_{1c}$ ≤ 6.5%)	(1)		(1)	
Poor (HbA$_{1c}$ > 6.5%)	2.16 (1.08–4.32)	**0.03***	1.97 (0.95–4.10)	0.07
Diabetic Complications				
Yes	1.39 (0.83–2.32)	0.21	0.94 (0.53–1.65)	0.83
No	(1)		(1)	

*Indicate P < 0.05, (1) — reference group, adjusted for gender, ethnicity, BMI, diabetes duration, glycemic control, DM complications

ment, foot self-care advice and training to prevent the development of SMDC are important in patients with T2DM complicated by with peripheral neuropathy and peripheral vascular disease. There was no association between diabetic dermopathy and retinopathy among the participants of this study although diabetic der-

Table 5. Risk factors for SMDC type of cutaneous manifestation of T2DM

Variables	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Gender				
Male	0.54 (0.10–2.97)	0.48	0.19 (0.02–2.26)	0.19
Female	(1)		(1)	
BMI				
Underweight/normal	(1)		(1)	
Overweight/obesity	0.34 (0.06–1.89)	0.22	0.39 (0.04–3.74)	0.41
Duration of DM				
< 5 years	(1)		(1)	
$\geq$ 5 years	1.08 (0.12–9.44)	0.10	0.13 (0.01–3.77)	0.24
Glycemic control				
Good (HbA$_{1c}$ $\leq$ 6.5%)	(1)		(1)	
Poor (HbA$_{1c}$ > 6.5%)	1.43 (0.16–12.50)	0.95	1.58 (0.11–23.63)	0.74
Neuropathy				
Yes	10.33 (1.83–58.15)	**0.01***	23.26 (1.19–454.2)	**0.04***
No	(1)		(1)	
Nephropathy				
Yes	2.73 (0.54–13.85)	0.23	1.89 (0.24–14.78)	0.55
No	(1)		(1)	
Retinopathy				
Yes	5.91 (1.06–33)	**0.04***	3.07 (0.34–27.72)	0.32
No	(1)		(1)	
Peripheral vascular disease				
Yes	32 (4.57–23)	**0.00***	102.36 (4.01–261)	**0.01***
No	(1)		(1)	

*Indicate P < 0.05, (1) — reference group, adjusted for gender, DMI, duration of DM, glycemic control, diabetic neuropathy, nephropathy, retinopathy, and peripheral vascular disease

mopathy is considered as a diabetic microangiopathy. Half of the patients with diabetic dermopathy were found to have retinopathy [28]. A prospective cohort study would yield more information on the association between diabetic dermopathy and retinopathy. Limitation of this study is that peripheral vascular disease was evaluated clinically and not confirmed using arterial-brachial pressure index (ABSI) or Doppler ultrasound which gives a more objective evaluation.

Conclusions

The prevalence of cutaneous manifestation among T2DM in this study was high, affecting almost two thirds of the participants. The commonest cutaneous manifestation was infection and diabetic dermopathy. Fungus was the most common cause for infection presenting as onychomycosis. Risk factors for cutaneous manifestation of T2DM are males and duration of diabetes of 5 years and more. Diabetic neuropathy and peripheral vascular disease are risks for SMDC diabetic

foot and trophic ulcers. Our study did not demonstrate an association between glycemic control and cutaneous manifestations of T2DM. A prospective study looking at glycemic control over a longer duration would be useful to elicit the association. T2DM patients should be screened early for skin manifestations especially males, T2DM $\geq$ 5 years, those with diabetic neuropathy and peripheral vascular disease so that management can be instituted early to prevent complications.

Acknowledgements

Conflict of interest

The authors have no competing interests to declare.

REFERENCES

1. Nanditha A, Ma RCW, Ramachandran A, et al. Diabetes in Asia and the Pacific: Implications for the Global Epidemic. Diabetes Care. 2016; 39(3): 472–485, doi: 10.2337/dc15-1536, indexed in Pubmed: 26908931.
2. Feisul MI, Azmi S. (Eds). National Diabetes Registry Report, Volume 1, 2009-2012. Ministry of Health Malaysia; Kuala Lumpur; 2013.
3. Miller J, Marks H, James G. Lookingbill and Marks' Principles of Dermatology. 6th Ed. Elsevier; 2019, doi.org/10.1016/C2015-0-00881-4.
4. Behm B, Schreml S, Landthaler M, et al. Skin signs in diabetes mellitus. J Eur Acad Dermatol Venereol. 2012; 26(10): 1203–1211, doi: 10.1111/j.1468-3083.2012.04475.x, indexed in Pubmed: 22348239.
5. de Macedo GM, Nunes S, Barreto T. Skin disorders in diabetes mellitus: an epidemiology and physiopathology review. Diabetol Metab Syndr. 2016; 8(1): 63, doi: 10.1186/s13098-016-0176-y, indexed in Pubmed: 27583022.
6. Bustan RS, Wasim D, Yderstræde KB, et al. Specific skin signs as a cutaneous marker of diabetes mellitus and the prediabetic state — a systematic review. Dan Med J. 2017; 64(1), indexed in Pubmed: 28007053.
7. Mahmood T, ul Bari A, Agha H. Cutaneous manifestations of diabetes mellitus. J Pak Assoc Dermatol. 2016; 15(3): 227–232.
8. Khoharo HK, Ansari S, Qureshi F. Frequency of skin manifestations in 120 type 2 diabetics presenting at tertiary care hospital. J Liaquat Uni Med Sci. 2009; 8: 12–5.
9. Rao S, Naga M, Lakshmi PV, et al. 2015. A prospective study of cutaneous abnormalitis in patients with diabetes mellitus. Int J Pharm, Chem & Biol Sci. 2015; 5(1): 276–286.
10. Majeed M, Iqbal F, Mehboob A. Frequency and association of cutaneous manifestations of diabetes mellitus with HbA1c . Postgrad Med Inst . 2004; 18(2): 85–89.
11. Niaz F, Bashir F, Shams N, et al. Cutaneous manifestations of diabetes mellitus type 2: prevalence and association with glycemic control. J Pak Assoc Dermatol. 2016; 26(1): 4–11.
12. Kamaruddin, N, Omar A. Clinical practice guideline on management of type 2 diabetes mellitus. 5th Edition; Ministry of Health Malaysia; Kuala Lumpur; 2015. https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Endocrine/3a.pdf.
13. Ferringer T, Miller OF. Cutaneous manifestations of diabetes mellitus. Dermatologic clinics. 2002; 20(3): 483-492, doi.org/10 1016/S0733. 8635; 02: 00018–9, doi: 10.1016/S0733-8635(02)00018-9.
14. Callen JP, Jorizzo JL, Zone JJ, et al. Dermatological signs of systemic disease. 5th Ed; Elsevier, 2016.
15. Gupta V, Kudyar RP, Bhat Y. Cutaneous manifestations of diabetes mellitus. Int J Diab Dev Ctries. 2006; 26(4): 152–155, doi: 10.4103/0973-3930.33180.
16. Yeung SW, Chan PF, Lai K, et al. The Prevalence and the Associated Factors of Cutaneous Manifestations in Chinese Patients with Type II Diabetes Mellitus in a Primary Care Diabetes Clinic in Hong Kong. J Diab Res Ther. 2018; 4(1), doi: 10.16966/2380-5544.136.
17. Chang SJ, Hsu SC, Tien KJ, et al. Metabolic syndrome associated with toenail onychomycosis in Taiwanese with diabetes mellitus. Int J Dermatol. 2008; 47(5): 467–472, doi: 10.1111/j.1365-4632.2008.03606.x, indexed in Pubmed: 18412863.
18. Fatima K, Naheed A, Khan SA. Skin manifestations of diabetes mellitus. Journal of Rawalpindi Medical College (JRMC). 2018; 22(3): 252–255.
19. Galdeano F, Zaccaria S, Parra V. Cutaneous manifestations of diabetes mellitus: clinical meaning. Dermatol Argent . 2010; 16(2): 117–121.
20. Mendes AL, Miot HA, Haddad V. Diabetes mellitus and the skin. An Bras Dermatol. 2017; 92(1): 8–20, doi: 10.1590/abd1806-4841.20175514, indexed in Pubmed: 28225950.
21. Dao H, Kazin R. Gender differences in skin: A review of the literature. Gender Medicine. 2007; 4(4): 308–328, doi: 10.1016/s1550-8579(07)80061-1.
22. Chatterjee N, Chattopadhyay C, Sengupta N, et al. An observational study of cutaneous manifestations in diabetes mellitus in a tertiary care Hospital of Eastern India. Indian J Endocrinol Metab. 2014; 18(2): 217–220, doi: 10.4103/2230-8210.129115, indexed in Pubmed: 24741520.
23. Timshina DK, Thappa DM, Agrawal A. A clinical study of dermatoses in diabetes to establish its markers. Indian J Dermatol. 2012; 57(1): 20–25, doi: 10.4103/0019-5154.92671, indexed in Pubmed: 22470203.
24. Rayfield EJ, Ault MJ, Keusch GT. Infection and diabetes: The case for glucose control. Am J Med. 1982; 72(439): 450, doi: 10.1016/0278-2391(82)90129-x.
25. Khan Y, Khan M, Jain A, et al. A study of association of Diabetic Foot Ulcers and Peripheral Vascular Disease. International Journal of Advances in Medicine. 2018; 5(6): 1454, doi: 10.18203/2349-3933.ijam20184756.
26. Crawford F, Cezard G, Chappell FM, et al. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). Health Technol Assess. 2015; 19(57): 1–210, doi: 10.3310/hta19570, indexed in Pubmed: 26211920.
27. Ab Rahman NK, Abd Aziz A, Mohammad W, et al. Prognostic factors of major amputation among hospitalized diabetic foot patients in a tertiary teaching hospital. Malaysian Journal of Public Health Medicine. 2016; 16 (2): 41–47.
28. Morgan AJ, Schwartz RA. Diabetic dermopathy: A subtle sign with grave implications. J Am Acad Dermatol. 2008; 58(3): 447–451, doi: 10.1016/j.jaad.2007.11.013, indexed in Pubmed: 18155320.

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Cost and quality of diabetes care: comparisons between Rzeszow, Podkarpacie, Poland and Waukesha, Wisconsin, United States

ABSTRACT

Background. The cost of diabetes care increases world-wide and is highest in the United States (US), while the quality of care remains unsatisfactory.

The aim of this study was to compare the quality and cost of type 2 diabetes mellitus (DM) care between Waukesha, Wisconsin, US and Rzeszów, Poland.

Methods. DM quality data for the Polish cohort were abstracted from the charts of 79 DM patients in Rzeszow, Podkarpacie from 1 January 2013 to 31 December 2014. Cost data were attained from the Polish National Health Fund. Seventy-nine DM patients, matched for age, body mass index, and sex, from Waukesha, Wisconsin were chosen as comparators. DM quality data was obtained from the medical record and cost data from health system decision support staff.

Results. Average HbA_{1c} (%, mean ± SD) in the Polish and US cohorts were 7.4 ± 1.4 and 8.0 ± 2.1, respectively (P = 0.03). Mean systolic/diastolic blood pressure (mm Hg) in the two cohorts was 150 ± 17/81 ± 12 and 132 ± 17/74 ± 11 (P < 0.001), respectively. The rates of statin usage were 90% and 86% (P = 0.45), respec-tively. Costs of direct medical care (hospitalizations, outpatient care, and medications) in the Polish and US cohorts were 1,263 US dollars (USD) and 10,121 USD, per annum, respectively.

Conclusion. This study reports significant differences in cost with relatively small differences in quality and of DM care between Poland and the US. As the US continues to attempt healthcare reform in order to decrease cost and increase quality, this study suggests that gains in cost and quality may not be mutually exclusive. (Clin Diabetol 2020; 9; 6: 469–474)

Key words: diabetes, the cost of care, quality of care, Poland, United States

Introduction

Healthcare costs in the United States (US) are the highest in the world and are rising [1, 2]. In contrast, healthcare spending is much lower in European coun-tries; e.g., 9,892 US dollars (USD) per capita in the US versus 6,647 USD per capita in Norway in 2016 which has the fourth-highest healthcare spending per capita in the world [3]. Other countries in Europe, such as Poland, have even lower healthcare costs [3]. According to the Organization for Economic Cooperation and De-velopment (OECD), Poland spent just 6.4% of its gross domestic product (GDP) on healthcare in 2013, while the US spent 16.9% of its GDP on healthcare that same year. Despite the higher cost of healthcare in the US, life expectancies at birth were similar: 77.7 years in Poland and 78.8 years in the US for a person born in the same year [4]. In the healthcare cost debate occurring in the US, there are perhaps lessons to be learned from the global community [5].

Chronic diseases like type 2 diabetes mellitus (DM) account for a significant proportion of the total money spent on healthcare in the US [6]. Patients with DM account for 1 in 4 healthcare dollars spent in the US, with nearly half of that expenditure related directly to DM [6]. Previous studies estimated that the direct medical cost per patient with DM in the US was ~10,000 USD/year in 2017 [6, 7]. In other middle- and high-income countries, costs are significantly lower [8–10]. One of the lingering questions in the healthcare cost debate is whether the amount of money spent correlates with the quality of care [2, 11, 12]. Life expectancy data noted above seem to indicate that cost and quality may not always correlate; however, there are no data directly comparing the quality and the cost of DM care between the US and a middle-income country such as Poland.

Any analysis comparing the health systems of the two countries must control for potential variables that may confound the conclusion [13]. Significant potential confounders include patient-level demographics that would affect the cost or quality of care in a way that is unrelated to the health system. Other potential confounders include socioeconomic status and race.

The goal of this study is to compare the quality of care and approximate costs for DM care between two cities in the US and Poland   Waukesha, US and Rzeszow, Poland while controlling for potential confounders. The study will seek to answer whether an increase in the cost of care leads to a commensurate increase in quality of care.

Methods

Subjects

Charts from seventy-nine patients with DM attending a Diabetic Outpatient Clinic of the second level of reference in Rzeszow, Poland (regional capital of Podkarpacie region of Poland) during the years 2013–2014 were randomly selected and quality of care data were collected. An equal number of patients (with a mailing address in the city of Waukesha, WI, US) attending an Endocrinology Clinic in the Froedtert Health system (State of Wisconsin) were reviewed and quality of care data was similarly extracted. Charts in both cohorts were only included if patients were aged $\geq$ 18 years, had an established DM diagnosis, had documented glycated hemoglobin (HbA$_{1c}$) values during the years of review, and an up-to-date medication list. Patients had to have received care (an office visit) at the above clinics at least once during the years 2013–2014. Both groups were cared for by board-certified Diabetologist or Endocrinologists.

Subjects in the two cohorts were matched for gender, the decade of life, and the World Health Organization (WHO) body mass index (BMI) category. The Polish cohort was the basis for selecting matched patients in the Wisconsin cohort. The initial Wisconsin cohort was identified using a database extracted from the health system's electronic medical record (EMR) database and resulted in an initial cohort of ~5000 patients. Subsequently, the cohort was narrowed down to those who matched on WHO BMI category, gender, and the decade of life. Froedtert Health system consists of several large hospitals and over one million outpatient visits each year [14]. Institutional Review Board approval was obtained from both Rzeszow University in Rzeszow, Poland and the Medical College of Wisconsin in Milwaukee, Wisconsin.

Regions of comparison

The cities in this study were selected as comparators due to similarities in size, racial makeup, median income, and unemployment rate. Rzeszow is a city with a population of 188,606 in 2016, nearly 100% white, a median income of 28,847 USD in 2015, and an unemployment rate of 7.3% in 2015 [15]. Waukesha, WI is a city with a population of 72,363 in 2016, 86% white, a median income of 31,874 USD in 2015, and an unemployment rate of 6.3% in 2015 [16]. Waukesha, WI was the closest in socioeconomic indicators to Rzeszow, Podkarpacie among the surrounding cities served by Froedtert Health system and was therefore used as a comparison city. The income levels were normalized based on Purchasing Power Parity (PPP) 2015 Polish zloty (PLN) and 2015 US dollars (USD) of 1.76 PLN per USD [17]. PPP normalizes for both the exchange rate and local purchasing power of each currency [18].

Quality of DM care

Quality metrics were selected from the American Diabetes Association (ADA) clinical guidelines [19]. The quality measures that were collected for both Rzeszow and Waukesha included HbA$_{1c}$, blood pressure (BP), rates of statin usage, nephropathy, and retinopathy. Rate of statin usage is defined as a prescribed statin in the chart or a documented statin allergy. Nephropathy is defined as a lab test positive for proteinuria or documentation of nephropathy in the provider note. Retinopathy is defined as documentation of such by an ophthalmologist on a dilated eye exam. These data were collected through chart reviews in Poland. Data for the WI cohort were collected through the EMR database (HbA$_{1c}$ and BP), and the remainder (statin usage, nephropathy and retinopathy) were obtained through chart review.

HbA$_{1c}$ and albuminuria measurements were performed using a DCA 2000®+ analyzer (Siemens,

Elkhart, IN, USA) using the monoclonal antibody method in Poland. In the US cohort, HbA_{1c} measurements were performed using the same DCA 2000®+ analyzer while albuminuria assessments were performed using a Roche Cobas 8000 (Roche Diagnostics, Mannheim, Germany).

Cost of DM care

The cost of care data for the Polish cohort was provided by the Polish National Health Fund (NFZ), which is a Polish government entity that pays for the vast majority of care in Poland [20]. The NFZ provided data in aggregate for the region of Podkarpacie. Cost data included the cost of visits granted by NFZ in outpatient DM clinics, hospitalizations of patients with DM (including DM as comorbidity), and reimbursement of DM medications for patients with DM in the Podkarpacie region during years 2013–2014. The NFZ reported the number of unique patients with DM included in the cost data. The cost data was converted into USD using PPP for the year in which the service was given. The total direct medical cost was calculated by adding together the costs of medications, outpatient visits, and inpatient care. The cost calculated in this study is an average for patients with DM living in Podkarpacie, Poland.

The cost of care for the Waukesha cohort was calculated directly from the hospital and professional billing records captured in the Froedtert Health system. Cost is reported as the direct medical cost during the years 2013–2014 at the estimated Medicare reimbursement, regardless of patient's insurance coverage, for a given service as calculated by Froedtert Health system decision support staff. Direct medical cost includes the costs of medications, outpatient visits, and inpatient care. The cost of medications only includes data from pharmacies operated by the health system. Additionally, the cost is reported as a percentage of gross national income (GNI) in 2013 as reported by the OECD for both Poland and the US.

Data analyses

All data were extracted into an Excel spreadsheet. Descriptive statistics (mean, standard deviation, sample proportions, etc.) were used to describe the distribution of quality variables and complications within the study sample. Continuous variables are presented as the mean (standard deviation). Two-tailed t-tests were used to test for differences across groups for continuous variables and a chi-square test was used for categorical variables. Significance level was set at $P < 0.008$ to account for multiple comparisons (0.05/6) using Bonferroni correction [21].

Results

Quality of care data was collected from 158 patients (43% women in both cohorts) with DM in Podkarpacie and Wisconsin. Mean ages of patients from Poland and the US cohorts were 63.6 (9.0) and 63.3 (9.7) years (P = .83), respectively. Mean BMI was 31.9 (4.7) and 32.4 (5.0) kg/m^2 (P = .57) in the Polish and US cohorts, respectively.

Comparison of quality of care

HbA_{1c} level and nephropathy rate were significantly lower in Polish cohort, while both systolic and diastolic BP values were lower in the US patients. Statin use and retinopathy prevalence were not significantly different (Table 1). In the Polish and US cohorts, 84% and 99%, respectively, were screened for nephropathy, while 100% and 85%, respectively, were tested for diabetic retinopathy.

Comparison of costs

The mean direct cost of care (cost of hospitalizations, outpatient care, and medications) per patient expressed in USD and as % of the GNI per capita was considerably higher in the US compared to Poland (Fig. 1).

Discussion

In this study of two cohorts from comparable cities in Poland and the US, we found that glycemic control as measured by HbA_{1c} was not statistically different between the two groups, but there was a significant difference in direct care costs. BP levels were statistically significantly lower in the US cohort compared to the Polish cohort. Nephropathy rates were higher in the US cohort although fewer patients were evaluated for nephropathy in the Polish cohort. Retinopathy rates and statin usage were not significantly different between the two groups. This is the first study, of which we are aware, to compare the quality of care in cohorts between two countries with different healthcare systems in matched cohorts.

