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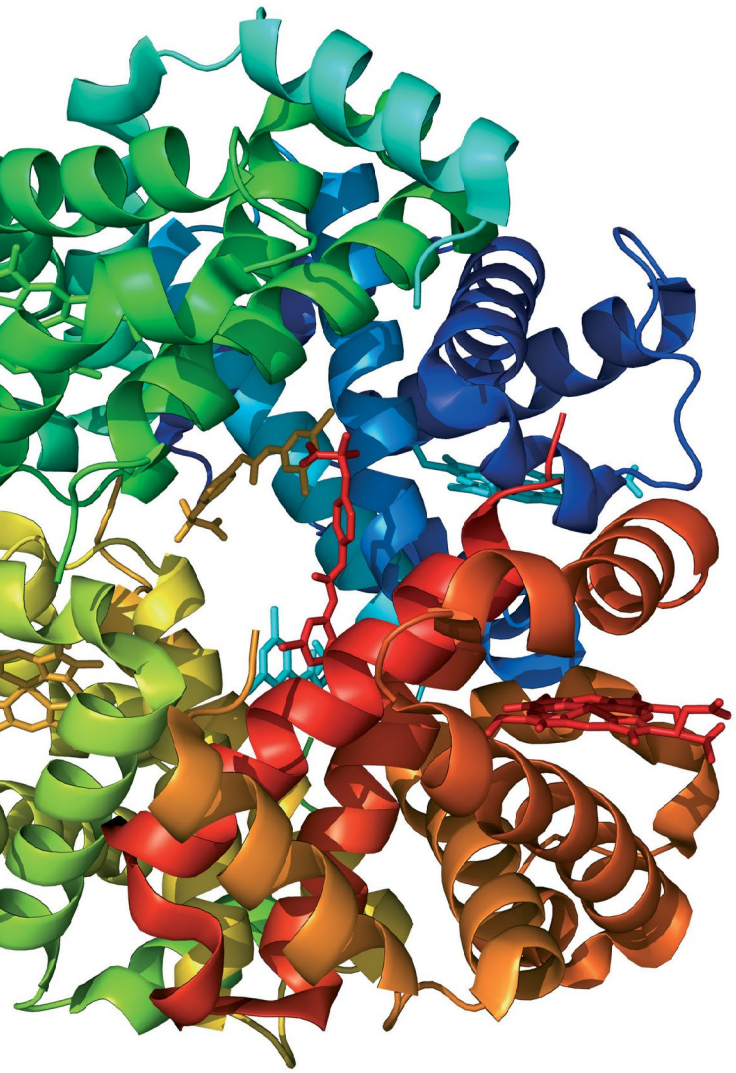

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Phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60
e-mail: redakcja@viamedica.pl, dim@viamedica.pl,
http://www.viamedica.pl, wap.viamedica.pl

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Editorial Address:
Katedra i Klinika Chorób Wewnętrznych, Diabetologii i Nefrologii
Śląski Uniwersytet Medyczny
ul. 3 Maja 13/15, 41–800 Zabrze
Phone: +48 (32) 271 25 11, fax +48 (32) 271 46 17
e-mail: jgumprecht@sum.edu.pl

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*na podstawie rozporządzenia Ministerstwa Zdrowia z dnia 6 października 2004 r. w sprawie sposobów dopełnienia obowiązku doskonalenia zawodowego lekarzy i lekarzy dentystów (Dz.U. 04.231.2326 z dnia 22 października 2004 r.)

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CLINICAL DIABETOLOGY

JOURNAL OF THE DIABETES POLAND

2019, Vol. 8, No. 2

Contents

The Voice of the Editor-in-Chief

Dear Colleagues,

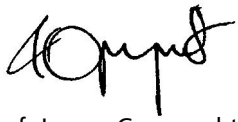
Traditionally, new clinical guidelines of Diabetes Poland are issued at the beginning of the year. The current guidelines of our Society, similarly to those developed by other Societies, take into account significant changes in the philosophy of treatment of type 2 diabetes and individualization of therapy that goes beyond the glucocentric approach. The key issue determining the choice of an antidiabetic drug has become whether the patient is suffering from cardiovascular or kidney disease or not. The preferred drug for treatment intensification (add-on to metformin) in patients with these diseases should be a GLP-1 analogue or an SGLT2 inhibitor, as these drugs provide many benefits in the field of cardiovascular and kidney protection, in addition to reducing blood glucose *per se*.