In this study, we chose objective measures to assess the quality of DM care. American Diabetes Association guidelines recommend measurement of HbA_{1c} every 3–6 months, assessment of BP at every visit with a goal systolic pressure less than 130 mm Hg, annual screening for microalbuminuria and retinopathy, and statin therapy for patients with clinical cardiovascular disease or age $\geq$ 40 years, regardless of baseline lipid levels [19]. Previously published quality metrics data from a US population (n = 3131 in Minnesota) showed similar HbA_{1c} of 7.3% and mean systolic BP of 133 mm Hg, however, the rates of nephropathy and retinopathy

Table 1. Quality of care measures in the Polish (Rzeszów) and American (Waukesha) cohorts

Parameter	Rzeszów n = 79	Waukesha n = 79	P value
HbA$_{1c}$ (%) mean ± SD	7.41 ± 1.41	8.04 ± 2.14	0.033
Systolic blood pressure [mm Hg]	150.39 ± 16.66	131.99 ± 16.71	< 0.001
Diastolic blood pressure [mm Hg]	80.62 ± 11.51	73.56 ± 11.26	< 0.001
Statin usage (%)	90	86	0.450
Nephropathy rate (%)	17	37	0.006
Retinopathy rate (%)	10	21	0.069
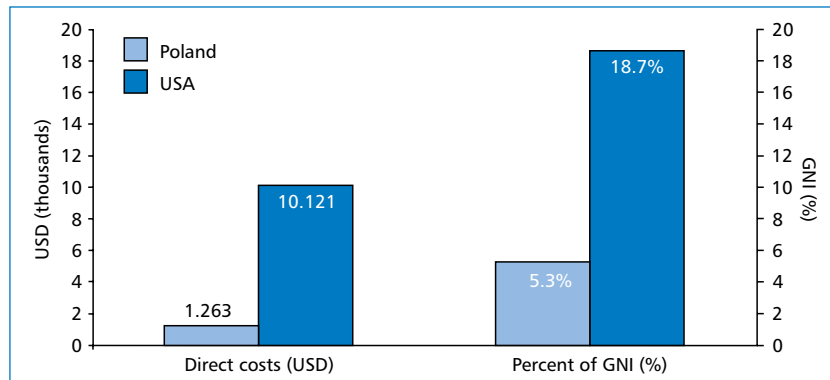
Figure 1. Direct medical costs of diabetes care in Rzeszów (Poland) and Waukesha (US) expressed in US dollars (USD) and as percent of Gross National Income (GNI) per capita

were significantly lower. Nephropathy and retinopathy rates in the cohort from Poland were significantly lower than in the US cohort [22]. The Wisconsin Collaborative for Healthcare Quality (WCHQ) reported 83% statin usage at a clinic in Waukesha, WI which is consistent with our report in the US cohort [23]. A Polish study in 2013 described the quality of DM care for a 249-person cohort [24]. The mean HbA$_{1c}$ was 7.3% and the mean systolic BP was 131 mm Hg. The rate of statin usage was 81%. The rates of nephropathy and retinopathy were 31% and 42%, respectively. While HbA$_{1c}$ was comparable, BP level and statin usage were slightly higher in our Polish cohort compared to this previously published study. The rates of both nephropathy and retinopathy were both lower in our cohort.

The costs of care we estimated in our study are similar to previous studies in both countries. Our estimate of 1,263 USD for direct medical care in Poland is in line with previous estimates of approximately 1,000 USD in 2009 [24, 25]. Our estimate of 10,121 USD per year for direct medical care for patients with diabetes in the US is similar to previous estimates of approximately 10,000 USD per year in 2017 [6, 7]. Substitution of the estimated Medicare reimbursement for the actual reimbursement likely artificially lowered the US cost reported in this study.

Previous studies have either addressed cost or quality of diabetes care in isolation of each other, which makes it difficult to infer relationships between the quality of care and cost due to a paucity of controlled variables [13]. This is the first study to estimate both measures in the same study in populations matched for age, gender, BMI and socioeconomic status. Previous studies have used statistical methods to control for demographic variables. No other studies have utilized a matched cohort. Additionally, the similar quality results of our study are also unique in that it examines a chronic disease, instead of a particular procedure or episode of care. Examining a chronic disease that touches many different components of the health system using a matched cohort suggests that differences in cost are due to foundational differences in the health system. The results of our study suggest that the US health system delivers a similar quality of DM care at a significantly higher cost. Both groups were cared for by a sub-specialist. In addition, we attempted to control socioeconomic factors by matching for the city in which they primarily live in.

Burgeoning healthcare costs in the US threaten the fiscal sustainability of the country [26, 27]. The high cost of healthcare in the US has been attributed to multiple reasons including wasteful spending, prescrip-

tion drug costs, and advances in medical technology (technology creep). In addition, an aging workforce, unhealthy lifestyles, high administrative costs, lack of patient ownership of their care, and consolidation of provider practices all create an environment for unfettered cost growth [26, 27]. Previous debates have focused on delineating whether the high cost of healthcare in the US is due to high prices or high utilization [12, 28]. This debate has by no means reached a consensus because many of these analyses focus on a single procedure or episode of care [28, 29]. While our study did not valuate all of these factors, we did control for demographic features that can be considered as a higher risk for health care costs (i.e. older age, obesity, and care by a sub-specialist).

Our study is not free from several limitations. The first one is its retrospective nature and the exact study design was not able to be replicated in each region due to differences in health system infrastructure. In addition, the data cover the period 2013–2014, i.e. before the wider introduction to market newer drug classes: SGLT-2 (sodium-glucose cotransporter-2) inhibitors and GLP-1(glucagon-like peptide-1) receptor agonists. Moreover, the tariffs for inpatient and outpatients services in Poland may not reflect the cost covered as in the US. In Poland, but also in the US, apart from the direct medical cost per patient covered by national payer or medical insurance services, substantial role can play patient's co-payment, especially for not-reimbursed or partly reimbursed drugs which depends on legal regulations and not necessarily on clinical practice. Despite we matched patients for gender, the decade of life and BMI to minimize bias, there are still many variables that could differ in each cohort, e.g. diabetes duration, presence of comorbidities, including cardiovascular disease (CVD) and the treatment used. We are aware that the list of the quality measures could be longer, but we were focused on the measures strictly associated with diabetes care i.e. glycemic control, blood pressure control, statin use and presence of microvascular complications. Macrovascular complications can develop independently of diabetes and frequently precede diabetes diagnosis, thus, we decided not to include this variable into quality measures. Additionally, another potential confounder is the severity of DM in each cohort. It is possible that primary care providers referred to less complex DM patients to an Endocrinologist in one of the cohorts. We were unable to evaluate other ADA recommendations such as annual dental care, and annual comprehensive foot exam. We also acknowledge that the political climate, patient and societal expectations, and litigation environments are mark-

edly different between each country. Due to all these limitations, our findings cannot be generalized to the whole populations of both countries. Nevertheless, irrespective of these limitations, our study, conducted in comparable cohorts, indicate that similar diabetes control can be attained, in case of Poland, with substantially lower expenses.

Conclusion

The US continues to attempt healthcare reform in order to decrease cost and increase quality. This study reports minimal differences in quality and significant differences in cost between a matched cohort in Poland and the US and thus fills a critical gap in the literature by suggesting that gains in cost and quality may not be mutually exclusive. Further research is needed to understand how to best apply these lessons as health policy.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Davis K. Slowing the growth of health care costs — learning from international experience. N Engl J Med. 2008; 359(17): 1751–1755, doi: 10.1056/NEJMp0805261, indexed in Pubmed: 18946060.
2. Shi L, Singh D. Delivering health care in America: a systems approach. Sixth edition. Jones & Bartlett Learning, Burlington 2015.
3. Health resources — Health spending — OECD Data. Organization for Economic Cooperation and Development. http://data.oecd.org/healthres/health-spending.htm (19.04.2018).

4. Health status — Life expectancy at birth — OECD Data. theOECD. http://data.oecd.org/healthstat/life-expectancy-at-birth.htm (19.04.2018).

5. Glass RI. What the United States has to gain from global health research. JAMA. 2013; 310(9): 903–904, doi: 10.1001/jama.2013.276558, indexed in Pubmed: 24002270.

6. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018; 41(5): 917–928, doi: 10.2337/dci18-0007, indexed in Pubmed: 29567642.

7. Ozieh MN, Bishu KG, Dismuke CE, et al. Trends in health care expenditure in U.S. adults with diabetes: 2002-2011. Diabetes Care. 2015; 38(10): 1844–1851, doi: 10.2337/dc15-0369, indexed in Pubmed: 26203060.

8. Mata-Cases M, Casajuana M, Franch-Nadal J, et al. Direct medical costs attributable to type 2 diabetes mellitus: a population-based study in Catalonia, Spain. Eur J Health Econ. 2016; 17(8): 1001–1010, doi: 10.1007/s10198-015-0742-5, indexed in Pubmed: 26542160.

9. Dawson KG, Gomes D, Gerstein H, et al. The economic cost of diabetes in Canada, 1998. Diabetes Care. 2002; 25(8): 1303–1307, doi: 10.2337/diacare.25.8.1303, indexed in Pubmed: 12145225.

10. Köster I, Huppertz E, Hauner H, et al. Direct costs of diabetes mellitus in Germany — CoDiM 2000–2007. Exp Clin Endocrinol Diabetes. 2011; 119(6): 377–385, doi: 10.1055/s-0030-1269847, indexed in Pubmed: 21264804.

11. Anderson GF, Chalkidou K. Spending on medical care: more is better? JAMA. 2008; 299(20): 2444–2445, doi: 10.1001/jama.299.20.2444, indexed in Pubmed: 18505956.

12. Dieleman JL, Squires E, Bui AL, et al. Factors associated with increases in US health care spending, 1996–2013. JAMA. 2017; 318(17): 1668–1678, doi: 10.1001/jama.2017.15927, indexed in Pubmed: 29114831.

13. Hussey PS, Wertheimer S, Mehrotra A. The association between health care quality and cost: a systematic review. Ann Intern Med. 2013; 158(1): 27–34, doi: 10.7326/0003-4819-158-1-201301010-00006, indexed in Pubmed: 23277898.

14. About the Froedtert & MCW Health Network | Froedtert & the Medical College of Wis. https://www.froedtert.com/about (19.04.2019).

15. Information Service Rzeszow-Rzeszow in numbers. http://www.rzeszow.pl/miasto-rzeszow/dane-statystyczne/rzeszow-w-liczbach (25.04.2018).

16. American FactFinder - Community Facts. U.S. Census Bureau. https://factfinder.census.gov/faces/nav/jsf/pages/community_facts.xhtml# (25.04.2018).

17. Purchasing Power Parities for GDP and Related Indicators. OECD; 2018.

18. Vogel F. What Is a Purchasing Power Parity? World Bank 4.

19. American Diabetes Assocation. Standards of Medical Care in Diabetes. Diabetes Care. 2018; 41(Supplement 1).

20. Sagan A, Panteli D, Borkowski W, et al. Poland health system review. Health Syst Transit. 2011; 13(8): 1–193, indexed in Pubmed: 22551527.

21. Rogers A, Weiss ST. Epidemiologic and population genetic studies. Clinical and Translational Science. 2017: 313–326, doi: 10.1016/b978-0-12-802101-9.00017-x.

22. Peterson KA, Radosevich DM, O'Connor PJ, et al. Improving Diabetes Care in Practice: findings from the TRANSLATE trial. Diabetes Care. 2008; 31(12): 2238–2243, doi: 10.2337/dc08-2034, indexed in Pubmed: 18809622.

23. Diabetes: Statin Use Unless Contraindicated. Wisconsin Collaborative for Healthcare Quality; 2017.

24. Kudaj-Kurowska A, Turek I, Józefowska M, et al. [The metabolic control in type 2 diabetic patients according to Polish Diabetes Association recommendation]. Diabet Klin. 2014; 3 (3): 92–99.

25. Leśniowska J, Schubert A, Wojna M, et al. Costs of diabetes and its complications in Poland. Eur J Health Econ. 2014; 15(6): 653–660, doi: 10.1007/s10198-014-0644-y.

26. Orszag PR, Ellis P. Addressing rising health care costs — a view from the Congressional Budget Office. N Engl J Med. 2007; 357(19): 1885–1887, doi: 10.1056/NEJMp078191, indexed in Pubmed: 17989379.

27. Chernew ME, Baicker K, Hsu J. The specter of financial Armageddon — health care and federal debt in the United States. N Engl J Med. 2010; 362(13): 1166–1168, doi: 10.1056/NEJMp1002873, indexed in Pubmed: 20237338.

28. Spiro T, Lee EO, Emanuel EJ. Price and utilization: why we must target both to curb health care costs. Ann Intern Med. 2012; 157(8): 586–590, doi: 10.7326/0003-4819-157-8-201210160-00014, indexed in Pubmed: 23070492.

29. Bodenheimer T, Fernandez A. High and rising health care costs. Part 4: can costs be controlled while preserving quality? Ann Intern Med. 2005; 143(1): 26–31, doi: 10.7326/0003-4819-143-1-200507050-00007, indexed in Pubmed: 15998752.

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Maternally inherited diabetes and deafness (MIDD) syndrome with m.3243A>G mutation associated with renal failure — a case report

ABSTRACT

Maternally-inherited diabetes with deafness (MIDD) is a rare form of monogenic diabetes that results, in most cases, from an A-to-G transition at position 3243 of mitochondrial DNA (m.3243A>G). The clinical presentation of m.3243A>G mutation is variable, ranging from mild to severe phenotypes. Diabetes is often accompanied by sensorineural deafness, cardiomyopathy, neuromuscular, psychiatric disorders, macular dystrophy and renal failure (kidney manifestations in adults presenting with this mutation remain poorly defined).

The study presents a case of a 40-years-old woman with a history of bilateral sensorineural deafness, renal failure and diabetes that was diagnosed due to increasing muscle weakness during exercise. MIDD was diagnosed based on the clinical picture and the results of laboratory studies including genetic testing. As far as we know, glomerulopathy with incomplete distal renal tubular acidosis has never been described

before as a cause of renal failure in MIDD patients. (Clin Diabetol 2020; 9; 6: 475–478)

Key words: mitochondrial diabetes, sensorineural deafness, m.3243A>G mutation, renal failure, incomplete distal renal tubular acidosis

Introduction

The relationship between the m.3243A>G mutation and maternally inherited diabetes mellitus and deafness syndrome (MIDD) was first described in 1992 by Ballinger et al. [1] Another disease associated with this mitochondrial mutation is MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) which has been described by Pavlakis et al. [2]. The prognosis for MIDD is better than in the case of MELAS syndrome and for other subtypes of diabetic mitochondrial disease. Such a number of presented phenotypes is attributed to the diverse distribution of defective mitochondria in tissues, which is associated with the level of heteroplasm. The age of the patient seems to be decisive in the development of symptoms. Diabetes is not a very common symptom in patients with the m.3243A>G (mtDNA) mitochondria mutation, it occurs only in 15% of cases [3]. However, the m.3243A>G mutation is found in only 1% of patients with diabetes in Europe [4]. In the course of MIDD syndrome, there may be development of: maculopathy, neuromuscular disorders, mental disorders and renal failure. In a multicenter study carried out in France, as

many as 43% of MIDD patients with the m.3243A>G mutation had myopathy, 28% had kidney symptoms, 18% had neuropsychiatric symptoms, and only 15% had cardiomyopathy [5, 6].

The abnormality of glucose metabolism in MIDD is associated with a gradual decrease in insulin excretion due to reduced ATP production in pancreatic β cells with abnormal mitochondria. In MIDD, diabetes develops and hearing loss usually occurs in mid-adulthood. Most often, the disease is diagnosed between the second and fifth decades of life. This rare cause of diabetes should be suspected in the case of maternal inheritance and concomitant deafness [7]. Additional tests show normal or reduced levels of C-peptide and normal autoimmune markers [6, 8]. Most often, hearing loss occurs before diabetes. Coexistence of deafness and mitochondrial diabetes in patients with the m.3243A>G mutation is found in 60% of cases [8]. It is also suggested that after exceeding a certain threshold of mutated mtDNA, there is a disturbance in mitochondrial protein synthesis and oxygen consumption, which results in a decrease in the level of ATP (adenosine triphosphate). This may cause disturbances in the balance of ion concentrations, resulting in accelerated and disproportionate cell death in the cochlea [9]. Factors such as the percentage of mutated mitochondria in different tissues and the failure threshold of each organ are responsible for the development of organ-specific symptoms [10]. Kidney manifestations in adults with m.3243A>G mutation remains poorly defined. Here, we report a case of glomerulopathy with incomplete distal renal tubular acidosis as a cause of renal failure in MIDD patient.

Case presentation

A 40-year-old woman was admitted to the Department of Neurology, in June 2012 due to 4-year history of progressive, generalized muscle weakness and pains (the symptoms increased during exercise), initially raising suspicion of peripheral polyneuropathy.

The patient had a bilateral progressive hearing loss since 1993, she also complained of tinnitus and sporadic vertigo. In 2009 and 2012 she underwent a cochlear implantation procedure for the left and right ear, respectively.

Renal failure was diagnosed in 2002, and diabetes in 2005. She received insulin, thiazide diuretic and angiotensin inhibitor for treating hypertension since 2005. There was no history of strokes, epilepsy and mental retardation. The family history revealed diabetes in her mother and hearing loss in her daughter.

On evaluation, the patient appeared alert. In the neurological examination, slight muscle weakness of the lower limbs was found, as well as the weakening of

deep reflexes. No cranial nerve damage, exteroceptive and proprioceptive sensation disturbances or symptoms of the cerebellar syndrome were observed.

In the course of neurological examination, computed tomography of the lumbar spine was performed and revealed no significant deviations. In addition, cerebral spectroscopy magnetic resonance was performed, showing a relatively increased concentration of lactates in all brain tissue (indicating a mitochondrial disease). Elevated concentration of lactic acid was found in the blood serum (lactic acid = 2.3 mmol/L). The echocardiogram examination and chest X-ray did not show abnormalities. Based on ophthalmic examination the hypertensive and diabetic maculopathy was excluded.

Due to the diagnosed renal failure accompanied by hypomagnesemia with unclear aetiology (previously undiagnosed), a decision was made to extend the nephrological evaluation.

In additional examinations (within 3 months), a doubled level of albumins excreted in the urine was also found, while the general urinalysis revealed inactive urine sediment. The patient did not agree for renal biopsy. Abdominal ultrasonography showed hypoechogenic renal pyramids with single parapyramidal calcifications. Due to the diagnosed hypomagnesemia in the blood serum and the suspected magnesium loss via the kidneys, the fractional excretion of magnesium in the urine was calculated based on the magnesium and creatinine concentration (measured in the serum and urine). $Fe_{Mg}\%$ (fractional excretion of filtered magnesium) amounted to 0.3%, which indicates a non-renal cause of hypomagnesemia (decreased delivery of food, malabsorption in the intestines). In addition, there were no other markers of proximal tube dysfunction (hypophosphatemia, hypouricemia or hypokalaemia in the blood serum). On the other hand, the increased concentration of low-molecular-weight alpha-2 macroglobulin protein seems to result from the energy dysfunction of proximal tube cells (extremely rich in mitochondria).

Based on the increased excretion of albumin in the urine, decreased excretion of citrates in the urine and an abnormal urinary pH, the patient was diagnosed with the chronic kidney disease in the course of glomerulonephritis and the incomplete distal tubular acidosis (due to the suspicion of a mitochondrial disease, the ammonium chloride loading test was omitted) (Table 1).

Mutation detection/genetic analyses

Due to suspected genetically transmitted disorder, genetic test was performed in the proband and her daughter. Total DNA was isolated from blood, hair follicles, urine sediment, nails and buccal mucosa smear

Table 1. Clinical characteristics in patient with mutation A3243G

BMI [kg/m^2]	20.0
HbA$_{1c}$ [4.8–5.9%]	**6.4**
Magnesium [1.6–2.6 mg/dL]	**1.4**
Potassium [3.5–5.1 mmol/L]	4.6
Sodium [135–145 mmol/L]	136
PTH [17.3–72.9 pg/mL]	33.8
Phosphorus [2.6–4.5 mmol/L]	3.9
Calcium [8.6–10.2 mg/dL]	9.6
Lactic acid [0.3–1.7 mmol/L]	**2.3**
Uric acid [2.4–5.7 mg/dL]	4.0
Serum creatinine kinase [0.7–1.2 mg/dL]	1.7
eGFR using MDRD [> 60 mL/min/m^2]	40
Alfa–1 mikroglobulin [< 20 mg/dL]	12.4
Alfa–2 makroglobulin [< 2 mg/dL]	2.55
Albumin in DUC [< 30 mg/24 h]	**117.0**
Urine specific:	
Gravity [1.016–1.022 g/L]	1.020
pH [4.8–6.4]	**6.0**
Leukocytes	Negative
Glucose	Negative
Erythrocytes	Negative
Electrolyte excretion in 24 h — urine collection:	
Citrates in DUC [0.4–3.4 mmol/24 h]	**0.16**
Oxalate in DUC [0.04–0.32 mmol/24 h]	0.22
Sodium [40–220 mmol/24 h]	83.0
Potassium [25–125 mmol/24 h]	28.0
Magnesium [32–307 mg/24 h]	**2.0**
Fe$_{Mg}$%	0.03
Uric acid [0.5–1.0 g/24 h]	**0.1**
Calcium [100–250 mg/24 h]	**3.0**
Phosphorus [0.8–2.0 g/24 h]	**0.2**
Venous blood gas:	
pH [7.35–7.45]	**7.29**
HC0$_3^-$ [21–25 mmol/L]	23.9
BE [from –2 to 2]	–2.5

BMI — body mass index; DUC — daily urine collection; HbA$_{1c}$ — hemoglobin A$_{1c}$; eGFR — estimated glomerular filtration rate; MDRD — modification of diet in renal disease; FeMg% — fractional excretion of filtered magnesium

according to standard protocols. Detection of the m.3243A>G was performed with a Real Time TaqMan assay on Demand (Applied Biosystems, Foster City, CA). Assessment of the heteroplasmy level was based on the PCR-RFLP method as previously described [15]. The analysis revealed pathogenic m.3243A>G mutation in the *MT-TL1* gene (tRNA^{leu}). The mutant mtDNA was distributed heteroplasmically in different tissues, with the highest proportion found in the urine sample (Table 2). On the basis of performed analysis the diagnosis of

Table 2. Level of the heteroplasmy for m.3243A>G mutation

	% of the 'G' allele				
Muscle	Blood cells	Hair follicles	Urine	Nail	Cheek mucosa
NA	12.6	33.1	54.7	6.7	5.6

*NA indicates that the sample was not obtained

maternally inherited diabetes with deafness, i.e. MIDD syndrome with accompanying glomerulopathy and incomplete distal renal tubular acidosis was established.