I would also like to draw your attention to the topics discussed in this issue of "Clinical Diabetology". Although more than 3,500 years have passed since the first description of the symptoms of diabetes in the Egyptian papyrus dated to around 1550 BC, diabetes is still an incurable disease and insulin therapy is the most effective method of decreasing blood glucose. Insulin is indispensable in the treatment of type 1 diabetes and is necessary in many cases of type 2 diabetes. Almost 100 years have passed since the discovery and first use of insulin. Behind us are years of research aimed at mimicking the body's physiological response to glycemic excursions and optimizing insulin therapy.

Over the last decades, there has been significant progress in devices supporting the treatment of diabetes, such as more and more technically advanced subcutaneous insulin pumps and continuous glucose monitoring systems that, on the one hand, improve glycemic control, and on the other hand, reduce the risk of hypoglycemic episodes and thus improve the patient's comfort of life. What is even more important, this also translates into a reduction in the risk of development and progression of chronic vascular complications of diabetes, which are still a key clinical problem of modern diabetology. One of such devices, the FreeStyle LIBRE continuous blood glucose monitoring system, was evaluated by a remarkable group of experts in the current edition of "Clinical Diabetology". Worth reading are also two articles providing a theoretical supplement to the discussion on continuous glycemic monitoring systems: a review paper discussing the measurement of glucose in the interstitial fluid and a report from *Diabetes Innovations Day*, a meeting dedicated to diabetes innovations and their use by physicians and patients that was held on 23–24 November 2018 in Poznan. Another important topic is diabetes occurring in pregnant women and its impact on a child as well as the woman herself and her future risk of developing type 2 diabetes. In this aspect, I encourage you to read an original paper assessing the effect of breastfeeding on carbohydrate metabolism among women with a history of gestational diabetes. A constant element in the development of "Clinical Diabetology" is the publication of articles sent by foreign authors. This issue includes a very interesting article that will expand our knowledge about the diagnosis of type 1 diabetes in India.

At the end, I would like to thank you for all the articles sent to us and encourage you to further cooperation. See you in Lublin at the 20th Scientific Congress of Diabetes Poland.

Editor-in-Chief



Prof. Janusz Gumprecht

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[1]Department of Internal Medicine and Diabetology, Medical University of Lodz, Poland
[2]Department of Structural Biology, Medical University of Lodz, Poland

The impact of lactation on glucose and insulin response and CRP concentration in women with prior GDM diagnosed according to WHO criteria — a prospective 18-month observation

ABSTRACT

Introduction. Gestational diabetes mellitus (GDM) is defined as glucose intolerance with an onset or first recognition during pregnancy. Previous GDM predisposes the woman to prediabetes or overt diabetes later in life. Lactation seems to have a protective impact on metabolic profile of the women with previous GDM but the results of available studies are conflicting. The aim of our study was to prospectively investigate in a 18-month observation whether lactation duration and intensity influences glucose and insulin response among women with prior GDM, diagnosed according to WHO criteria.

Material and methods. The study population consisted of 144 white caucasian women that were initially included in the study. During enrollment visit, between 26th and 30th week of gestation, maternal medical history, the result of 75 g oral glucose tolerance test (75 g OGTT), and anthropometric parameters were collected. Blood samples were collected for additional tests. Final analysis comprised 68 subjects (47.2%) that participated in the follow-up visit 18 months after delivery. Data on delivery and lactation as well as anthropometric data were gathered and 75 g OGTT was performed. The participants were then compared according to lactation duration [longer (> 12 weeks) or shorter (≤ 12 weeks)] or lactation intensity [more intensively (> 70% of the total infant milk consumption coming from breastfeeding) or less intensively (< 70% of the total infant milk consumption coming from breastfeeding)].