Discussion

Some reports suggest a relation between m.3243A>G mutation and renal failure which typically occurs in the mean age of 35 years [11]. Renal biopsy usually reveals focal and segmental glomerulosclerotic (FSGS) changes most often of steroid-resistant type and tubulointerstitial nephropathy. The renal biopsy was not performed in our patient due to the significant reduction of the kidney cortex. Therefore, the precise diagnosis of glomerulopathy could not be made. However, the lack of renal biopsy did not influence the tubular disorders diagnostic as well as the therapeutic procedure.

Changes in renal glomerulus are not specific for those found in diabetes type 2. Diabetes is usually recognized a few years after the diagnosis of renal failure is made. It took place also in our patient - the diagnosis of renal insufficiency was made 3 years prior to diagnosis of diabetes. It means that the increased glucose concentration could accelerate renal disease only after the diabetes was diagnosed. Additionally the decreased number of abnormal mitochondria in renal tubules and podocytes are observed [11]. Patients with dominant damage of renal glomerulus have clinically significant proteinuria. The m.3243A>G mutation is observed in some patients with FSGS of unknown cause in which other systems are not affected. According to Löwik et al. [12] the steroid-resistant nephrotic proteinuria is also common in these patients. On the other hand, Hott et al. [13] reported FSGS with m.3243A>G mutation that proceeded with non-nephrotic proteinuria. Based on the screening examination of m.3243A>G mutation in patients who had a history of maternally inherited diabetes, sensorineural hearing loss, Jansen et al. reported a few patients who incurred from progressive non-diabetic kidney disease [4]. In another patients with possible Alport syndrome, the m.3243A>G mutation was detected [2]. Both proximal and distal tubules were affected due to m.3243A>G mutation. Proximal tubular dysfunction with Fanconi syndrome is the most

frequent presentation due to mitochondriopathy, less often, nonspecific chronic tubulointerstitial disease [14].

Management of patients with MIDD is symptomatic. Pharmacological treatment based on oral antidiabetic agents or insulin therapy and coenzyme Q10 (supplementation has been proposed). Non-pharmacology treatment consists of avoiding excessive physical activity and dehydration. Treatment of MIDD should be initiated at an early stage, since complications may lead to renal disease and electrolyte disturbances in the case of incomplete distal renal tubular acidosis.

Conclusion

It is the first case of a MIDD patient diagnosed with renal failure due to glomerulopathy and incomplete distal renal tubular acidosis. The described case is an example of a diagnostic challenge combined with a diagnosis of mitochondrial aetiology of diabetes. Making an early diagnosis is important because of unique management issues and associated comorbidities.

The genetic test performed in mother and daughter in 2012 confirmed the presence of the same maternal mutation in both patients and allowed the early diagnosis of disease in daughter.

This is particularly important in terms of differentiating the causes of renal failure and its prevention in MIDD patients with m.3243A>G mutation (here exemplified by the patient's daughter).

The diagnosis would not be possible without genetic test. It should be also underlined that the genetic engineering role and usefulness in medicine is increasing.

Competing interests

The authors declare that they have no competing interests.

REFERENCES

1. Ballinger SW, Shoffner JM, Hedaya EV, et al. Maternally transmitted diabetes and deafness associated with a 10.4 kb mitochondrial DNA deletion. Nat Genet. 1992; 1(1): 11–15, doi: 10.1038/ng0492-11, indexed in Pubmed: 1301992.
2. Pavlakis SG, Phillips PC, DiMauro S, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. Ann Neurol. 1984; 16(4): 481–488, doi: 10.1002/ana.410160409, indexed in Pubmed: 6093682.
3. Chinnery P. Molecular pathology of MELAS and MERRF. The relationship between mutation load and clinical phenotypes. Brain. 1997; 120(10): 1713–1721, doi: 10.1093/brain/120.10.1713.
4. Jansen JJ, Maassen JA, van der Woude FJ, et al. Mutation in mitochondrial tRNA(Leu(UUR)) gene associated with progressive kidney disease. J Am Soc Nephrol. 1997; 8(7): 1118–1124, indexed in Pubmed: 9219161.
5. Takeshima T, Nakashima K. MIDD and MELAS: a clinical spectrum. Intern Med. 2005; 44(4): 276–277, doi: 10.2169/internalmedicine.44.276, indexed in Pubmed: 15897633.
6. Guéry B, Choukroun G, Noël LH. The spectrum of systemic involvement in adults presenting with renal lesion and mitochondrial tRNA(Leu) gene mutation. J Am Soc Nephrol. 2003; 14(8): 2099, indexed in Pubmed: 12874464.
7. Małecki M, Skupień J. Problems in differential diagnosis of diabetes types. Polish Archives of Internal Medicine. 2008; 118(7-8): 435–440, doi: 10.20452/pamw.444.
8. Gerbitz KD, Ouweland Jv, Maassen J, et al. Mitochondrial diabetes mellitus: a review. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 1995; 1271(1): 253–260, doi: 10.1016/0925-4439(95)00036-4.
9. Sue CM, Lipsett LJ, Crimmins DS, et al. Cochlear origin of hearing loss in MELAS syndrome. Ann Neurol. 1998; 43(3): 350–359, doi: 10.1002/ana.410430313, indexed in Pubmed: 9506552.
10. Yoneda M, Chomyn A, Martinuzzi A, et al. Marked replicative advantage of human mtDNA carrying a point mutation that causes the MELAS encephalomyopathy. Proc Natl Acad Sci U S A. 1992; 89(23): 11164–11168, doi: 10.1073/pnas.89.23.11164, indexed in Pubmed: 1454794.
11. Dinour D, Mini S, Polak-Charcon S, et al. Progressive nephropathy associated with mitochondrial tRNA gene mutation. Clin Nephrol. 2004; 62(2): 149–154, doi: 10.5414/cnp62149, indexed in Pubmed: 15356973.
12. Löwik MM, Hol FA, Steenbergen EJ, et al. Mitochondrial tRNALeu(UUR) mutation in a patient with steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2005; 20(2): 336–341, doi: 10.1093/ndt/gfh546, indexed in Pubmed: 15585516.
13. Hotta O, Inoue CN, Miyabayashi S, et al. Clinical and pathologic features of focal segmental glomerulosclerosis with mitochondrial tRNALeu(UUR) gene mutation. Kidney Int. 2001; 59(4): 1236–1243, doi: 10.1046/j.1523-1755.2001.0590041236.x, indexed in Pubmed: 11260383.
14. Szabolcs MJ, Seigle R, Shanske S, et al. Mitochondrial DNA deletion: a cause of chronic tubulointerstitial nephropathy. Kidney Int. 1994; 45(5): 1388–1396, doi: 10.1038/ki.1994.181, indexed in Pubmed: 8072250.
15. Iwanicka-Pronicka K, Pollak A, Skórka A, et al. Postlingual Hearing Loss as a Mitochondrial 3243A>G Mutation Phenotype. PLoS ONE. 2012; 7(10): e44054, doi: 10.1371/journal.pone.0044054.

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Changes in the Polish Diabetes Society nutritional recommendations in 2005–2020. Evolution or revolution?

ABSTRACT

The first Polish Diabetes Society (Diabetes Poland) guidelines on the management of diabetic patients were published in 2005. Since then, they have been updated annually to provide best care for diabetic patients based on the state-of-the-art knowledge. The present article summarizes changes in the nutritional recommendations for diabetic patients that have been introduced over the last 15 years. We analysed both general recommendations regarding the goals and strategies of nutritional treatment, and specific recommendations regarding the intake of major food components including carbohydrates, protein, and fat. We also analysed changes in the recommendations regarding additional dietary constituents such as salt, alcohol, and vitamin and mineral supplements. (Clin Diabetol 2020; 9; 6: 479–484)

Key words: diabetes, nutritional recommendations, carbohydrates, proteins, fats, dietary fibre

Introduction

The Polish Diabetes Society has been publishing detailed comprehensive guidelines on the management of diabetic patients (Diabetes Poland) since 2005. These guidelines are a cooperative effort of experts represent-

ing multiple clinical specialties, encompassing diagnosis and prevention of diabetes, organization of diabetes care, treatment of diabetes and its complication, and patient education (including behavioural therapy aimed at healthy nutrition and physical activity).

Nutritional recommendations for diabetic patients have been included in the Diabetes Poland guidelines since their inception. It has been well known that in addition to appropriate drug therapy, an appropriate diet is of key importance for metabolic control. Each year, the published guidelines have included general recommendations regarding the overall approach to nutrition and detailed recommendation regarding such dietary components as carbohydrates, protein, fat, vitamins and minerals, salt, as alcohol. The present article summarizes changes in the Polish Diabetes Society nutritional recommendations for diabetic patients that have been introduced over the last 15 years.

General recommendations

In 2005–2007, nutritional recommendations [1–3] focused only on specific dietary components, and did not include the overall principles, goals, and strategies of nutritional therapy.

In 2008, in addition to the basic recommendations [4] regarding individual dietary components, a number of additional recommendations were added, including those related to:
— Both quantitative and qualitative effect of consumed carbohydrates on blood glucose levels;
— No indications for low-carbohydrate diets (> 130 g/day) in diabetic patients, and the need for body weight reduction in patients with overweight and obesity, and patients with diabetes type 2 at risk of obesity. Body weight should be reduced by life-style modifications including reduced caloric in-

take and/or increased physical activity. The guidelines endorsed moderate reduction of caloric intake (in the range of 500–1000 kcal/d) and did not recommend low-energy diets (< 1000 kcal in women and < 1200 kcal in men).

In 2009, the general recommendations [5] included the following basic dietary recommendations:
— Avoiding consumption of simple carbohydrates;
— Consuming frequent meals of a defined caloric value;
— Universal recommendation of high vegetable intake and low saturated fat intake, targeted for all healthy persons.

According to the 2009 recommendations, patients with diabetes type 1 should avoid simple carbohydrates and have their insulin therapy adjusted to their daily activity. In patients with diabetes type 2, appropriate diet should contribute to metabolic control and reduction of excessive body weight by a moderate reduction of caloric intake (daily calorie deficit of 500–1000 kcal).

In 2010, the general recommendations [6] included for the first time a goal of nutrition therapy, i.e., maintaining normal glucose and lipid levels and optimal blood pressure values. The same goal reappeared in 2011. Basic dietary recommendations in 2010–2011, similarly to those from 2009, mostly included avoiding simple carbohydrates, consuming frequent meals of a defined caloric value, and adhering to the universal recommendation of high vegetable intake and low saturated fat intake.

Similarly to the previous year, it was recommended that persons with diabetes type 1 avoided simple carbohydrates and had their insulin therapy adjusted to their daily activity, and patients with diabetes type 2 reduced excessive body weight by appropriate nutrition. In addition, the 2011 recommendations [7] included an algorithm for calculating daily calorie requirement depending on the level of daily activity and the desired body weight.

In 2012–2012, the general recommendations [8, 9] were similar to those from previous years. The goals of nutritional treatment included maintenance of near-normal blood glucose levels, normal cholesterol and lipoprotein levels, and optimal blood pressure. The importance of appropriate nutritional education for metabolic control was also highlighted, with its provision by authorized healthcare personnel such as physicians, dietitians, diabetic nurses, or diabetes educators. According to these recommendations, in addition to adhering to general recommendations targeted at healthy people, diabetic patients should monitor carbohydrate intake both overall and during individual meals, limit simple carbohydrates, and

consume frequent meals. Patients with diabetes type 1 were recommended to avoid fast-absorbing carbohydrates and to adhere to an appropriately balanced diet which should be adjusted to their individual lifestyle. Use of the carbohydrate exchanges, glycaemic index, and glycaemic load was recommended. Major recommendations for diabetes type 2 included maintenance of normal metabolic control and reducing and maintaining desirable body weight, which puts an emphasis on the overall caloric intake which should be adjusted to age, current body weight and physical activity. Similarly to previous years, it was recommended that body weight reduction should be achieved by moderate reduction of caloric intake (negative energy balance of 500–1000 kcal/d).

In 2014–2016, the general recommendations [10–12] regarding the goals and basic nutritional recommendations were the same as in 2012–2013. In addition, the strategy of nutritional treatment was highlighted, including:
— Evaluation of individual diet;
— Nutritional diagnosis;
— Nutritional intervention (individual and group);
— Monitoring of nutrition and its effects.

In addition, the guidelines included recommendations regarding the prevention and treatment in patients with diabetes type 2 at increased cardiovascular risk by employing the Mediterranean diet or the Dietary Approaches to Stop Hypertension (DASH) diet in 2014–2015, and in 2016 also vegetarian or vegan diet, low-fat diet or low-carbohydrate diet. A low-carbohydrate diet was considered a gold standard for body weight reduction in diabetic patients.

The general recommendations [13–14] from 2017–2018 were similar to those from previous years. The goals of nutritional treatment were the same, as is the strategy of nutritional treatment which, in addition to the evaluation of individual diet, nutritional diagnosis, nutritional intervention, and monitoring, also includes corrective measures if therapeutic goals are not met. Similarly to the previous years, patients with diabetes type 1 and normal body weight should adhere to the general healthy nutrition recommendations and avoid simple carbohydrates. Insulin therapy should be adjusted to the patient lifestyle. A system of estimating fast-absorbing carbohydrate content in meals, e.g., by using the carbohydrate exchanges, was highlighted. Similarly to the previous years, paying attention to the glycaemic index and glycaemic load was also recommended. A need for patient education regarding the glycaemic effect of protein and fat intake, and detailed education of the elderly patients to provide adequate protein intake in this age group was noted.

The recommendations for patients with diabetes type 2 were the same as in 2016. These included mostly the need for body weight reduction in overweight or obese patients by individually adjusted reduction of caloric intake. Depending on patient preferences, the DASH, portfolio, vegetarian, vegan, low-fat, or low-carbohydrate diet may be used, the latter remaining the gold standard. However, fasting-based diets were not recommended. It was noted that reducing body weight by as little as 5% may already result in measurable benefits in terms of blood glucose control. According to the 2019 and 2020 Polish Diabetes Society guidelines,[15-16] body weight should be optimally reduced by at least 7%. Since 2019, recommendations regarding the use of specific calorie-reducing diets (such as the DASH diet, vegetarian diet etc.) were retracted, as was the recommendation regarding long-term use of low-carbohydrate diets. In addition, all overweight and obese patients were advised to control portion size. In 2020, an attention was also paid to the form of messages regarding nutritional recommendations. According to the current guidelines, nutritional messages should be generally positive, showing multiple options of composing personal diet based on individual needs and preferences, while the negative messages should be limited.

Specific recommendations
Carbohydrates

In the first Polish Diabetes Society guidelines of 2005 [1], the recommended dietary content of carbohydrates along with monounsaturated fats was set at 50–60% of the total caloric intake. The diet should be based on carbohydrates from unrefined grains, fruits, vegetables, and low-fat milk. It was recommended to reduce sucrose intake by replacing it with carbohydrates from other sources. Sweeteners were allowed to be consumed in the amounts recommended by the manufacturers. The minimum intake of dietary fibre was set at 15 g/day. The guidelines also highlighted the need to keep constant daily carbohydrate intake in patients treated with insulin.

In 2006, the recommendations [2] regarding carbohydrate sources, sweetener intake, and reducing sucrose intake were the same as in 2005. The major change in that year's guidelines was a reduction in the recommended dietary carbohydrate content, set at 45–50% of the total caloric intake. The recommended dietary fibre intake was also changed to 25–35 g/day.

In 2007–2008, the recommendations [3, 4] regarding the intake and dietary sources of carbohydrate were not changes, as were the recommendations regarding the intake of dietary fibre. It was, however, recommended, that low glycaemic-index carbohydrate-sources should be preferred.

In 2009–2010, the recommended total dietary carbohydrate content was also set at 45–50% of the total caloric intake [5, 6]. A major recommendation was to reduce the intake of simple carbohydrates to a minimum. The recommendations regarding sweeteners and dietary fibre remained unchanged.

The recommendations from 2011–2015 [7–11] are very similar to those from the previous years. The only change was that the recommended dietary carbohydrate content was then set at 40–50% of the total caloric intake. In addition, the recommendations regarding dietary fibre were changed since 2012, when the intake of 25–40 g/day was recommended, with a preference for soluble fibre. Also since that year, fructose was no longer recommended as a substitute for sugar.

In 2016 [12], there was no longer any recommendation regarding the total dietary carbohydrate content due to lacking scientific evidence that would allow determining their optimal intake. Unrefined grain products with a low glycaemic index should remain the main source of dietary carbohydrates. The other recommendations regarding simple carbohydrates, sweeteners, fructose and the recommended dietary fibre intake remained unchanged.

In 2017–2020, the position was upheld [13–16] that no adequate scientific evidence was available to inform a recommendation regarding the total dietary carbohydrate content but it was suggested to be at about 45% of the total caloric intake. However, the total dietary carbohydrate content may be up to 60% of the total caloric intake if low-glycaemic index products with a high fibre content are the major dietary source of carbohydrates, and in individuals with a high level of physical activity. If physical activity is low and cannot be increased, it is recommended to reduce the total dietary carbohydrate content to about 25–45% of the total caloric intake. The recommendations regarding preferred consumption of carbohydrates from low glycaemic index sources and the intake of sweeteners did not change, while these were changed for fructose, the recommended intake of which should not exceed 50 g/day, although it is still not recommended as a substitute for sugar. Another change was made regarding the recommended intake of dietary fibre which should be consumed at 25–50 g/day or 15–25 g/1000 kcal. Similarly to the previous years, intake of soluble fibre should be preferred. Since 2018, it is recommended to supplement fibre, particularly its soluble fraction, in individuals who are not able to consume the recom-

Table 1. Recommendations regarding carbohydrate intake

Year	Carbohydrates (as % of the total caloric intake)
2005	50–60%
2006	45–50%
2007	45–50%
2008	45–50%
2009	45–50%
2010	45–50%
2011	40–50%
2012	40–50%
2013	40–50%
2014	40–50%
2015	40–50%
2016	No recommendation
2017	45%, high physical activity up to 60%, low physical activity 25–45%
2018	45%, high physical activity 60%, low physical activity 25–45%
2019	45%, high physical activity 60%, low physical activity 25–45%
2020	45%, high physical activity 60%, low physical activity 25–45%

Table 2. Recommendations regarding dietary fibre intake.

Year	Dietary fibre
2005	15 g/d
2006	25–35 g/d
2007	25–35 g/d
2008	25–35 g/d
2009	25–35 g/d
2010	25–35 g/d
2011	25–35 g/d
2012	25–40 g/d
2013	25–40 g/d
2014	25–40 g/d
2015	25–40 g/d
2016	25–40 g/d
2017	25–50 g/d or 15–25/100 kcal
2018	25–50 g/d or 15–25/100 kcal
2019	25–50 g/d or 15–25/100 kcal
2020	25–50 g/d or 15–25/100 kcal

mended amounts of fibre, and to increase the intake of resistant starch (Tables 1, 2).

Fats

In the first Polish Diabetes Society guidelines published in 2005 [1], the recommended dietary fat intake was set at 30% of the total caloric intake, of which saturated fatty acids should comprise not more than 10%, and 7% in patients with low-density lipoprotein (LDL) cholesterol levels ≥ 100 mg/dL (≥ 2.6 mmol/L). In addition, these guidelines recommended that the intake of monounsaturated fatty acids (MUFA) should be at 10%, and of polyunsaturated fatty acids (PUFA) at 7–10% of the total caloric intake.

In 2006, minor changes were introduced[2] regarding the recommended dietary fat intake, defined as 30–35% of the total caloric intake. The recommendations regarding saturated and unsaturated fat intake remained unchanged, in contrast to those regarding PUFA, with their recommended dietary intake defined as 6–10% of the total caloric intake, including 5–8% as omega-6 fatty acids and 1–2% as omega-3 fatty acids. The recommended dietary cholesterol intake was up to 300 mg/day (7.8 mmol/day) in individuals with normal LDL cholesterol level and 200 mg/day (5.2 mmol/day) in those with LDL cholesterol level ≥ 100 mg/dL (2.6 mmol/L). In addition, a recommendation was given to

limit the intake of trans fatty acids. These recommendations [3–6] were upheld in 2007–2010.

Minor changes in the recommendations [7] were introduced in 2011, as the recommended dietary MUFA intake was increased to 10–15% of the total caloric intake. These modified recommendations [7–12] regarding fat intake were kept until 2017, when possible benefits of introducing plant stanols and sterols to the diet of individuals with elevated LDL cholesterol levels were noted [13].

In 2018, these recommendations [14] underwent some modifications. According to these recommendations, dietary fat intake should be similar to that recommended in healthy individuals, at 25–40% of the total caloric intake. Particular attention was paid to specific types of fatty acids. Saturated fat intake, similarly to the previous years, should not exceed 10% of the total caloric intake. Intake of MUFA should be up to 20%, and intake of PUFA should be at 6–10% of the total caloric intake (no distinction was made between omega-3 and omega-6 fatty acids). The recommendations regarding cholesterol did not change, and its recommended intake was up to 300 mg/day (7.8 mmol/day) in individuals with normal LDL cholesterol level and 200 mg/day (5.2 mmol/day) in those with LDL cholesterol level ≥ 100 mg/dL (2.6 mmol/L). The recommendations regarding trans fatty acids also remained unchanged. Consumption of plant sterols or stanols at 2–3 g/day was considered indicated in patients with hypercholesterolemia.

In 2019–2020, the recommendations [15, 16] regarding fat intake did not change. It was only specified

Table 3. Recommendations regarding fat intake

Year	Fat overall	SFA	MUFA	PUFA	Omega-6	Omega-3
2005	30.00%	10% (7% if elevated LDL cholesterol levels)	10.00%	7–10%	–	–
2006	30–35%	10% (7% if elevated LDL cholesterol levels)	10.00%	6–10%	5–8%	1–2%
2007	30–35%	10% (7% if elevated LDL cholesterol levels)	10.00%	6–10%	5–8%	1–2%
2008	30–35%	10% (7% if elevated LDL cholesterol levels)	10.00%	6–10%	5–8%	1–2%
2009	30–35%	10% (7% if elevated LDL cholesterol levels)	10.00%	6–10%	5–8%	1–2%
2010	30–35%	10% (7% if elevated LDL cholesterol levels)	10.00%	6–10%	5–8%	1–2%
2011	30–35%	10% (7% if elevated LDL cholesterol levels)	10–15%	6–10%	5–8%	1–2%
2012	30–35%	10% (7% if elevated LDL cholesterol levels)	10–15%	6–10%	5–8%	1–2%
2013	30–35%	10% (7% if elevated LDL cholesterol levels)	10–15%	6–10%	5–8%	1–2%
2014	30–35%	10% (7% if elevated LDL cholesterol levels)	10–15%	6–10%	5–8%	1–2%
2015	30–35%	10% (7% if elevated LDL cholesterol levels)	10–15%	6–10%	5–8%	1–2%
2016	30–35%	10% (7% if elevated LDL cholesterol levels)	10–15%	6–10%	5–8%	1–2%
2017	30–35%	10% (7% if elevated LDL cholesterol levels)	10–15%	6–10%	5–8%	1–2%
2018	25–40%	10.00%	Up to 20%	6–10%	—	—
2019	25–40%	10.00%	Up to 20%	6–10%	—	—
2020	25–40%	10.00%	Up to 20%	6–10%	—	—

LDL — low-density lipoprotein; MUFA — monounsaturated fatty acid; PUFA — polyunsaturated fatty acids; SFA — saturated fatty acid

that the recommended type of fat are vegetable oils, except for palm oil and coconut oil (Table 3).

Proteins

In 2005–2008, the recommended [1–4] protein intake was 15–20% of the total caloric intake, with the ratio of animal to plant protein of at least 50:50. No glycaemic effect of protein intake in patients with controlled diabetes type 2 and a possibility of increased protein requirement in patients with uncontrolled diabetes (although protein intake should not exceed the generally recommended level) were noted. In the above recommendations, it was assumed that low-carbohydrate protein with increased protein content may contribute to body weight reduction and better metabolic control of diabetes.

In 2009–2011, the recommendations [5–7] no longer included the statements about no glycaemic effect of protein intake in patients with controlled diabetes type 2 and possible increased protein requirement in patients with uncontrolled diabetes. The remaining recommendations remained unchanged.

In 2012–2016, the recommendations [8–12] only included the information about the recommended dietary protein intake, which remained unchanged since the first guidelines (15–20% of the total caloric intake), and the recommended animal to plant protein ratio (50:50).

In 2017–2020, the recommendations [13–20] underwent some modifications. The recommended protein intake in most patients is 15–20% of the total

caloric intake, corresponding to about 1–1.5 g of protein per kg of body weight per day. In patients with diabetes type 2 and excessive body weight, a calorie-reduction diet may be used with an increased protein intake up to 20–30% of the total caloric intake. In patients with chronic kidney disease, it is recommended to limit protein intake to 0.8–1 g of protein per kg of body weight per day. No limitation of animal protein intake is recommended, although possible benefits from substituting plant proteins, e.g. soy proteins, for animal proteins were noted. In addition, no evidence for adverse effects of high-protein diets in diabetic patients has been noted in the guidelines since 2018 [14–16] (Table 4).

Vitamins and microelements

In the 2005–2008 guidelines [1–4], vitamin and mineral supplementation in patients without known deficiencies was not recommended due to insufficient supporting evidence. The exceptions were folic acid supplementation which was recommended in women contemplating pregnancy and pregnant women, and calcium supplementation in the prevention of osteoporosis.

In 2009–2016, the recommendations regarding folic acid and calcium supplementation were removed from the guidelines [5–12]. The only mention left was that of no indications for vitamin and mineral supplementation in individuals without known deficiencies.

In 2017–2018, the position [13–14] regarding no indications for vitamin and mineral supplementation in

Table 4. Recommendations regarding protein intake

Year	Protein
2005	15–20%
2006	15–20%
2007	15–20%
2008	15–20%
2009	15–20%
2010	15–20%
2011	15–20%
2012	15–20%
2013	15–20%
2014	15–20%
2015	15–20%
2016	15–20%
2017	15–20%, excessive body weight and diabetes type 2 up to do 20–30%, chronic kidney disease 0.8–1 g/kg
2018	15–20%, excessive body weight and diabetes type 2 up to do 20–30%, chronic kidney disease 0.8–1 g/kg
2019	15–20%, excessive body weight and diabetes type 2 up to do 20–30%, chronic kidney disease 0.8–1 g/kg
2020	15–20%, excessive body weight and diabetes type 2 up to do 20–30%, chronic kidney disease 0.8–1 g/kg

patients without known deficiencies was upheld. However, two exceptions were vitamin D3 supplementation as recommended in the general population during the autumn and winter and supplementation of 400 μg/d of folic acid in pregnant women.

In 2019, a recommendation was added [15] for vitamin B12 supplementation in patients with confirmed vitamin B12 deficiency during chronic metformin therapy.

In 2020, it was also mentioned [16] that multivitamin supplementation may be necessary in the elderly, those on a vegetarian or vegan diet, and those on reduced-calorie diets.

Alcohol

In the first Polish Diabetes Society guidelines [1] of 2005, it was stated that low alcohol consumption may not necessarily lead to worse metabolic control of diabetes. It was recommended, however, that alcohol should be consumed with meals to avoid the risk of hypoglycaemia.

In 2006–2008, daily limits of alcohol consumption at the level of 20 g in women and 30 g in men were added to the above position [2–4]. The other recommendations remained unchanged.

Since 2009, alcohol consumption by diabetic patients has been considered [5] unadvisable. The guidelines also note that patients should be informed about blood glucose-lowering effect of alcohol that

might lead to hypoglycaemia. The accepted limits of daily alcohol intake are 20 g in women and 30 g in men. The 2009 recommendations were upheld in 2010 [6].

In 2011, an information was added [7] that alcohol should not be consumed by individuals with hypertriglyceridemia, neuropathy, and pancreatitis. These recommendations have been retained to the present time, including the most recent 2020 guidelines [8–16].

Salt

In 2005–2009, the Polish Diabetes Society guidelines [1–5] did not include any recommendations on salt consumption by diabetic patients.

In 2010, a recommendation on sodium intake was added [6]. The recommended sodium intake was 2400–3000 mg/day. In patients with moderate hypertension, the recommended sodium intake was up to 2400 mg/day, and in those with hypertension and nephropathy up to 2000 mg/day.

In 2011, a recommendation was given [7] regarding salt consumption. It was recommended that daily salt consumption should not exceed 5000–6000 mg. In patients with moderate hypertension, salt consumption up to 4800 mg/day was recommended, and in those with hypertension and diabetic nephropathy up to 4000 mg/day. These recommendations were upheld until 2015 [8–11].

In 2016, these recommendations [12] were slightly modified, and it was recommended that salt consumption should not exceed 6 g/day. In addition, patients with hypertensions were advised to adhere to the DASH diet.

In 2017–2018, the maximum recommended [13. 14] level of salt consumption was reduced from 6 g/day to 5 g/day. The recommendation for dietary restrictions consistent with the DASH diet in patients with hypertension was not changed.

In 2019 and 2020, the recommendations regarding salt consumptions remained unchanged [15, 16]. It was noted, however, that the evidence for benefits from reducing sodium intake below 1500 mg/day is unclear.

Conclusions

Over the last 15 years, the nutritional recommendations were adjusted based on careful analysis of the most recent research to allow best metabolic control in diabetic patients. As noted, there were no major changes in the recommendations. The recommended intakes of dietary components underwent minor modifications. Often, the same recommendations regarding a given dietary component were kept for several years.

One of the most notable changes in the general recommendations is their individualization depending on such factors as physical activity or body weight.

The most dynamic changes occurred in the recommendations regarding carbohydrates and dietary fibre. In addition to the recommended dietary carbohydrate intake which was modified several times over the years, attention was also paid to such factors as carbohydrate quality, best measured by the glycaemic index and load, and dietary sources of carbohydrates. The recommendations regarding dietary carbohydrate intake are particularly important in diabetic patients. Appropriate dietary carbohydrate intake in terms of their quantity and quality may significantly affect blood glucose control, and for this reason the recommended upper limit of dietary fibre intake was significantly increased over time. The guidelines are lacking detailed information on how to calculate carbohydrate and protein-fat exchanges which are particularly important in the treatment of diabetes type 1.

Similarly, the recommendations regarding dietary fat were also modified several times. Over the years, the upper limit of recommended dietary intake was increased for both overall fat and MUFA, while the recommendations regarding the intake of omega-3 and omega-6 fatty acids were abandoned. Over time, attention was paid not only to the quantity but also to the quality of dietary fat, taking into account, among others, the beneficial effects of plant stanols and sterols. This is of a particular importance due to an increased cardiovascular risk in diabetic patients.

The recommendations regarding protein intake did not undergo major changes. The upper limit of recommended dietary intake remained the same in most patients. In the recent years, however, recommendations were added regarding increased protein intake in patients with excessive body weight and patients with diabetes, and reduction of protein intake in individuals with chronic kidney disease. It was also noted that there is insufficient evidence for unfavourable effects of high-protein diets in patients with diabetes.

The situation is similar regarding vitamins and minerals. The position of the Polish Diabetes Society remained generally unchanged, indicating no need for supplementation in individuals without known deficiencies, except for some situations. These exceptions include vitamin D3 supplementation in the autumn and winter period, folic acid supplementation in pregnant women, vitamin B12 supplementation in patients with confirmed vitamin B12 deficiency during chronic metformin therapy, and possible need for multivitamin supplementation in the elderly, those on a vegetarian or vegan diet, and those on reduced-calorie diets.

The position regarding alcohol consumption by diabetic patients also did not change much. In most recommendations, the daily limits for alcohol consumption were upheld. Over time, however, it was noted that alcohol consumption by diabetic individuals is inadvisable, particularly in patients with hypertriglyceridemia, neuropathy, and pancreatitis.

The recommendations regarding salt consumption were modified several times over the last 15 years. Initially, the Polish Diabetes Society guidelines did not include a recommendation regarding salt consumption by diabetic patients. The current upper limit of salt consumption was finally set in 2017 but the rationale for restrictive salt consumption in patients with hypertension remains unclear.

In summary, the changes in the recommendations were rather evolutionary than revolutionary. Over the last 15 years, they were modified to allow optimal diabetes control in accordance with the state-of-the-art knowledge.

The guidelines highlight some basic issues such as the strategy of nutritional treatment and the recommended intake of major dietary components. However, they lack more detailed patient guidance, for example regarding recommended or contraindicated food products, and the ways to implement these recommendations in the daily life.

None of the Polish Diabetes Society guidelines included recommendations on fluid intake. When various dietary components are considered, it would be worthwhile to indicate both the amount and the type of the recommended fluids. Such recommendations were included in the nutritional treatment guidelines by the Polish Society of Dietetics [17] and the dietary allowances for the Polish population developed by the National Food and Nutrition Institute [18].

It would also be worthwhile to provide more detailed recommendations regarding low-calorie sweeteners and polyols as alternative for simple sugars, as limiting sugar intake has been consistently recommended by the Polish Diabetes Society. Such recommendations were included, among others, in the Polish Society of Dietetics guidelines [17] and the American Diabetes Association guidelines [19].

Both the evolving guidelines of the Polish Diabetes Society and the guidelines by other societies, such as the Polish Society of Dietetics [17] and the American Diabetes Association [19], have highlighted the need for an individualized approach to the nutritional treatment of diabetes in terms of the most important aspects of nutritional therapy, such as the general strategy of nutritional treatment and the appropriate intake of specific dietary components.

Conflict of interests

The authors declare no conflicts of interests.

REFERENCES

1. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2005. Diabetologia Praktyczna 2004, tom 5, supl. D.
2. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2006. Diabetologia Praktyczna 2006, tom 7, supl. A.
3. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2007. Diabetologia Praktyczna 2007, tom 8, supl. A.
4. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2008. Diabetologia Praktyczna 2008, tom 9, supl. A.
5. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2009. Diabetologia Praktyczna 2009, tom 10, supl. A.
6. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2010. Diabetologia Praktyczna 2010, tom 11, supl. A.
7. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2011. Diabetologia Praktyczna 2011, tom 12, supl. A.
8. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2012. Diabetol. Klin., 2012; 1 (supl. A): A8-A9.
9. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2013. Diabetol. Klin., 2013; 2 (supl. A).
10. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2014. Diabetol. Klin., 2014; 3 (supl. A).
11. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania u chorych na cukrzycę 2015. Diabetol. Klin., 2015; 4 (supl. A).
12. Polskie Towarzystwo Diabetologiczne: Zalecenia kliniczne dotyczące postępowania z chorymi na cukrzycę 2016. Diabetol. Klin., 2016; 5 (supl. A).
13. Diabetes Poland. 2017 Guidelines on the management of diabetic patients. A position of Diabetes Poland. Clinical Diabetology. 2017; 6(A): 1–80, doi: 10.5603/dk.2017.0001.
14. Diabetes Poland. 2018 Guidelines on the management of diabetic patients. A position of Diabetes Poland. Clinical Diabetology. 2018; 7(1): 1–90, doi: 10.5603/dk.2018.0001.
15. Diabetes Poland. 2019 Guidelines on the management of diabetic patients. A position of Diabetes Poland. Clin Diabet 2019; 8, 1, doi: 10.5603/DK.2019.0001.
16. Diabetes Poland. 2020 Guidelines on the management of diabetic patients. A position of Diabetes Poland. Clin Diabetol 2020; 9, 1.
17. Polskie Towarzystwo Dietetyki. Rekomendacje postępowania dietetycznego w cukrzycy. Stanowisko Polskiego Towarzystwa Dietetyki 2017. Dietetyka. 2017; 10: 23–24.
18. Normy żywienia dla populacji Polski. Red. M. Jarosz. Instytut Żywności i Żywienia 2017: 255.
19. Standards of medical care in diabetes 2020. American Diabetes Association. Diabetes Care. 2020; 43(Suppl. 1): S50–S54.

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Fear of hypoglycaemia — from normality to pathology. Diagnostic criteria and therapeutic directions

ABSTRACT

The aim of the article is to summarize the current knowledge on the phenomenon of fear of hypoglycaemia and its impact on the metabolic control and well-being of the population of diabetic patients. The article proposes a description of clinical criteria useful for the diagnosis of the fear of hypoglycaemia in a non-normative and harmful form. Therapeutic directions are presented that have been proven effective in the recent years in reducing the level of maladaptive fear of hypoglycaemia, while also protecting the mental health of the patients. Despite extensive knowledge and numerous clinical trials undertaken in other countries, further research on diabetes-related anxiety disorders in Polish patients is needed. It is also advisable to create a database of culturally adapted management protocols for specialists that could increase the quality and effectiveness of the assistance provided in the outpatient health care. (Clin Diabetol 2020; 9; 6: 487–492)

Key words: diabetes, fear of hypoglycaemia, diagnostic criteria, psychotherapy

Introduction

Hypoglycaemia has always been an important issue in the scientific discussions regarding the management of diabetes [1]. Hypoglycaemia is often described as

one of the greatest barriers on the patient's path to normoglycaemia and a risk factor that might lead to the development of life-threatening complications [2, 3]. The experience of hypoglycaemia may be incidental but very unpleasant, leading to lifelong memories of the event.

For reasons that are justified, the occurrence and perspective of experiencing hypoglycaemia may elicit strong emotions in patients. Fear of hypoglycaemia has its legitimate background and an adaptive meaning. Careful self-management and appropriate decisions when managing insulin therapy may successfully protect patients from hypoglycaemia and related consequences. However, fear is associated with some risk. Although it is a universal, primary and natural experience not only for humans, in specific settings it may acquire pathological features, initiate maladaptive mechanisms, and severely disorganize human's life. For good reason, fear has been termed the backbone of the most syndromes known in the contemporary psychiatric practice [4].

Multiple clinical studies have performed regarding the fear of hypoglycaemia and its effect on the therapeutic process, mental health, and subjective wellbeing of the diabetic population. Unfortunately, fear of hypoglycaemia remains very difficult to identify in the inpatient and outpatient practice, as no clear criteria are available to diagnose it in its non-normative, harmful form. However, the most troublesome is the lack of a culturally adapted management protocol that would be dedicated to that issue.

Hypoglycaemia — diagnosis and risk factors

Hypoglycaemia is a common phenomenon in diabetic patients treated with insulin and oral glucose-

-lowering drugs such as sulphonylureas [5]. It has been estimated that hypoglycaemia, both symptomatic and asymptomatic, may occur thousands of times during the lifespan of an average patient [6].

According to the Polish Diabetes Association guidelines [7], hypoglycaemia should be categorized using three glycaemic/symptomatic thresholds. Alert blood glucose level (level 1) is defined as values below 70 mg/dL (3.9 mmol/L) regardless of the presence of absence of concomitant symptoms. Clinically significant hypoglycaemia (level 2) is defined as blood glucose level below 54 mg/dL (3.0 mmol/L). Severe hypoglycaemia (level 3) is diagnosed based on clinical symptoms associated with severe cognitive dysfunction, without any blood glucose level criterion. A third party intervention is required to terminate a severe hypoglycaemia episode.

At the physiological level, early response to hypoglycaemia involves activation of the autonomic nervous system. Early neurovegetative (adrenergic) symptoms include pallor, muscle tremor, profuse sweating, dizziness and/or headache, anxiety, and nervousness. Later, due to shortage of glucose in the central nervous system cells, neuroglycopenia ensues which is associated with cognitive dysfunction (e.g., confusion, disorientation, attention and memory deficits) and neurological symptoms (slurred speech, irrational or uncontrolled behaviours, loss of consciousness, seizures, nystagmus, reduced responsiveness to stimuli) [8]. The experience and recognition of the above clinical symptoms of hypoglycaemia may show large interindividual variation in the diabetic patient population [9].