Results. 53 (78%) women breastfed more than 12 weeks, and 52 (76%) had intensive lactation. The women lactating longer than 12 weeks had significantly higher body weight (p = 0.038) and BMI (p = 0.001) than the women lactating for a shorter period of time. There was a 3-fold higher number of women treated with insulin in the group lactating for a longer period of time (p = 0.038). The women lactating more intensively had significantly lower HOMA 2 IR (p = 0.019) compared to the women breastfeeding less intensively. They had also lower HOMA 2 %B (p = 0.05). The number of subjects with isolated impaired glucose tolerance was significantly higher in the women lactating less intensively (18.7% *vs.* 1.9%, p = 0.037). A significant negative correlation between lactation duration and fasting glucose concentration (r = –0.282, p < 0.05) as well as fasting insulin concentration (r = –0.251, p < 0.05) was detected. Similar correlation was noticed as concerns 2-h post-load insulin concentration (p = 0.05). Moreover, a significant negative correlation between lactation intensity and fasting

Address for correspondence:
dr n. med. Marcin Kosiński
Klinika Chorób Wewnętrznych i Diabetologii
Uniwersytet Medyczny w Łodzi
e-mail: cosa@mp.pl
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insulin concentration ($r = -0.251$, $p < 0.05$) was found. In multiple regression model analysis, prepregnancy BMI and gestational weight gain appeared to be the strongest factors influencing the obtained results. Neither lactation duration nor intensity appeared as the significant factors in the model.

Conclusions. Our data provide evidence that lactation may have favorable effects on insulin and glucose response after delivery among women with prior GDM who are at high future cardiometabolic risk. The effects seems to be more evident with longer lactation duration as well as higher lactation intensity. (Clin Diabetol 2019; 8, 2: 99–109)

Key words: gestational diabetes mellitus, lactation

Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with an onset or first recognition during pregnancy. It results from increasing insulin resistance during pregnancy which may exceed the compensatory rise in insulin secretion and consequently lead to the development of glucose intolerance [1]. GDM tends to remit completely short after delivery but the disturbances concerning insulin secretion and/ /or action often remain in the post partum period [2]. Previous GDM predisposes the woman to prediabetes or overt diabetes later in life. Available data indicate that the risk of diabetes is even 7-fold higher than in the women with normoglycaemic pregnancy [3] and the rate of any glucose intolerance after GDM ranges from 2.6% to 70% [4]. These differences result mainly from the time of follow-up, studied population, and the screening criteria used for GDM diagnosis. Previous GDM is also associated with an increased risk of all other features of metabolic syndrome such as obesity, hypertension and dyslipidemia [5–7]. Recent studies have also shown that the women with prior GDM have a higher risk of coronary heart disease and myocardial infarction [7].

It is widely known that intensive lifestyle modification is effective in delaying or even preventing type 2 diabetes mellitus (T2DM) in women after GDM but adopting a healthy lifestyle is usually quite difficult [8]. Lactation seems to have a protective impact on metabolic profile of the women with previous GDM. Some results of available studies suggest that it increases insulin sensitivity and/or insulin secretion and finally improves glucose tolerance, thus lowering the risk of diabetes [9–12]. Moreover, it seems to prolong the period of time to development of diabetes [13]. On the other hand, there are also studies that did not confirm the health benefits of lactation in this particular group [14]. Recently published meta-analysis has shown that longer lactation in the women with a history of GDM had reduced the risk of (T2DM) compared with shorter lactation. Additionally, exclusive lactation compared with exclusive formula feeding had also lowered the risk of (T2DM). These findings support the evidence that longer and exclusive lactation may be beneficial for (T2DM) prevention in women with previous GDM. However, the evidence relies only on observational, and in majority retrospective, studies. What is more, analyses with stratification by the participants' characteristics such as ethnicity, BMI and other affecting factors were not possible because of inadequate information. These limitations deterred the authors from drawing tailored and general conclusion for each woman in real practice [15]. It was documented that breastfeeding rate among subjects with a history of GDM is lower compared with women after normoglycaemic pregnancies [16].

Because the majority of studies was carried out short after delivery, and the longer-term studies were in vast majority retrospective, the aim of our study was to prospectively investigate in a 18-month observation whether lactation duration and intensity influences glucose and insulin response among women with prior GDM, which was diagnosed according to WHO diagnostic criteria. We hypothesized that longer and more intense lactation ameliorates insulin secretion and sensitivity as well as glucose tolerance in this group of women.