The likelihood of an adverse fall in blood glucose level depends on many variables. The major iatrogenic risk factor are inadequate, excessive or maladjusted doses of insulin (or a substance that stimulates insulin release) in relation to the individual requirement, dietary intake (exogenous glucose) and/or planned physical activity [10].

The risk of hypoglycaemia is increased in the settings of reduced endogenous glucose production (e.g., following excessive alcohol intake or in liver failure), increased carbohydrate utilization, or reduces hepatic glycogen stores (e.g., during intense exercise or dieting). Additional risk settings include increased insulin sensitivity (e.g., during or immediately after exercise or during nocturnal rest) and reduced insulin clearance (e.g., in progressive renal failure) [11, 12]. Other risk factors are diabetes duration and type, patient age, reduced hypoglycaemia awareness, and past experience of severe hypoglycaemia [13–16].

Recurrent hypoglycaemia is associated with a risk of irreversible changes and may lead to further complications. Particular risks are associated with cardiovas-

cular changes and events induced by hypoglycaemia. Cardiovascular events may increase the likelihood of sudden cardiac death [13, 17, 18]. Severe hypoglycaemia may affect the vascular system and activate prothrombotic, proinflammatory and proatherogenic mechanisms [19]. Recurrent hypoglycaemia attenuates symptomatic and hormonal responses to the episodes of low blood glucose level, leading to the development of hypoglycaemia unawareness syndrome. The latter is characterized by a reduced or absent ability to identify the onset of hypoglycaemia despite blood glucose level lowering to the values usually associated with warning symptoms [20]. This significantly increases the risk of severe hypoglycaemia [14].

Hypoglycaemia has a major effect on worsened wellbeing and reduced quality of life of diabetic patients [21, 22]. It may also result in reduced professional productivity, increased absence from work, and increased overall costs related to health status [23]. Severe and recurrent hypoglycaemia may increase the overall level of anxiety [24]. Unfortunately, an increasing severity of anxiety is not always a desirable effect in these settings.

Fear of hypoglycaemia — from the norm to pathology

In general, anxiety may be described as a condition of unpleasant discomfort, tension and/or unrest which is accompanied by an increased level of excitation or even specific somatic experiences such as palpitation, tremor, and dyspnoea. In contrast to fear which is felt in response to a defined, recognizable stimulus, anxiety is an anticipatory reaction to an impending stimulus (may arise without a clear cause). From the functional perspective, human ability to feel anxiety is of major importance when safety of an individual is at stake — the protective or defensive reaction is a priority to ensure survival and protection of what is the most valuable [25].

Anxiety is a very complex phenomenon which depends on genetic factors, environmental influences, and combination of both [26]. It is an adaptive signalling-protective mechanism which is important from the perspective of the theory of evolution [27]. Already at the subconscious level, anxiety organizes perception systems, participates in processing information from the sensory channels, directs attention processes (e.g., selection) and memory, engages systems responsible for learning and leads to activation of body's physiological reactions — involuntary but dependent on the form of perceived danger. Most importantly, anxiety contributes much to the overall decision process in the context of choosing the best available behaviour in the situation of a perceived danger [28].

Clinically, non-normative anxiety is recurrent, persistent, and/or objectively inadequate for a given situation [27]. The criterion of inadequacy for a given situation may involve two forms — either excessive anxiety for a low level of danger (e.g., phobia), or inadequately low anxiety for a high level of danger (e.g., denial).

In the context of fear of hypoglycaemia, its adaptive nature depends on the criterion of adequacy of the felt anxiety in relation to the objective risk of hypoglycaemia [29]. Inadequately high level of anxiety in relation to a low risk of hypoglycaemia will lead to escalation of protective and avoidance behaviours. In this situation, the actual danger for the patient is chronic hyperglycaemia induced by interventions aimed to protect from blood glucose level lowering. Conversely, inadequately low level of anxiety in relation to a high risk of hypoglycaemia may also create danger. In this case, hypoglycaemia itself will be a major risk for the patient, as the patient will not try to protect from it, and with time he or she will not even recognize its symptoms due to habituation.

Psychopatologically, anxiety disorder is said to occur when the subjective severity of anxiety, its intensity and frequency lead to disorganization of the individual's life, resulting in suffering [30]. The diabetes self-management process itself should protect the patient from suffering, and at the same time allow active social and professional functioning tailored to the patient's needs, as well as pursuing pastime hobbies and other activities aimed at achieving individual wellbeing and adequate mental health status. Unfortunately, inadequate fear of hypoglycaemia and associated behaviours generate secondary effects in many areas important for the patient, affecting the subjective assessment of quality of life and the severity of depression in both adults and children [30].

Diagnosis of non-adaptive fear of hypoglycaemia

Inadequate fear of hypoglycaemia may be identified based on observation and history taking [32] and may be reflected by laboratory test results (haemoglobin A_{1c} [HbA_{1c}] level) [33]. Studies on the relation between fear of hypoglycaemia and metabolic control of diabetes provided strong evidence that fear may motivate patients to actions directed at preventing hypoglycaemia, thus leading to chronic hyperglycaemia. Obviously, this association is much more complex and involves interactions with many variables, and thus not all studies may be expected to confirm the relation between metabolic control and the severity of fear of hypoglycaemia [29, 34]. For example, some patients may present with adequate metabolic control, while fear of hyperglycaemia may be reflected in excessive blood glucose level measurements, home isolation, and lifestyle restrictions that preclude professional activities.

The risk of developing non-normative fear of hypoglycaemia is associated with many patient personality features, such as the overall severity of the anxiety as a general feature and the level of neuroticism [29]. However, as shown in multiple studies, the strongest risk factor is patient's previous experience of hypoglycaemia. Fear of hypoglycaemia is associated with both the severity and frequency of previous hypoglycaemia episodes [34, 35]. This phenomenon affects not only diabetic patients but also their close persons (e.g., family members, caretakers of minors with diabetes, partners) [36, 37].

Based on the current studies, one of the best known self-descriptive tools to measure the severity of fear of hypoglycaemia is the Hypoglycaemia Fear Survey (HFS and HFS-II) developed by Cox, Irvine, Gonder-Frederick et al. [38]. This questionnaire includes 33 items measuring the behavioural and affective-cognitive dimensions of the fear of hypoglycaemia. Other screening tools have also been developed during the last 20 years, including the Quick Screening for Fear of Hypoglycaemia (QSFH) [39], an abbreviated and improved version of HFS known as the Fear of Hypoglycaemia Scale (FH-15) [40], and the paediatric version known as the Children's Hypoglycaemia Index (CHI) [41]. Despite their promising psychometric properties, neither HFS-II, its abbreviated versions, nor QSFH and CHI have been adapted to or validated in the Polish population. As result, it is difficult to use them as screening tools in the outpatient diabetes care settings.

Further studies are recommended to identify the special at-risk group in which the problem of non-normative fear of hypoglycaemia might be revealed during the therapeutic process. As indicated by Böhme et al. [42], as healthcare professionals we still do not know enough about our patients, and our patients are too often reluctant to disclose their fear of hypoglycaemia.

Therapeutic directions in the management of fear of hypoglycaemia

Currently, the main therapeutic model in the management and prevention of recurrent hypoglycaemia in the context of non-normative fear of hypoglycaemia is holistic education and increasing awareness of individuals at risk of hypoglycaemia in regard to the risk, diagnosis and management of future hypoglycaemia episodes. Studies confirmed a significant effect of education on self-monitoring of blood glucose and avoidance of hypoglycaemia [43, 44].

The best known psychoeducation protocols targeted at hypoglycaemia include the Hypoglycaemia Anticipation, Awareness and Treatment Training (HAATT), HyPOS, and Blood Glucose Awareness Training II (BGAT-2) [45–47]. The common feature of these programs is combining home-based self-monitoring (e.g., keeping a hypoglycaemia diary) with group sessions over several weeks targeted at patient education covering the principles of insulin therapy management, planning actions directed at maintaining normoglycaemia, and coping with extreme situations (e.g., hypoglycaemia and ketoacidosis). Studies on these protocols showed that they are satisfactorily effective in increasing patients' hypoglycaemia awareness and reducing the number of hypoglycaemia episodes. In addition, the BGAT-2 program was also shown to be effective in reducing fear of hypoglycaemia and depressive symptoms and improving the perceived quality of life in patients with diabetes type 1 subjected to this intervention [48].

Fear of hypoglycaemia may also be addressed with cognitive-behavioural therapy (CBT)-based psychotherapy programs which were shown to be highly effective in the treatment of a wide spectrum of anxiety disorders [49]. The 8-week StyrKRAFT i Ditt Liv© (Power to Choose your Direction) program developed by Amsberg, Anderbro et al. [50], consisting of 2-hour CBT group sessions and support and monitoring interventions following the end of group sessions, was shown to be associated with significantly lower HbA$_{1c}$ levels in the intervention group at 8, 24 and 48 weeks after program conclusion. In addition, significant beneficial differences between the CBT and control group were also noted in the mean assessment of wellbeing, perceived distress, level of anxiety, and severity of depressive symptoms [51]. Similar effects of individual CBT psychotherapy were shown in a case study by O'Donnell et al. [52]. Graded exposition combined with CBT interventions employed in a patient with diagnosed fear of hypoglycaemia resulted in a reduced fear of hypoglycaemia and lower frequency of protective behaviours targeted at maintaining high blood glucose levels during the day. As a result, the intervention improved self-monitoring of blood glucose parameters and contributed to better mental functioning of the patients (reduction in generalized anxiety and depression).

An important component of the above psychoeducation programs and CBT interventions is an access to modern blood glucose monitoring technologies. These solutions play an important role, providing biofeedback to the patients' therapeutic efforts, which undoubtedly had an effect on the final therapy effect. For example, the HAATT protocol used Accucheck Easy BG, Medtronic's CGMS Gold was used in group CBT, and continuous glucose monitoring was used in the CBT case study. However, caution is advised in the available literature regarding the use of continuous glucose monitoring systems (CGMS) in patients suspected of anxiety disorders, as this may paradoxically increase their anxiety and lead to treatment discontinuation [52].

Unfortunately, despite many successes in the international arena, there are no Polish adaptations of programs such as HAATT, HyPOS, and BGAT-2 and thus, despite large demand, they are not available for the Polish population of diabetic patients. Developing such culturally adapted psychoeducation protocols is a desired future direction of work for the healthcare community involved in diabetes care and education. Promising results may be obtained with CBT-based psychotherapy. It is important, however, that these interventions be developed based on cooperation of certified psychotherapists and a wide community of specialists involved in diabetes care and education. Controlled access to modern technologies may be a helpful addition to the psychoeducation process and therapy, allowing the patients to monitor changes which highlight the effect of their decisions on the ultimate biopsychophysical outcomes.

Conclusions

Normative fear of hypoglycaemia is consistent with situations where a patient is able to self-identify the existing hypoglycaemia based on clinical symptoms and/or use of blood glucose level measurement technologies, which allows an adequate response to restore normoglycaemia. Adaptive fear of hypoglycaemia will also motivate the patient to plan future behaviours with the aim of maximizing the likelihood of maintaining normoglycaemia and minimizing the occurrences of both hypo- and hyperglycaemia. It will play a regulatory role in terms of daily functioning of the patient (his or her professional, personal, and social activities), his or her physical and mental health, and the subjective wellbeing and satisfaction from life.

Non-normative fear of hypoglycaemia may be diagnosed if it is inadequate to the individual risk of hypoglycaemia. It will induce a harmful effect on the patient's health which may be identified by observation, history taking and/or results of self-monitoring of blood glucose. The pathological component of fear of hypoglycaemia is said to be present when the non-adaptive level of fear and its consequences pose a threat for the patients' wellbeing and mental health, leading to a subjective suffering.

The diagnosis of harmful, non-normative fear of hypoglycaemia in the outpatient or inpatient setting should be preceded by detailed history taking regard-

ing the previous disease course and patient actions in the context of hypoglycaemia. Patients presenting with severe fear of hypoglycaemia should receive adequate medical and psychoterapeutic care. The issue of diagnosing and managing fear of hypoglycaemia should be an inherent component of the recommendations for healthcare personnel caring for diabetic patients. Prompt intervention and help offered to patients with non-normative fear of hypoglycaemia may contribute to better treatment outcomes and preservation of what is most important in the patient's life. Further research is needed on the possible directions of help and support for Polish diabetic patients affected by non-normative fear of hypoglycaemia.

Conflict of interest statement

The authors declare no conflict of interests.

REFERENCES

1. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005; 28(5): 1245–1249, doi: 10.2337/diacare.28.5.1245, indexed in Pubmed: 15855602.
2. Davis S, Alonso M. Hypoglycemia as a barrier to glycemic control. Journal of Diabetes and its Complications. 2004; 18(1): 60–68, doi: 10.1016/s1056-8727(03)00058-8.
3. Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. Endocr Pract. 2008; 14(6): 750–756, doi: 10.4158/EP.14.6.750, indexed in Pubmed: 18996798.
4. Kępiński A. Lęk. 1st ed. Wydawnictwo Literackie, Kraków 2002.
5. Tatoń J, Bernas M. Hipoglikemia i neuroglikopenii u osób z cukrzycą. In: Tatoń J, Czech A. (ed). Diabetologia. Wydawnictwo Lekarskie PZWL, Warszawa 2001: 386–400.
6. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008; 57(12): 3169–3176, doi: 10.2337/db08-1084.
7. Polish Diabetes Association. 2020 Guidelines on the management of diabetic patients. A position of Diabetes Poland. Clin Diabetol. 2020; 9(1): 1–101, doi: 10.5603/DK.2019.0001.
8. Szadkowska A. Ostre stany w cukrzycy. Family Medicine & Primary Care Review. 2012; 14(2): 286–290.
9. Wierzchowiecka A, Zozulińska-Ziółkiewicz D. Hipoglikemia w cukrzycy typu 1. Diabetol Prakt. 2011; 12(6): 210–215.
10. Cryer PE. Hypoglycaemia in Diabetes: Pathophysiology, Prevalence and Prevention. 2nd ed. Alexandria: American Diabetes Association. 2013.
11. Kalra S, Mukherjee JJ, Venkataraman S, et al. Hypoglycemia: The neglected complication. Indian J Endocrinol Metab. 2013; 17(5): 819–834, doi: 10.4103/2230-8210.117219, indexed in Pubmed: 24083163.
12. Kedia N. Treatment of severe diabetic hypoglycemia with glucagon: an underutilized therapeutic approach. Diabetes Metab Syndr Obes. 2011; 4: 337–346, doi: 10.2147/DMSO.S20633, indexed in Pubmed: 21969805.
13. Davis IC, Ahmadizadeh I, Randell J, et al. Understanding the impact of hypoglycemia on the cardiovascular system. Expert Rev Endocrinol Metab. 2017; 12(1): 21–33, doi: 10.1080/17446651.2017.1275960, indexed in Pubmed: 29109754.
14. Henderson JN, Allen KV, Deary IJ, et al. Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness. Diabet Med. 2003; 20(12): 1016–1021,

doi: 10.1046/j.1464-5491.2003.01072.x, indexed in Pubmed: 14632703.
15. McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabet Med. 2001; 18(9): 690–705, doi: 10.1046/j.1464-5491.2001.00620.x, indexed in Pubmed: 11606166.
16. Gama R, Teale JD, Marks V. Best practice No 173: clinical and laboratory investigation of adult spontaneous hypoglycaemia. J Clin Pathol. 2003; 56(9): 641–646, doi: 10.1136/jcp.56.9.641, indexed in Pubmed: 12944543.
17. Seaquist ER, Miller ME, Bonds DE, et al. ACCORD Investigators. The impact of frequent and unrecognized hypoglycemia on mortality in the ACCORD study. Diabetes Care. 2012; 35(2): 409–414, doi: 10.2337/dc11-0996, indexed in Pubmed: 22179956.
18. Yang SW, Park KH, Zhou YJ. The Impact of Hypoglycemia on the Cardiovascular System: Physiology and Pathophysiology. Angiology. 2016; 67(9): 802–809, doi: 10.1177/0003319715623400, indexed in Pubmed: 26685181.
19. Gogitidze Joy N, Hedrington MS, Briscoe VJ, et al. Effects of acute hypoglycemia on inflammatory and pro-atherothrombotic biomarkers in individuals with type 1 diabetes and healthy individuals. Diabetes Care. 2010; 33(7): 1529–1535, doi: 10.2337/dc09-0354, indexed in Pubmed: 20587723.
20. Vignesh JP, Mohan V. Hypoglycaemia unawareness. J Assoc Physicians India. 2004; 52: 727–732, indexed in Pubmed: 15839452.
21. Ahammed A, Pathan F, Afsana F, et al. The Burden of Severe Hypoglycemia on Quality of Life among Diabetes Mellitus Patients in a Tertiary Level Hospital of Bangladesh. Indian J Endocrinol Metab. 2018; 22(4): 499–504, doi: 10.4103/ijem.IJEM_338_17, indexed in Pubmed: 30148097.
22. Polonsky WH, Fisher L, Hessler D. The impact of non-severe hypoglycemia on quality of life in patients with type 2 diabetes. J Diabetes Complications. 2018; 32(4): 373–378, doi: 10.1016/j.jdiacomp.2018.01.014, indexed in Pubmed: 29496364.
23. Pawaskar M, Iglay K, Witt EA, et al. Impact of the severity of hypoglycemia on health — Related quality of life, productivity, resource use, and costs among US patients with type 2 diabetes. J Diabetes Complications. 2018; 32(5): 451–457, doi: 10.1016/j.jdiacomp.2018.01.012, indexed in Pubmed: 29496365.
24. Wredling RA, Theorell PG, Roll HM, et al. Psychosocial state of patients with IDDM prone to recurrent episodes of severe hypoglycemia. Diabetes Care. 1992; 15(4): 518–521, doi: 10.2337/diacare.15.4.518, indexed in Pubmed: 1499468.
25. Rachman S. Anxiety. 2nd ed. Psychology Press, New York. 2004.
26. Clément Y, Calatayud F, Belzung C. Genetic basis of anxiety-like behaviour: a critical review. Brain Res Bull. 2002; 57(1): 57–71, doi: 10.1016/s0361-9230(01)00637-2, indexed in Pubmed: 11827738.
27. Óhman A. Strach i lęk z perspektywy ewolucyjnej, poznawczej i klinicznej. W: Lewis M, Haviland-Jones JM. Psychologa emocji. Gdańskie Wydawnictwo Psychologiczne, Gdańsk. 2005: 719.
28. Cosmides L, Tooby J. Psychologia ewolucyjna a emocje. In: Lewis M, Haviland-Jones JM. Psychologia emocji. Gdańskie Wydawnictwo Psychologiczne, Gdańsk 2005: 128.
29. Irvine A, Cox D, Gonder-Frederick L. The Fear of Hypoglycaemia Scale. W: Bradley C. 1st ed. Handbook of Psychology and Diabetes: a guide to psychological measurement in diabetes research and practice. Psychology Press, New York 2006.
30. LeDoux J. Lęk. Neuronauka na tropie źródeł lęku i strachu. 1st ed. Copernicus Center Press, Kraków 2017.
31. Anderbro T, Gonder-Frederick L, Bolinder J, et al. Fear of hypoglycemia: relationship to hypoglycemic risk and psychological factors. Acta Diabetol. 2015; 52(3): 581–589, doi: 10.1007/s00592-014-0694-8, indexed in Pubmed: 25528005.
32. Shiu AT, Wong RY. Fear of hypoglycaemia among insulin-treated Hong Kong Chinese patients: implications for diabetes patient education. Patient Educ Couns. 2000; 41(3): 251–261, doi: 10.1016/s0738-3991(99)00084-1, indexed in Pubmed: 11042428.
33. Cox DJ, Gonder-Frederick L, Antoun B, et al. Psychobehavioral metabolic parameters of severe hypoglycemic episodes. Diabe-

tes Care. 1990; 13(4): 458–459, doi: 10.2337/diacare.13.4.458, indexed in Pubmed: 2318112.

34. Irvine AA, Cox D, Gonder-Frederick L. Fear of hypoglycemia: relationship to physical and psychological symptoms in patients with insulin-dependent diabetes mellitus. Health Psychol. 1992; 11(2): 135–138, doi: 10.1037//0278-6133.11.2.135, indexed in Pubmed: 1582382.

35. Polonsky WH, Davis CL, Jacobson AM, et al. Correlates of hypoglycemic fear in type I and type II diabetes mellitus. Health Psychol. 1992; 11(3): 199–202, doi: 10.1037//0278-6133.11.3.199, indexed in Pubmed: 1618174.

36. Clarke WL, Gonder-Frederick A, Snyder AL, et al. Maternal fear of hypoglycemia in their children with insulin dependent diabetes mellitus. J Pediatr Endocrinol Metab. 1998; 11 Suppl 1: 189–194, doi: 10.1515/jpem.1998.11.s1.189, indexed in Pubmed: 9642659.

37. Monaghan MC, Hilliard ME, Cogen FR, et al. Nighttime caregiving behaviors among parents of young children with type 1 diabetes: associations with illness characteristics and parent functioning. Fam Syst Health. 2009; 27(1): 28–38, doi: 10.1037/a0014770, indexed in Pubmed: 19630443.

38. Cox DJ, Irvine A, Gonder-Frederick L, et al. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care. 1987; 10(5): 617–621, doi: 10.2337/diacare.10.5.617, indexed in Pubmed: 3677982.

39. Schmidt CB, Potter van Loon BJ, Kiliç E, et al. Validation of a quick screening instrument for measuring fear of hypoglycaemia in persons with diabetes. J Diabetes Complications. 2017; 31(8): 1360–1361, doi: 10.1016/j.jdiacomp.2017.05.009, indexed in Pubmed: 28579312.

40. Anarte Ortiz MT, Caballero FF, Ruiz de Adana MS, et al. Development of a new fear of hypoglycemia scale: FH-15. Psychol Assess. 2011; 23(2): 398–405, doi: 10.1037/a0021927, indexed in Pubmed: 21381839.

41. Kamps JL, Roberts MC, Varela RE. Development of a new fear of hypoglycemia scale: preliminary results. J Pediatr Psychol. 2005; 30(3): 287–291, doi: 10.1093/jpepsy/jsi038, indexed in Pubmed: 15784924.

42. Böhme P, Bertin E, Cosson E, et al. GEODE group. Fear of hypoglycaemia in patients with type 1 diabetes: do patients and diabetologists feel the same way? Diabetes Metab. 2013; 39(1): 63–70, doi: 10.1016/j.diabet.2012.10.006, indexed in Pubmed: 23266467.

43. Yong YM, Shin KM, Lee KM, et al. Intensive individualized reinforcement education is important for the prevention of hypoglycemia in patients with type 2 diabetes. Diabetes Metab J. 2015; 39(2): 154–163, doi: 10.4093/dmj.2015.39.2.154, indexed in Pubmed: 25922810.

44. Bhutani G, Kalra S, Lamba S, et al. Effect of diabetic education on the knowledge, attitude and practices of diabetic patients towards prevention of hypoglycemia. Indian J Endocrinol Metab. 2015; 19(3): 383–386, doi: 10.4103/2230-8210.152781, indexed in Pubmed: 25932395.

45. Cox DJ, Kovatchev B, Koev D, et al. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. Int J Behav Med. 2004; 11(4): 212–218, doi: 10.1207/s15327558ijbm1104_4, indexed in Pubmed: 15657021.

46. Hermanns N, Kulzer B, Kubiak T, et al. The effect of an education programme (HyPOS) to treat hypoglycaemia problems in patients with type 1 diabetes. Diabetes Metab Res Rev. 2007; 23(7): 528–538, doi: 10.1002/dmrr.710, indexed in Pubmed: 17245692.

47. Cox D, Gonder-Frederick L, Polonsky W, et al. A multicenter evaluation of blood glucose awareness training-II. Diabetes Care. 1995; 18(4): 523–528, doi: 10.2337/diacare.18.4.523, indexed in Pubmed: 7497863.

48. Cox DJ, Gonder-Frederick L, Polonsky W, et al. Blood glucose awareness training (BGAT-2): long-term benefits. Diabetes Care. 2001; 24(4): 637–642, doi: 10.2337/diacare.24.4.637, indexed in Pubmed: 11315822.

49. Popiel A, Pragłowska E. Psychoterapia poznawczo-behawioralna — praktyka oparta na badaniach empirycznych. Psychiatria w Praktyce Klinicznej. 2009; 2(3): 146–155.

50. Amsberg S, Anderbro T, Wredling R, et al. A cognitive behavior therapy-based intervention among poorly controlled adult type 1 diabetes patients — a randomized controlled trial. Patient Educ Couns. 2009; 77(1): 72–80, doi: 10.1016/j.pec.2009.01.015, indexed in Pubmed: 19297117.

51. Anderbro T. Behavior change intervention and fear of hypoglycaemia in type 1 diabetes. Karolinska Institutet, Stockholm 2012.

52. O'Donnell HK, Berget C, Wooldridge JS, et al. Graduated exposure to treat fear of hypoglycemia in a young adult with type 1 diabetes: A case study. Pediatr Diabetes. 2019; 20(1): 113–118, doi: 10.1111/pedi.12791, indexed in Pubmed: 30370639.

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Ophthalmologic disorders in adolescents with type 1 diabetes

ABSTRACT

Chronic complications of diabetes, including damage to the eye, are seen in patients with type 2 diabetes often soon after diagnosis. This type of diabetes is often diagnosed after a long period of unrecognized and untreated disease. Type 1 diabetes is one of the most common metabolic diseases diagnosed in children, and is associated with the risk of developing multiple chronic complications. Diabetic eye disease can be associated with abnormalities in various eye structures. It should be remembered that early changes in the organ of vision may not give clear clinical symptoms. Their detection requires the use of modern diagnostic methods, which also allow early detection of changes that threaten damage to the eye. The degree of metabolic control, the presence of dyslipidemia, as well as micro- and macroangiopathy affect the development of chronic complications, including changes in the eye. Damage to small blood vessels leads to changes in retinal perfusion and to macular edema. As a result of these changes, diabetic retinopathy develops. Early diagnosis of the above complications allows prevention of their development. (Clin Diabetol 2020; 9; 6: 493–496)

Key words: diabetic cataract, diabetic retinopathy, intraocular pressure, metabolic control, type 1 diabetes, visual impairment

Introduction

In diabetes mellitus, first described by John Rollo in 1798, vision complications often occur. The history of diabetes goes back to ancient times. The first reports date back to 3500 B.C.E. and come from ancient Egypt. The term 'diabetes', which in Greek meant 'siphon' and 'water flowing through the body', was first used by Areteus of Cappadocia (30–90 CE). He was also the first to provide a full clinical description of diabetes. In 1889, Minkowski and von Mering proved that there is a correlation between diabetes and the islets of Langerhans. Insulin discovery in 1922 by Banting, Macleod, Best, and Collip was of breakthrough significance [1–3]. Chronic complications in patients with type 2 diabetes, including damage to the eye, are often seen soon after diagnosis. This type of diabetes is often diagnosed after a long period of unrecognized and untreated disease [4, 5]. In type 1 diabetes, anatomical changes in the eye usually appear after a longer duration of diabetes. Descriptions of eye complications in adolescent diabetic patients have a long history [6–9]. In the past, these complications were common due to difficulties in balancing glucose metabolism. Long-term studies on the relationship between the level of glucose control reflected by the examination of HbA_{1c} levels and diabetic retinopathy in juvenile patients with type 1 diabetes have been recently presented by Swedish authors [10]. Other authors have also presented the results of similar studies [11–13]. A comprehensive discussion of recommendations for the diagnosis and treatment of ophthalmologic complications in diabetes is presented in the recommendations of the Diabetes Poland [14]. According to these recommendations, the first ophthalmological examination should be performed at diagnosis in patients with type 2 diabetes, and for type 1 diabetes patients, such examination is usually performed after 5 years of the disease. During

puberty, adolescents usually have their first examination earlier. The main reason for the development of complications is chronic hyperglycemia with high concentration of glycated hemoglobin. In addition, it should be remembered that apart from anatomical complications associated with lens opacities and vascular changes in diabetes, there may also be certain functional complications resulting from acute disorders of glycemic homeostasis. These symptoms often occur at the onset of the disease in patients with type 1 diabetes and are the result of glucose homeostasis disorders. Visual disturbances can be a consequence of both hyperglycemia and hypoglycemia. Hyperglycemia causes an increase in osmotic pressure and refractive disorders, whereas in hypoglycemia, glucose delivery to photoreceptors is reduced. Visual disturbances associated with lens refractive disorders often occur when type 1 diabetes is diagnosed. They are a consequence of frequently elevated glucose levels in blood and aqueous humor at that time. Blood glucose control usually resolves the symptoms.

Cataract

The cataract is manifested by the clouding of the lens of the eye, and is one of the pre-existing chronic complications of diabetes. Its prevalence in type 1 diabetes is estimated to be around 10%, and in type 2 diabetes the percentage is higher. Bilateral cataracts, which appear as the first symptom of diabetes and lead to its diagnosis, are unusual and only a few such cases have been described in the literature [15]. There are juvenile cataracts and cataracts in adults. In type 1 diabetes, there is often a snowflake cataract characterized by fine haze that may be present in the cortex or around the anterior and posterior lens capsule [16]. The only effective way to improve vision in people affected by this disease is to remove the cloudy cornea and implant an artificial lens in its place. Changes in the fundus manifesting as diabetic macular edema (DME) may be yet another vision disorder in diabetes. Diabetic maculopathy may be associated with cataract surgery because the latter often accelerates or intensifies diabetic macular edema (DME) [17]. Chronic hyperglycemia, leading to the production of inflammatory cytokines and leukocyte adhesion, is important in the development of this condition. What is more, capillaries in the central part of the retina become narrower and ischemia leads to the disappearance of pericytes and damage to the endothelium of small blood vessels. The vessel wall is damaged and micro-aneurysms are formed. Damage to the vascular wall and increased blood viscosity lead to retinal hypoxia and retinal exudate. As a result of the weakened vessel wall being ruptured, blood strokes appear inside the eye. Datta et al. observed four important clinical features in five children with newly diagnosed diabetes who developed early cataracts. These features include the prolonged duration of symptoms before diagnosis, high HbA1 levels at diagnosis, a clear predominance of girls and the age of puberty [18]. The possibility of using modern diagnostic methods allows early detection of changes that threaten eye damage [19, 20]. Through optical coherent tomography (OCT) we can assess the condition of the macula and optic disc. Fluorescein angiography is a method which accurately locates the sites of leakage of diseased vessels and ischemia zones, and OCT angiography allows us to accurately visualize vascular changes without the need for contrast agents. In addition, there are a number of other methods that allow accurate diagnosis of lesions within the eye at an early stage of their development [21–23]. Recently, Chinese authors have presented results of their research on the thickness of choroid, optic disc, and macular thickness in children with type 1 diabetes [24]. Other authors have also drawn attention to the need to use modern diagnostic methods for early detection of changes in the organ of vision in adolescent diabetic patients [25].

Diabetic retinopathy

Diabetic retinopathy is estimated to be the most common complication of diabetes and can lead to complete blindness. In a study by Wang et al. [26], 20.1% of 2,240 subjects with type 1 diabetes and 7.2% of 1,768 subjects with type 2 diabetes developed retinopathy over a median follow-up period of 3.2 and 3.1 years, respectively. Moreover, Kernell et al. [27] found that in children and adolescents with insulin-dependent diabetes, retinopathy was diagnosed in 6% and 18% of patients in pubertal stages one and five, respectively. The cause of diabetic retinopathy is microangiopathy, which is damage to small blood vessels, which leads to damage to the retina itself. Recently, an analysis of retrospective studies has been presented, which suggested that genetic conditions may have an impact on the development of diabetic retinopathy [28]. However, according to the authors of this study, this requires further research, and a greater number of patients, especially children with type 1 diabetes without known visual impairment and diabetic retinopathy. Results of studies on the relationship between the occurrence of atherosclerotic changes in the carotid arteries and the occurrence of diabetic retinopathy have been presented [29]. In the group of patients with type 1 diabetes free from cardiovascular diseases, an ultrasound of carotid arteries was performed, the results of which were compared with the incidence and severity of diabetic

retinopathy. Advanced stages of diabetic retinopathy have been shown to indicate an increased risk of carotid atherosclerosis. German authors have pointed out the coexistence of chronic macro- and microvascular complications, including retinopathy, in young children with type 1 diabetes [30]. In addition, they have highlighted the need for prevention in early type 1 diabetes to reduce the significant risk of complications and comorbidities at an early age. The appearance of other chronic complications may be the first sign of changes in the eye. Malerbi et al. have pointed out that very accurate diagnostic methods allow us to detect changes in retinal perfusion in patients with normal fundus [31]. Fluorescein angiography is indicated in patients with impaired renal glomerular filtration. There are three stages of diabetic retinopathy – non-proliferative retinopathy, pre-proliferative retinopathy, and proliferative retinopathy. This classification does not include maculopathy, which can occur at any stage of retinopathy. Recently, there have been a number of reports on the assessment of the degree of morphological changes in the retina in adolescent patients with type 1 diabetes [32–34]. Important risk factors for the development of retinopathy are lipid disorders, obesity, hypertension, frequent infections, blood clotting disorders, and anemia. People who develop other late complications in diabetes, such as diabetic nephropathy, are at risk. An extensive report has been published regarding the occurrence of changes in the organ of vision in patients with type 1 and type 2 diabetes, based on the analysis of the frequency of changes in patients in north-eastern Poland. Of the respondents, 26% were patients with type 1 diabetes and 74% were patients with type 2 diabetes. Diabetic retinopathy was found in 25.48% of subjects. In patients with type 1 diabetes, 32.58% of cases were diagnosed with non-proliferative diabetic retinopathy, while in 24.44% of cases, patients developed proliferative retinopathy [35]. The authors believe that the results obtained may reflect the degree of diabetes care. Future research should focus on preventing diabetic complications in young patients and explaining the above connections.

Conclusions

Recently, there has been a report in Polish literature discussing the results of eye examinations in adolescent patients with type 1 diabetes. These results confirm that it is necessary to use modern diagnostic methods for the early detection of ocular complications in adolescent patients [25, 31]. It should be remembered that early changes in the organ of vision may not give clear clinical symptoms, and their detection requires the use of modern diagnostic methods. It is very important to make diabetologists dealing with adolescent patients aware of the need to intensify these tests in adolescent patients, and refer these patient for ophthalmologist consultations.

Conflict of interests

The authors declare to have no conflict of interests.

REFERENCES

1. Matuszewski W, Bandurska-Stankiewicz E, Modzelewski R, et al. Diagnosis and treatment of diabetic retinopathy — historical overview. Clinical Diabetology. 2017; 6(5): 182–188, doi: 10.5603/dk.2017.0030.
2. Polonsky KS. The past 200 years in diabetes. N Engl J Med. 2012; 367(14): 1332–1340, doi: 10.1056/NEJMra1110560, indexed in Pubmed: 23034021.
3. Watkins P. Evolution of diabetes care over half a century. Clin Med (Lond). 2007; 7(2): 109–113, doi: 10.7861/clinmedicine.7-2-109, indexed in Pubmed: 17491493.
4. Otto-Buczkowska E, Chwalba A. Prediabetes — it is a very important and still not solved the problem! Forum Medycyny Rodzinnej. 2017; 11(4): 107–112, doi: 1.
5. Dudek A, Otto-Buczkowska E. Can type 2 diabetes be cured? IJSRM Human. 2020; 15 (2): 304–310.
6. Ehrlich RM, Kirsch S, Daneman D. Cataracts in children with diabetes mellitus. Diabetes Care. 1987; 10(6): 798–799, doi: 10.2337/diacare.10.6.798, indexed in Pubmed: 3428060.
7. Falck A, Laatikainen L. Diabetic cataract in children. Acta Ophthalmol Scand. 1998; 76(2): 238–240, doi: 10.1034/j.1600-0420.1998.760223.x, indexed in Pubmed: 9591961.
8. Martín Carballo G, Peralta Calvo J, Alonso Criado S, et al. Bilateral cataract in the initial phase of insulin dependent diabetes mellitus in childhood. An Esp Pediatr. 1993; 39(5): 453–454, indexed in Pubmed: 8285465.
9. Otto-Buczkowska E, Szumilas K, Sońta-Jakimczyk D. Eye changes in children with diabetes. Pol Tyg Lek. 1971; 26(28): 1065–1067, indexed in Pubmed: 5096673.
10. Andreasson R, Ekelund C, Landin-Olsson M, et al. HbA1c levels in children with type 1 diabetes and correlation to diabetic retinopathy. J Pediatr Endocrinol Metab. 2018; 31(4): 369–374, doi: 10.1515/jpem-2017-0417, indexed in Pubmed: 29494341.
11. Hautala N, Siiskonen M, Hannula V, et al. Early glycaemic control for maintaining visual function in type 1 diabetes: The Oulu cohort study of diabetic retinopathy. Eur J Ophthalmol. 2018; 28(6): 684–689, doi: 10.1177/1120672117750053, indexed in Pubmed: 29554811.
12. Öberg D, Salemyr J, Örtqvist E, et al. A longitudinal study of serum insulin-like growth factor-I levels over 6 years in a large cohort of children and adolescents with type 1 diabetes mellitus: A marker reflecting diabetic retinopathy. Pediatr Diabetes. 2018; 19(5): 972–978, doi: 10.1111/pedi.12681, indexed in Pubmed: 29663652.
13. Virk SA, Donaghue KC, Cho YHi, et al. Association between HbA1c variability and risk of microvascular complications in adolescents with type 1 diabetes. J Clin Endocrinol Metab. 2016; 101(9): 3257–3263, doi: 10.1210/jc.2015-3604, indexed in Pubmed: 27186858.
14. 2020 Guidelines on the management of diabetic patients. Clinical Diabetology. 2020; 9(1): 48–51.
15. Pakhetra R, Jyotsna VP. Bilateral early cataracts in type 1 diabetes. Med J Armed Forces India. 2009; 65(1): 71–72, doi: 10.1016/S0377-1237(09)80063-4, indexed in Pubmed: 27408198.
16. Ehrlich RM, Kirsch S, Daneman D. Cataracts in children with diabetes mellitus. Diabetes Care. 1987; 10(6): 798–799, doi: 10.2337/diacare.10.6.798, indexed in Pubmed: 3428060.

17. Boscia F, Giancipoli E, D'Amico Ricci G, et al. Management of macular oedema in diabetic patients undergoing cataract surgery. Curr Opin Ophthalmol. 2017; 28(1): 23–28, doi: 10.1097/ICU.0000000000000328, indexed in Pubmed: 27661663.

18. Datta V, Swift PG, Woodruff GH, et al. Metabolic cataracts in newly diagnosed diabetes. Arch Dis Child. 1997; 76(2): 118–120, doi: 10.1136/adc.76.2.118, indexed in Pubmed: 9068299.

19. De Benedetto U, Querques G, Lattanzio R, et al. Macular dysfunction is common in both type 1 and type 2 diabetic patients without macular edema. Retina. 2014; 34(11): 2171–2177, doi: 10.1097/IAE.0000000000000205, indexed in Pubmed: 24978668.

20. Srinivasan S, Dehghani C, Pritchard N, et al. Ophthalmic and clinical factors that predict four-year development and worsening of diabetic retinopathy in type 1 diabetes. J Diabetes Complications. 2018; 32(1): 67–74, doi: 10.1016/j.jdiacomp.2017.09.002, indexed in Pubmed: 29097055.

21. Gerendas BS, Hatz K, Kaider A, et al. Ganglion cell layer thickening in well-controlled patients with type 1 diabetes: an early sign for diabetic retinopathy? Acta Ophthalmol. 2020; 98(3): e292–e300, doi: 10.1111/aos.14273, indexed in Pubmed: 31654495.

22. Stem MS, Dunbar GE, Jackson GR, et al. Glucose variability and inner retinal sensory neuropathy in persons with type 1 diabetes mellitus. Eye (Lond). 2016; 30(6): 825–832, doi: 10.1038/eye.2016.48, indexed in Pubmed: 27034201.

23. Tekin K, Inanc M, Kurnaz E, et al. Quantitative evaluation of early retinal changes in children with type 1 diabetes mellitus without retinopathy. Clin Exp Optom. 2018; 101(5): 680–685, doi: 10.1111/cxo.12667, indexed in Pubmed: 29488254.

24. Li T, Jia Y, Wang S, et al. Change in peripapillary and macular choroidal thickness change in children with type 1 diabetes mellitus without visual impairment or diabetic retinopathy. Acta Ophthalmol. 2020; 98(2): e203–e211, doi: 10.1111/aos.14225.

25. Kołodziej M, Waszczykowska A, Korzeniewska-Dyl I, et al. The HD-OCT study may be useful in searching for markers of preclinical stage of diabetic retinopathy in patients with type 1 diabetes. Diagnostics (Basel). 2019; 9(3), doi: 10.3390/diagnostics9030105, indexed in Pubmed: 31454902.

26. Wang SY, Andrews CA, Herman WH, et al. Incidence and risk factors for developing diabetic retinopathy among youths with type 1 or type 2 diabetes throughout the United States. Ophthalmology. 2017; 124(4): 424–430, doi: 10.1016/j.ophtha.2016.10.031, indexed in Pubmed: 27914837.

27. Kernell A, Dedorsson I, Johansson B, et al. Prevalence of diabetic retinopathy in children and adolescents with IDDM. A population-based multicentre study. Diabetologia. 1997; 40(3): 307–310, doi: 10.1007/s001250050679, indexed in Pubmed: 9084969.

28. Broadgate S, Kiire C, Halford S, et al. Diabetic macular oedema: under-represented in the genetic analysis of diabetic retinopathy. Acta Ophthalmol. 2018; 96 Suppl A111: 1–51, doi: 10.1111/aos.13678, indexed in Pubmed: 29682912.

29. Carbonell M, Castelblanco E, Valldeperas X, et al. Diabetic retinopathy is associated with the presence and burden of subclinical carotid atherosclerosis in type 1 diabetes. Cardiovasc Diabetol. 2018; 17(1): 66, doi: 10.1186/s12933-018-0706-z, indexed in Pubmed: 29728117.

30. Tönnies T, Stahl-Pehe A, Baechle C, et al. Risk of microvascular complications and macrovascular risk factors in early-onset type 1 diabetes after at least 10 years duration: an analysis of three population-based cross-sectional surveys in Germany between 2009 and 2016. Int J Endocrinol. 2018; 2018: 7806980, doi: 10.1155/2018/7806980, indexed in Pubmed: 29808091.

31. Malerbi FK, Regatieri CV, de Sa JR, et al. Retinal malperfusion in albuminuric Type 1 diabetes mellitus patients without clinical signs of diabetic retinopathy: a prospective pilot study. Int J Retina Vitreous. 2017; 3: 49, doi: 10.1186/s40942-017-0102-y, indexed in Pubmed: 29270314.

32. Gołębiewska J, Olechowski A, Wysocka-Mincewicz M, et al. Choroidal thickness and ganglion cell complex in pubescent children with type 1 diabetes without diabetic retinopathy analyzed by spectral domain optical coherence tomography. J Diabetes Res. 2018; 2018: 5458015, doi: 10.1155/2018/5458015, indexed in Pubmed: 29850607.

33. Melvin A, Redahan L, Hatunic M, et al. Microvascular diabetes complications in a specialist young adult diabetes service. Ir J Med Sci. 2019; 188(1): 129–134, doi: 10.1007/s11845-018-1827-9, indexed in Pubmed: 29732503.

34. Ruiz-Ocaña P, Espinoza Requena P, Alonso-Ojembarrena A, et al. Decreased retinal thickness in type 1 diabetic children with signs of nonproliferative diabetic retinopathy. Int J Endocrinol. 2018; 2018: 1078531, doi: 10.1155/2018/1078531, indexed in Pubmed: 29853875.

35. Matuszewski W, Baranowska-Jurkun A, Stefanowicz-Rutkowska MM, et al. Prevalence of diabetic retinopathy in type 1 and type 2 diabetes mellitus patients in north-east Poland. Medicina (Kaunas). 2020; 56(4), doi: 10.3390/medicina56040164, indexed in Pubmed: 32268561.

VIA MEDICA

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Vitamin B$_{12}$ in diabetes — a new treatment paradigm?

ABSTRACT

Vitamin B$_{12}$ supplementation in specific clinical conditions in diabetic patients has been recommended in the guidelines. These recommendations reflect reports confirming the importance of vitamin B$_{12}$ supplementation in the treatment of diabetic complications, as well as to correct its deficiency during metformin treatment. In the present article, we reviewed the issue of vitamin B$_{12}$ deficiency, the relevant diagnostic approach, and the rationale for vitamin B$_{12}$ supplementation in diabetic patients. (Clin Diabetol 2020; 9; 6: 489–496)

Key words: vitamin B$_{12}$, diabetes, metformin, diabetic neuropathy

## Do we know how important is vitamin B$_{12}$ in humans?

Vitamin B$_{12}$ is absorbed in the terminal part of the ileum. A prerequisite for this process is the presence of a glycoprotein known as the intrinsic factor which is produced by the parietal cells of the stomach. When bound to the intrinsic factor, cobalamin forms a hematopoietic factor which plays a role in cell formation in the hematopoietic system. In addition, it is a necessary factor for erythropoiesis in bone marrow and DNA and RNA synthesis in erythroblasts. Vitamin B$_{12}$ is also involved in purine and pyrimidine metabolism [1, 2].

The effects of vitamin B12 or cobalamin on the human body are complex. It is directly involved in the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A (Fig. 1). This reaction creates a substrate for the Krebs cycle, thus providing energy for multiple processes in the human body. Body systems that particularly actively use this process include the nervous, gastrointestinal, immunologic, and hematopoietic systems [3, 4].

Methionine synthesis is another biochemical process vitamin B$_{12}$ is a cofactor of (Fig. 2). An adequate rate of this process is necessary for myelinization (formation of nerve sheaths) which is necessary for maintaining appropriate nerve conduction. In addition, there is an association between methionine synthesis and synthesis of some neurotransmitters (dopamine, noradrenaline, and serotonin) [4, 5].
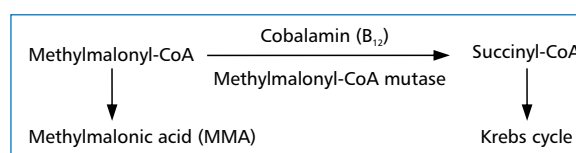
Figure 1. Conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A
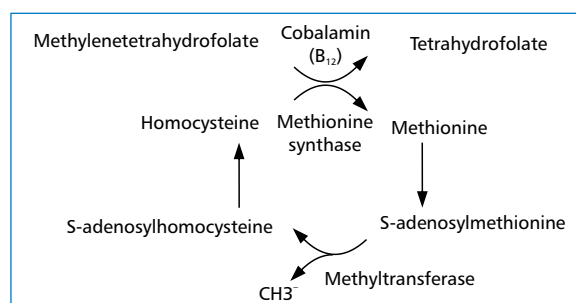
Figure 2. Methionin synthesis

Table 1. Effects of vitamin B$_{12}$ deficiency

Nervous system	Peripheral neuropathy
	Myelopathy
	Optic nerve atrophy
	Spastic paralysis
	Cognitive dysfunction
	Mood disturbances
	Chronic fatigue syndrome
Hematopoietic system	Macrocytosis
	Megaloblastic anaemia
	Leukopenia
	Thrombocytopenia
Gastrointestinal system	Gastrointestinal mucosal atrophy
	Stomatitis
	Change in bowel movement pattern

Due to vitamin B$_{12}$ involvement in the above mentioned processes, its deficiency may have various clinical manifestations (Table 1) [1, 2].

What are the primary sources of vitamin B$_{12}$?

The process of cobalamin absorption from the food and its utilization in the body is complex and thus may be adversely affected by multiple clinical conditions.

One of the most important determinants of vitamin B$_{12}$ level is its dietary intake. The average vitamin B$_{12}$ dietary content is 3–30 μg, and the daily requirement is only 0.6–1.2 μg. Patients on a diet poor in cobalamin sources (meat, milk, eggs, cheese, fish) are at particular risk of cobalamin deficiency. Body cobalamin stores are large enough to make a deficiency exclusively due to poor dietary intake unlikely, unless an individual is on a restrictive vegetarian or vegan diet. As the latter dietary choices are increasingly popular, this risk should be recognized and patients should be reminded of a potential need for cobalamin supplementation [6].

Vitamin B$_{12}$ deficiency may be due to gastrointestinal disease. Cobalamin absorption in the gastrointestinal tract depends on the presence of several factors that protect the cobalamin moiety and transport it to the target tissues. These include haptocorrin (produced by the salivary glands), intrinsic factor (produced by the gastric parietal cells) and transcobalamin II (present in the ileum where cobalamin is ultimately absorbed to bloodstream). Gastrointestinal pathologies may result in reduced levels of these protective factors, leading to impaired cobalamin absorption and reduction of its serum level [7, 8].

Diseases commonly perceived as inducing vitamin B$_{12}$ deficiency include inflammatory bowel disease (ulcerative colitis and Crohn's disease) and pernicious (Addison-Biermer) anaemia. However, diseases less frequently associated with vitamin B$_{12}$ deficiency, such as celiac disease, chronic pancreatitis and liver disease, may also become major reasons for the need for vitamin B$_{12}$ supplementation [9–11]. Several mechanisms leading to vitamin B$_{12}$ deficiency may operate in chronic alcohol abuse, including chronic gastric and duodenal mucosal inflammation, chronic pancreatitis, and cirrhosis. Finally, small intestine bacterial overgrowth (SIBO) may predispose to impaired absorption of micro- and macronutrients, and another potential cause is the presence of gastrointestinal parasites [3, 4, 12].

Impaired absorption may also have iatrogenic causes, in particular in patients after resection procedures involving those gastrointestinal tract segments which are responsible for vitamin B$_{12}$ absorption, in particular the stomach and the ileum. In the present era of growing popularity of bariatric surgery, it is particularly important to monitor vitamin B$_{12}$ deficiencies and provide adequate supplementation in this patient group [13].

Medications may be a common cause for impaired vitamin B$_{12}$ absorption. These include metformin, proton pump inhibitors, H2 receptor blockers, antibiotics, anticonvulsants, calcium antagonists, and 5-aminosalicylates [14–16]. Paradoxically, the latter stabilize inflammation in inflammatory bowel diseases but may themselves predispose to cobalamin deficiency [17].

What are the causes of vitamin B$_{12}$ deficiency in diabetes?

Diabetic patients are particularly prone to vitamin B$_{12}$ deficiency. The causes of the latter may be somewhat different in patients with type 1 and type 2 diabetes.

In type 1 diabetes, this is mostly associated with an increased risk of concomitant autoimmune disease, such as autoimmune thyroiditis. Individuals with hypothyroidism were shown to have macrocytosis, and often also resultant macrocytic anaemia [18]. It may be a sign of thyroid disease or result from a concomitant autoimmune disease limiting cobalamine absorption. Celiac disease and Addison-Biermer anaemia are also more common in patients with type 1 diabetes [19, 20]. A typical feature of long-standing poorly controlled type 1 diabetes are microangiopathic complications which may result in autonomic neuropathy involving the gastrointestinal system, manifesting with gastroparesis and enteropathy [21].

Patients with type 2 diabetes more often present with macroangiopathic complications resulting in potentially more diffuse perfusion abnormalities [22].

One such manifestation may be atherosclerotic mesenteric artery disease, potentially leading to significantly impaired intestinal absorption due to ischemia, or even intestinal necrosis with more severe ischemic events such as mesenteric artery embolism. Patients with type 2 diabetes are also at a higher risk of inflammatory conditions, resulting in more frequent use of antibiotics [23]. In addition, bariatric procedures are often performed in these patients due to concomitant obesity, depriving them of a large intestinal surface to absorb vitamin B12 [13]. Diabetic patients are often subjected to various dietary interventions. If these are misunderstood or overly restrictive, they may lead to an unbalanced diet with potential deficiencies of multiple micro- and macronutrients.

The effect of medications on cobalamin absorption seems more important in diabetic patients compared to those without diabetes. In addition to metformin, which has been frequently highlighted in this regard in the recent literature, these patients are more commonly treated with calcium antagonists, proton pump inhibitors, and acetylsalicylic acid [14, 15, 24].

Apart from these typical predispositions, it should be always borne in mind during the diagnostic process that vitamin B$_{12}$ deficiency in a diabetic patient may result from clinical conditions independent from diabetes.

What may be the consequences of long-standing vitamin B$_{12}$ deficiency in a diabetic patient?

Vitamin B$_{12}$ deficiency in a diabetic patient may potentially affect both micro- and macroangiopathic changes.

Neuropathy is of major importance among the microangiopathic complications, and it may result from vitamin B$_{12}$ deficiency even without concomitant diabetes. Among various types of neuropathy, thick motor fibres are most sensitive to vitamin B$_{12}$ deficiency, which may manifest with loss of balance or foot deformities. In a diabetic patient, it is difficult to ascertain the primary cause: whether it is uncontrolled diabetes, its long duration, unidentified genetic factors, or vitamin B deficiencies [25]. However, it seems logical that in a patient with diabetic neuropathy, an additional contributing factor may be present. It was shown that cobalamine deficiency accompanying diabetes promotes peripheral neuropathy due to impaired nerve myelinization and may alter its clinical presentation, rendering it more atypical. Other common causes of neuropathy that may coexist with diabetes include alcohol abuse (also via cobalamin-independent mechanisms), use of neurotoxic drugs, and advanced chronic kidney disease (mediated by uremic toxins) [25].

It was initially thought that the major consequence of cobalamin deficiency is damage to thick nerve fibres but a number of recent studies showed an association between vitamin B$_{12}$ deficiency and various components of autonomic nervous system damage. In particular, multiple studies focused on the association between cobalamin deficiency and cardiovascular autonomic dysfunction, including orthostatic hypotension. Hansen et al. [26] showed that vitamin B$_{12}$ deficiency was associated with cardiovascular autonomic dysfunction in patients with type 2 diabetes. Beitzke et al. [27] suggested that orthostatic hypotension in diabetic patients may be caused by vitamin B$_{12}$ deficiency, warranting investigation for the latter. Similar associations were reported for autonomic neuropathy involving the gastrointestinal system (gastroparesis, enteropathy, sialorrhoea), the genitourinary system (neurogenic bladder, erectile dysfunction), and thermoregulation mechanisms (excessive sweating). However, no evidence is available for a direct causal role of vitamin B$_{12}$ deficiency in the development of autonomic neuropathy [28].

Another complication of diabetes is diabetic retinopathy. However, some fundoscopy findings are not specific for diabetic retinopathy. In their study, Satyanayarana et al. [29] suggested that vitamin B$_{12}$ deficiency may be an independent risk factor for the development of diabetic retinopathy. Retinal bleeding identified by ophthalmoscopy may accompany severe anaemia or thrombocytopenia, including due to vitamin B$_{12}$ deficiency. These case reports highlighted the role of hypoxia as a factor that damages the endothelium. Abnormal repair and homeostatic processes are also operating. Retinal lesions seem more frequent in patients with thrombocytopenia accompanying anaemia due to vitamin B$_{12}$ deficiency [30, 31].

In addition to typical retinal pathology, cobalamin deficiency may also result in bilateral optic nerve neuropathy. Clinically, it manifests mostly with centrocecal scotoma and slowly developing optic nerve atrophy. The mechanism of this pathology remains unknown but it seems to be related to the role of vitamin B$_{12}$ as a potent free radical scavenger. Chan et al. [32] found that the antioxidant effect of cobalamin was a protective factor for the optic nerve. These authors showed in vitro and in an animal model that intravitreal cobalamin administration following iatrogenic optic nerve damage reduced oxidative stress and the degree of nerve damage, promoting survival of retinal ganglion cells.

Links between vitamin B$_{12}$ deficiencies and the development of macroangiopathy have been sought for a long time. Such a link may be related to the discussion on the role of homocysteine, particularly in the development of coronary artery disease. Until

recently, homocysteine level measurement was recommended as a cardiovascular risk marker [33, 34]. However, these hopes were not substantiated in later studies. In contrast, Yigit et al. [35] showed a potential association between a MTHFR gene mutation and the presence of diabetic peripheral neuropathy. The genotype distribution and allele frequencies differed significantly between patients with diabetic neuropathy and the control group and correlated with a history of diabetic retinopathy. It was hypothesized that both direct and indirect effects of hyperhomocysteinaemia on endothelial cells led to occlusion of small capillaries which would explain the effect of vitamin B_{12} deficiency on the development of neuropathy.

Does chronic metformin use lead to vitamin B_{12} deficiencies?

In the recent years, numerous reports have indicated that metformin, particularly if used for many years, significantly affects body vitamin B_{12} stores. It was shown in diabetic patients treated with metformin, women with polycystic ovary syndrome receiving metformin treatment, and in healthy women administered metformin in trials evaluating its anticancer effects [36–38]. In 1971, Tomkin et al. [39] were the first to note an association between metformin use and reduced vitamin B_{12} absorption. Randomized clinical trials showed that metformin administration for several months may significantly reduce vitamin B_{12} level [36, 40]. One of the strongest evidence for this association comes from a randomized clinical trial with more than 4 years of follow-up, reported by De Jager et al. [41]. This study showed that vitamin B_{12} level was reduced by as much as 19%. It was the first study to show gradual vitamin B_{12} level reduction in patients receiving metformin, and the first to show the potential of metformin to reduce vitamin B_{12} level to values that usually require pharmacological substitution. The relation reported by De Jager et al. has been supported by more recent metaanalyses and clinical studies [42, 43].

Several theories have been put forward to explain metformin-induced vitamin B_{12} deficiency. One of the earliest proposed explanations was intestinal bacterial overgrowth resulting in binding the intrinsic factor-vitamin B_{12} complex by the bacteria instead of its absorption [44]. Another postulated mechanism was acceleration of intestinal passage by metformin, resulting in reduced vitamin absorption [45]. According to the currently most popular explanation, metformin affects calcium channels in the small intestine which are responsible for absorption of the intrinsic factor-vitamin B_{12} complex [24]. This mechanism is also supported by reversal of defective vitamin B_{12} absorption by oral calcium supplementation. In their study, Bauman et al. [24] divided patients with type 2 diabetes into two groups, one receiving metformin and the other receiving a sulphonylurea. In the metformin group, a significant reduction in vitamin B_{12} and holotranscobalamin level was noted in the first 3 months but such effects were not observed in the sulphonylurea group. At the next step, oral calcium supplementation was initiated in patients receiving metformin. At one month, holotranscobalamin level in the study group increased by as much as 53%, and no intestinal bacterial overgrowth was confirmed [24]. The authors suggested that positively charged metformin moieties target the carbohydrate core of intestinal cell membrane, charging positively the membrane surface itself, and calcium cations are repelled from it as a result.

Does metformin induce neuropathy?

Should we afraid metformin due to vitamin B_{12} deficiencies developing during metformin therapy? It has been a leading anti-diabetic drug for decades, providing multidirectional benefits. Normalization of blood glucose levels associated with long-term improvement of insulin sensitivity protects from the development of diabetic neuropathy. Specific molecular mechanisms of the neuroprotective action of metformin independent from blood glucose control have also been investigated.

On the other hand, development of various forms of diabetes-independent neuropathy due to vitamin B_{12} deficiency may be expected in patients treated with metformin for many years [46]. In a 6-month observational study, Wile and Toth [47] showed a significant effect of metformin use on a reduction of cobalamin level, which was also associated with elevated homocysteine and methylmalonic acid levels. In addition, the severity of peripheral neuropathy was increased compared to the non-metformin treated group. Singh et al. [48] also showed an association between metformin use, vitamin B_{12} deficiency, and the presence of neuropathy. In contrast, Alharbi et al. [49] did not show a significantly higher rate of neuropathy in metformin-treated patients [49]. Older studies also did show a significant association between vitamin B_{12} deficiency and peripheral neuropathy in metformin-treated patients [50].

These apparently discrepant results may result from difficulties with matching the study groups being compared. In observational studies, yielding similar study groups for a comparison is probably impossible to achieve, as comparisons are only performed between metformin-treated versus non-patients, without taking into account other factors inducing neuropathy, which limits the credibility of the study findings. Future studies

with adequate sample sizes and use of more objective tools to evaluate peripheral neuropathy are needed to evaluate the relationship between metformin use and development of peripheral neuropathy in patients with type 2 diabetes [51].

Do other anti-diabetic drugs induce cobalamin deficiency?

A question arises whether other anti-diabetic drugs which also affect the gastrointestinal system function may potentially affect vitamin B$_{12}$ absorption. These include glucagon-like peptide-1 (GLP1) analogues. dipeptidyl peptidase-4 (DDP-4) inhibitors, and alpha-glucosidase inhibitors.

A 2018 study in an animal model showed that administering a conjugate of GLP1 analogue and vitamin B$_{12}$ improved blood glucose control and limited adverse effects associated with the use of GLP1 analogues (vomiting, nausea, fatigue). However, no evidence was provided that use of GLP1 analogues would lead to a reduction of vitamin B$_{12}$ level [52] No data are available in the literature regarding the effect of DPP-4 inhibitors and alpha-glucosidase inhibitors on vitamin B$_{12}$ levels.

Should vitamin B$_{12}$ level be measured, particularly with the presence of other factors predisposing to its deficiency?

Most guidelines recommend monitoring vitamin B$_{12}$ levels if risk factors for its deficiency are present, and the most recent diabetes management guidelines are consistent with this recommendation. The American Diabetes Association (ADA) suggests periodic cobalamin level measurements in patients receiving chronic metformin treatment, but without suggesting specific time intervals for this testing. ADA also recommended targeting individuals with concomitant neuropathy and anaemia [53]. In the most recent Diabetes Poland guidelines, correction of vitamin B$_{12}$ deficiency following its laboratory confirmation was recommended [29].

How reliable are blood vitamin B$_{12}$ level measurements?

In the routine clinical practice, vitamin B$_{12}$ levels are measured either to determine the cause of macrocytic anaemia or due to the presence of clinical manifestations suggesting vitamin B$_{12}$ deficiency. It has been questioned in the literature, however, whether plasma cobalamin levels reflect its clinical effects. Measuring serum cobalamin levels only does not allow an adequate insight into its total body stores, as the metabolic processes that use cobalamin as a cofactor occur at the intracellular level (Figs 1, 2). In addition, the effectiveness of these processes may be evaluated only

indirectly, based on plasma levels of transcobalamin, homocysteine, methylmalonic acid (MMA), S-adenosylmethionine (SAM), and S-adenosylhomocysteine (SAH). It seems that vitamin B$_{12}$ deficiency should be considered at two levels: actual (identified by laboratory test) and functional. The latter would be characterized by normal serum vitamin B$_{12}$ levels in the setting of its abnormal intracellular distribution, as reflected by abnormal levels of the above metabolites, the measurements of which are rarely available commercially [3, 54].

Obeid et al. [55] evaluated these relationships in patients with type 2 diabetes and a healthy control group. This study measured vitamin B$_{12}$ and its markers including red blood cell-vitamin B$_{12}$ (B$_{12}$-RBC), MMA, total transcobalamin (tTC), total homocysteine (tHcy) and methylation markers SAM and SAH. Cobalamin and transcobalamin levels in diabetic patients were similar to those in the healthy control group, while MMA level was higher, and B$_{12}$-RBC, SAM, and SAH levels were lower. These findings suggest that despite cobalamin levels within the laboratory reference range, its cellular distribution is disturbed. A reverse trend was observed in patients receiving metformin therapy, in whom cobalamin levels were lower compared to the control group. On the other hand, lower MMA levels and normal methylation index suggest normal cobalamin-dependent intracellular processes in these patients. Based on their findings, the authors postulated cellular resistance to vitamin B$_{12}$ in type 2 diabetes [55]. These results also indicate that interpretation of cobalamin level measurements should be cautious, and measuring other parameters listed above might be helpful.

Should cobalamin be supplemented in diabetic patients, particularly those receiving metformin treatment?

Vitamin B$_{12}$ supplementation has been long considered safe due to its hydrophilicity and easy elimination from the body in case of an excess supply. This has been recently questioned, however, by the study findings published by Flores-Guerrero et al. [56] in the Journal of the American Medical Association. These authors showed an association between higher cobalamin level and higher mortality in the general population. Surprisingly, this association became evident with plasma cobalamin levels within the reference range. This Dutch study followed more than 5000 adults for over 8 years. The identified association between cobalamin level and mortality was independent from age, gender, history of malignancies, renal and liver function parameters, concomitant type 2 diabetes, alcohol consumption, and smoking. Obesity, hypertension, dyslipidaemia, and hyperglycaemia were more common in patients with

plasma vitamin B_{12} levels in the upper quartile within the reference range. The exact significance of these correlations and their mechanisms remain unknown and require further analyses. Based on these findings, the authors suggested avoiding vitamin B_{12} supplementation unless its deficiency is documented [56].

How to supplement vitamin B_{12}?

In the past, the main approach to vitamin B_{12} supplementation were regular (usually monthly) intramuscular injections. Low popularity of oral intake was related to the belief that cobalamin absorption disturbances in various conditions lead to low bioavailability of the oral form. However, even with the absence of active cobalamin transport mechanism, it partially crosses the intestinal mucosa by passive diffusion. If an appropriately large vitamin B_{12} dose is administered via this route, achieving an adequate increase in its serum level is possible [3]. Effective sublingual cobalamin administration techniques have also been developed. A vitamin B_{12} preparation administered sublingually as an aerosol has been recently introduced in Poland.

Until recently, the literature reports of effective sublingual supplementation were limited to small studies and case reports. Bensky et al. [57] investigated the efficacy of sublingual supplementation compared to intramuscular cobalamin administration in nearly 4300 Israeli patients with vitamin B_{12} deficiency. Their study indicates that sublingual cobalamin administration effectively increased serum cobalamin level over a short time (the mean duration of follow-up was 7 months in the intramuscular cobalamin group and 9 months in the sublingual cobalamin group). The authors postulated superiority of this form of supplementation due to its convenience, lack of complications related to injections, and independence of the route of administration from the intrinsic factor and the gastrointestinal system status.

Sublingual administration results in cobalamin absorption directly to the bloodstream, avoiding potentially adverse pH of the stomach and bypassing the enterohepatic circulation, which might reduce the amount of actually absorbed active substance of the oral preparation. This route is also beneficial with concomitant dysphagia. It seems, however, that with large vitamin B_{12} deficiencies requiring more rapid correction, the time-honoured intramuscular administration remains the preferred approach as its efficacy is confirmed by years of experience. In the study by Bensky et al. [57], the diagnostic and therapeutic reasoning underlying the choice of a particular route of supplementation in a given patient was not investigated. The intramuscular administration group was smaller and these patients had lower baseline serum cobalamin levels compared to the sublingual supplementation group. Thus, it is difficult to establish whether sublingual supplementation is superior to intramuscular injections [57]. Routes alternative to intramuscular injections are worth considering when an improvement of the patient quality of life is the primary consideration. They are also good alternative if intramuscular administration is contraindicated, e.g., due to coagulopathy (including a iatrogenic one due to commonly used antithrombotic therapies).

Summary

The literature discussion on vitamin B_{12} supplementation in diabetic patients receiving metformin led to an increased interest in the importance of this vitamin in the management of diabetes and its complications. It seems that diabetic patients are at a potentially higher risk of cobalamin deficiency compared to individuals without diabetes. However, available laboratory tests do not allow discerning between blood levels of vitamin B_{12} and its tissue content that drives the clinical manifestations of vitamin B_{12} deficiency.

In addition to the natural disease course leading to micro- and macroangiopathic complications that might contribute to vitamin B_{12} deficiency, diabetic patients receive multi-drug therapy which may also aggravate this problem. In addition to metformin, most commonly used culprit medications include proton pump inhibitors, antibiotics, and non-steroidal anti-inflammatory drugs.

These discussions of the recent decade have been summarized in the diabetic societies' guidelines including those published by ADA and the Diabetes Poland which have indicated the need for an early correction of vitamin B_{12} deficiency.

Conflict of interest

None of the authors have a conflict of interest.

REFERENCES

1. Paoloni-Giacobino A, Grimble R, Pichard C. Genetics and nutrition. Clinical Nutrition. 2003; 22(5): 429–435, doi: 10.1016/s0261-5614(03)00064-5.
2. Kośmider A. Czaczyk, K. Witamina B12 — budowa, biosynteza, funkcje i metody oznaczania. Żywność Nauka Technologia Jakość. 2010; 17(5): 17–32.
3. Moridani M, Ben-Poorat S. Laboratory investigation of vitamin B12 deficiency. Laboratory Medicine. 2006; 37(3): 166–174, doi: 10.1309/cvhkle2r4w68k2nq.
4. Briani C, Dalla Torre C, Citton V, et al. Cobalamin deficiency: clinical picture and radiological findings. Nutrients. 2013; 5(11): 4521–4539, doi: 10.3390/nu5114521, indexed in Pubmed: 24248213.
5. Martínez Y, Li X, Liu G, et al. The role of methionine on metabolism, oxidative stress, and diseases. Amino Acids. 2017; 49(12): 2091–2098, doi: 10.1007/s00726-017-2494-2, indexed in Pubmed: 28929442.

6. Pawlak R, Lester SE, Babatunde T. The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B12: a review of literature. Eur J Clin Nutr. 2016; 70(7): 866, doi: 10.1038/ejcn.2016.81, indexed in Pubmed: 27381013.

7. Battat R, Kopylov U, Byer J, et al. Vitamin B12 deficiency in inflammatory bowel disease: a prospective observational pilot study. Eur J Gastroenterol Hepatol. 2017; 29(12): 1361–1367, doi: 10.1097/MEG.0000000000000970, indexed in Pubmed: 28953003.

8. Zheng S, Yang W, Wu C, et al. Association of ulcerative colitis with transcobalamin II gene polymorphisms and serum homocysteine, vitamin B, and folate levels in Chinese patients. Immunogenetics. 2017; 69(7): 421–428, doi: 10.1007/s00251-017-0998-2, indexed in Pubmed: 28526947.

9. Sutherland RJ, Cordes DO, Carthew GC. Ovine white liver disease — an hepatic dysfunction associated with vitamin B12 deficiency. N Z Vet J. 1979; 27(11): 227–232, doi: 10.1080/00480169.1979.34658, indexed in Pubmed: 294529.

10. Glasbrenner B, Malfertheiner P, Büchler M, et al. Vitamin B12 and folic acid deficiency in chronic pancreatitis: a relevant disorder? Klin Wochenschr. 1991; 69(4): 168–172, doi: 10.1007/BF01665861, indexed in Pubmed: 2041378.

11. Berry N, Basha J, Varma N, et al. Anemia in celiac disease is multifactorial in etiology: A prospective study from India. JGH Open. 2018; 2(5): 196–200, doi: 10.1002/jgh3.12073, indexed in Pubmed: 30483589.

12. Adamska A, Nowak M, Piłaciński S, et al. Small intestinal bacterial overgrowth in adult patients with type 1 diabetes: its prevalence and relationship with metabolic control and the presence of chronic complications of the disease. Pol Arch Med Wewn. 2016; 126(9): 628–634, doi: 10.20452/pamw.3501, indexed in Pubmed: 27535109.

13. Majumder S, Soriano J, Louie Cruz A, et al. Vitamin B12 deficiency in patients undergoing bariatric surgery: preventive strategies and key recommendations. Surg Obes Relat Dis. 2013; 9(6): 1013–1019, doi: 10.1016/j.soard.2013.04.017, indexed in Pubmed: 24091055.

14. Varughese GI, Scarpello JHB. Metformin and vitamin B12 deficiency: the role of H2 receptor antagonists and proton pump inhibitors. Age Ageing. 2007; 36(1): 110–1; discussion 111, doi: 10.1093/ageing/afl139, indexed in Pubmed: 17264140.

15. den Elzen WPJ, Groeneveld Y, de Ruijter W, et al. Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals. Aliment Pharmacol Ther. 2008; 27(6): 491–497, doi: 10.1111/j.1365-2036.2008.03601.x, indexed in Pubmed: 18194503.

16. Linnebank M, Moskau S, Semmler A, et al. Antiepileptic drugs interact with folate and vitamin B12 serum levels. Ann Neurol. 2011; 69(2): 352–359, doi: 10.1002/ana.22229, indexed in Pubmed: 21246600.

17. Lindenbaum J, Brown AS, Klonowski E, et al. Drugs and vitamin B12 and folate metabolism. Curr Concepts Nutr. 1983; 12: 73–87.

18. Antonijevic N, Nesovic M, Trbojevic B, et al. Anemia in hypothyroidism. Med Pregl. 1999; 52(3-5): 136–140.

19. Przybylik-Mazurek E, Kotlinowska B, Kasztelnik M, et al. [Autoimmunological and allergic disorders with Hashimoto and Graves disease]. Przegl Lek. 2006; 63(9): 719–722, indexed in Pubmed: 17479856.

20. Hagopian W, Lee HS, Liu E, et al. TEDDY Study Group. Co-occurrence of Type 1 Diabetes and Celiac Disease Autoimmunity. Pediatrics. 2017; 140(5), doi: 10.1542/peds.2017-1305, indexed in Pubmed: 29018046.

21. Shakil A, Church RJ, Rao SS. Gastrointestinal complications of diabetes. Am Fam Physician. 2008; 77(12): 1697–1702, indexed in Pubmed: 18619079.

22. Krishnamurthy G, Menon A, Kannan K, et al. Coronary artery disease and mesenteric artery stenosis - Two sides of the same coin? - Long term prospective analysis. Intractable Rare Dis Res. 2019; 8(4): 245–251, doi: 10.5582/irdr.2019.01087, indexed in Pubmed: 31890451.

23. Atreja A, Kalra S. Infections in diabetes. J Pak Med Assoc. 2015; 65(9): 1028–1030, indexed in Pubmed: 26338758.

24. Bauman WA, Shaw S, Jayatilleke E, et al. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care. 2000; 23(9): 1227–1231, doi: 10.2337/diacare.23.9.1227, indexed in Pubmed: 10977010.

25. Freeman R. Not all neuropathy in diabetes is of diabetic etiology: differential diagnosis of diabetic neuropathy. Curr Diab Rep. 2009; 9(6): 423–431, doi: 10.1007/s11892-009-0069-7, indexed in Pubmed: 19954686.

26. Hansen CS, Jensen JS, Ridderstråle M, et al. Vitamin B12 deficiency is associated with cardiovascular autonomic neuropathy in patients with type 2 diabetes. J Diabetes Complications. 2017; 31(1): 202–208, doi: 10.1016/j.jdiacomp.2016.08.025, indexed in Pubmed: 27638143.

27. Beitzke M, Pfister P, Fortin J, et al. Autonomic dysfunction and hemodynamics in vitamin B12 deficiency. Auton Neurosci. 2002; 97(1): 45–54, doi: 10.1016/s1566-0702(01)00393-9, indexed in Pubmed: 12036186.

28. de Greef BTA, Hoeijmakers JGJ, Gorissen-Brouwers CML, et al. Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. Eur J Neurol. 2018; 25(2): 348––355, doi: 10.1111/ene.13508, indexed in Pubmed: 29112785.

29. Satyanarayana A, Balakrishna N, Pitla S, et al. Status of B-vitamins and homocysteine in diabetic retinopathy: association with vitamin-B12 deficiency and hyperhomocysteinemia. PLoS One. 2011; 6(11): e26747, doi: 10.1371/journal.pone.0026747, indexed in Pubmed: 22069468.

30. Zehetner C, Bechrakis NE. White centered retinal hemorrhages in vitamin b(12) deficiency anemia. Case Rep Ophthalmol. 2011; 2(2): 140–144, doi: 10.1159/000328123, indexed in Pubmed: 22087102.

31. Azenha C, Costa JF, Fonseca P. You are what you eat: ophthalmological manifestations of severe B deficiency. BMJ Case Rep. 2017; 2017, doi: 10.1136/bcr-2016-218558, indexed in Pubmed: 28478387.

32. Chan W, Almasieh M, Catrinescu MM, et al. Cobalamin-associated superoxide scavenging in neuronal cells is a potential mechanism for vitamin B-deprivation optic neuropathy. Am J Pathol. 2018; 188(1): 160–172, doi: 10.1016/j.ajpath.2017.08.032, indexed in Pubmed: 29037851.

33. Drzewoski J, Czupryniak L, Chwatko G, et al. Hyperhomocysteinemia in poorly controlled type 2 diabetes patients. Diabetes Nutr Metab. 2000; 13(6): 319–324, indexed in Pubmed: 11232756.

34. Sreckovic B, Sreckovic VD, Soldatovic I, et al. Homocysteine is a marker for metabolic syndrome and atherosclerosis. Diabetes Metab Syndr. 2017; 11(3): 179–182, doi: 10.1016/j.dsx.2016.08.026, indexed in Pubmed: 27600468.

35. Yigit S, Karakus N, Inanir A. Association of MTHFR gene C677T mutation with diabetic peripheral neuropathy and diabetic retinopathy. Mol Vis. 2013; 19: 1626–1630, indexed in Pubmed: 23901246.

36. Carlsen SM, Kjøtrød S, Vanky E, et al. Homocysteine levels are unaffected by metformin treatment in both nonpregnant and pregnant women with polycystic ovary syndrome. Acta Obstet Gynecol Scand. 2007; 86(2): 145–150, doi: 10.1080/00016340600855946, indexed in Pubmed: 17364275.

37. Reinstatler L, Qi YP, Williamson RS, et al. Association of biochemical B deficiency with metformin therapy and vitamin B supplements: the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care. 2012; 35(2): 327–333, doi: 10.2337/dc11-1582, indexed in Pubmed: 22179958.

38. Ahmed MA. Metformin and vitamin B12 deficiency: where do we stand? J Pharm Pharm Sci. 2016; 19(3): 382–398, doi: 10.18433/J3PK7P, indexed in Pubmed: 27806244.

39. Tomkin GH, Hadden DR, Weaver JA, et al. Vitamin-B12 status of patients on long-term metformin therapy. Br Med J. 1971; 2(5763): 685–687, doi: 10.1136/bmj.2.5763.685, indexed in Pubmed: 5556053.

40. Sahin M, Tutuncu NB, Ertugrul D, et al. Effects of metformin or rosiglitazone on serum concentrations of homocysteine, folate, and vitamin B12 in patients with type 2 diabetes mellitus. J Diabetes Complications. 2007; 21(2): 118–123, doi: 10.1016/j.jdiacomp.2005.10.005, indexed in Pubmed: 17331860.

41. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010; 340: c2181, doi: 10.1136/bmj.c2181, indexed in Pubmed: 20488910.

42. Liu Q, Li S, Quan H, et al. Vitamin B12 status in metformin treated patients: systematic review. PLoS One. 2014; 9(6): e100379, doi: 10.1371/journal.pone.0100379, indexed in Pubmed: 24959880.

43. Aroda VR, Edelstein SL, Goldberg RB, et al. Diabetes prevention program research group. long-term metformin use and vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016; 101(4): 1754–1761, doi: 10.1210/jc.2015-3754, indexed in Pubmed: 26900641.

44. Caspary WF, Creutzfeldt W. Analysis of the inhibitory effect of biguanides on glucose absorption: inhibition of active sugar transport. Diabetologia. 1971; 7(5): 379–385, doi: 10.1007/BF01219474, indexed in Pubmed: 5134258.

45. Buvat DR. Use of metformin is a cause of vitamin B12 deficiency. Am Fam Physician. 2004; 69(2): 264; author reply 264, 266, indexed in Pubmed: 14765765.

46. Gupta K, Jain A, Rohatgi A. An observational study of vitamin b12 levels and peripheral neuropathy profile in patients of diabetes mellitus on metformin therapy. Diabetes Metab Syndr. 2018; 12(1): 51–58, doi: 10.1016/j.dsx.2017.08.014, indexed in Pubmed: 28882470.

47. Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes Care. 2010; 33(1): 156–161, doi: 10.2337/dc09-0606, indexed in Pubmed: 19846797.

48. Singh AK, Kumar A, Karmakar D, et al. Association of B12 deficiency and clinical neuropathy with metformin use in type 2 diabetes patients. J Postgrad Med. 2013; 59(4): 253–257, doi: 10.4103/0022-3859.123143, indexed in Pubmed: 24346380.

49. Alharbi TJ, Tourkmani AM, Abdelhay O, et al. The association of metformin use with vitamin B12 deficiency and peripheral neuropathy in Saudi individuals with type 2 diabetes mellitus. PLoS One. 2018; 13(10): e0204420, doi: 10.1371/journal.pone.0204420, indexed in Pubmed: 30321183.

50. Ahmed MA, Muntingh G, Rheeder P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. BMC Pharmacol Toxicol. 2016; 17(1): 44, doi: 10.1186/s40360-016-0088-3, indexed in Pubmed: 27716423.

51. Ahmed MA, Muntingh GL, Rheeder P. Perspectives on peripheral neuropathy as a consequence of metformin-induced vitamin B12 deficiency in T2DM. Int J Endocrinol. 2017; 2017: 2452853, doi: 10.1155/2017/2452853, indexed in Pubmed: 28932240.

52. Mietlicki-Baase EG, Liberini CG, Workinger JL, et al. A vitamin B12 conjugate of exendin-4 improves glucose tolerance without associated nausea or hypophagia in rodents. Diabetes Obes Metab. 2018; 20(5): 1223–1234, doi: 10.1111/dom.13222, indexed in Pubmed: 29327400.

53. Association AD. 1. Improving Care and promoting health in populations: standards of medical care in diabetes — 2020. Diabetes Care. 2020;43(Suppl 1):S7-S13. 10.2337/dc20-S001.

54. Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. BMJ. 2014; 349: g5226, doi: 10.1136/bmj.g5226, indexed in Pubmed: 25189324.

55. Obeid R, Jung J, Falk J, et al. Serum vitamin B12 not reflecting vitamin B12 status in patients with type 2 diabetes. Biochimie. 2013; 95(5): 1056–1061, doi: 10.1016/j.biochi.2012.10.028, indexed in Pubmed: 23168250.

56. Flores-Guerrero JL, Minovic I, Groothof D, et al. Association of plasma concentration of vitamin B12 with all-cause mortality in the general population in the Netherlands. JAMA Netw Open. 2020; 3(1): e1919274, doi: 10.1001/jamanetworkopen.2019.19274, indexed in Pubmed: 31940038.

57. Bensky MJ, Ayalon-Dangur I, Ayalon-Dangur R, et al. Comparison of sublingual vs. intramuscular administration of vitamin B12 for the treatment of patients with vitamin B12 deficiency. Drug Deliv Transl Res. 2019; 9(3): 625–630, doi: 10.1007/s13346-018-00613-y, indexed in Pubmed: 30632091.