Materials and methods

Study population

This is a prospective, cohort study curried out in Outpatient Department of Diabetology in Lodz, Poland between 2013 and 2016. All the women with a singleton pregnancy, attending the first visit between 26th and 30th gestational week with confirmed GDM diagnosis, that provided written informed consent to participate in the study, were enrolled to the study. The exclusion criteria were as follows: multiple pregnancy, prior glucose intolerance/diabetes (apart from previous GDM), already initiated insulin treatment or any concomitant cardiovascular diseases. The study population consisted of 144 white caucasian women that were initially included in the study. Gestational diabetes mellitus was diagnosed according to the World Health Organization (WHO 2013) criteria. GDM was diagnosed if at least one of the following criteria were met: fasting plasma glucose between 92 and 125 mg/dL (5.1–6.9 mmol/l); 1-h — post-load glucose concentration higher than 180 mg/dL (10.0 mmol/l); 2-h — post-load glucose level between 153 and 199 mg/dL (8.5–11.0 mmol/l).

The study protocol has been approved by the Ethics Committee of the Medical University of Lodz.

Data collection

Baseline data were collected during enrollment visit between 26th and 30th week of gestation. Information on age, education, parity, smoking, family history of diabetes, history of GDM in previous pregnancies, maternal birth weight as well as data concerning the day of GDM diagnosis and the result of 75 g oral glucose tolerance test (75 g OGTT) were gathered. Body weight and height were measured and body mass index (BMI) was calculated. Prepregnancy weight was self-reported and was used to calculate prepregnancy BMI. Blood sample was collected (see the description below). The women were informed about the potential benefits of lactation and were asked for making notes concerning lactation after delivery: 1) lactation (yes/ /no), 2) lactation intensity (exclusive/partial; if partial then percent of breastfeeding in relation to the infant total daily milk consumption), and 3) lactation duration in weeks. All the women were then invited for the follow-up visit 18 months (± 1 month) after delivery. They were given a written information concerning the visit, and then they were called before the estimated follow-up date in order to increase the attendance rate. At the follow-up visit data on gestational weight gain, actual weight and insulin use during pregnancy (yes/no), perinatal outcomes as well as lactation (see above) were collected.

The women attending the follow-up visit were then compared according to lactation duration [longer (> 12 weeks) or shorter (≤ 12 weeks)] or lactation intensity [more intensively (> 70% of the total infant milk consumption coming from breastfeeding) or less intensively (< 70% of the total infant milk consumption coming from breastfeeding)].

Laboratory measurements

The first blood sample was taken during pregnancy at baseline visit. Plasma glucose concentration was measured enzymatically while plasma insulin concentration was measured by RIA (Roche Diagnostics). Glycated haemoglobin (HbA_{1c}) was measured using HPLC method, and high sensitive C-reactive protein concentration was evaluated using immunoassay. 18 months after delivery a 75 g 2-h OGTT was performed in the morning after an overnight fast. Blood samples were collected at 0 and 120 minutes for the measurement of plasma glucose and insulin concentrations. All the participants were given written recommendations before delivery, as well as a telephone call just before the follow-up visit, concerning the standards of OGTT performance. They were also asked to breastfeed the infants just before the glucose load, and not during OGTT, as lactation may potentially affect both glucose and insulin concentrations. The test was performed after the meeting with the investigator to ensure that all the above conditions are met. All the tests were carried out in the central laboratory. Impaired fasting glycemia (IFG), impaired glucose tolerance (IGT), and diabetes mellitus (DM) were diagnosed according to WHO criteria.

The homeostasis model assessment for insulin sensitivity index (HOMA 2 %S), homeostasis model assessment for β-cell function index (HOMA 2 %B), and homeostasis model assessment for insulin resistance index (HOMA 2 IR) were calculated using the mathematical model developed by Jonathan Levy et al [17]. Calculations were done by the "HOMA Calculator" developed by Diabetes Trial Unit of The Oxford Centre for Diabetes, Endocrinology and Metabolism available for download and use on DTU's site. The QUICKI index was estimated by the following formula: 1/[log (fasting insulin μU/mL) + log (fasting glucose mg/dL)], https:// //www.dtu.ox.ac.uk/homocalculator/ [18].

Statistical analysis

Statistical analyses were performed using the PQStat statistical package, license no. 01500256 (PQStat Software, Poznań, Poland). Continuous data were expressed as mean ± standard deviation (SD) and categorical variables as percentages. The Kolmogorov--Smirnov test was first used to confirm whether the variables had a normal distribution. Normally-distributed dependent and independent variables were compared using the Student's t-test. For variables with a non-normal distribution, independent variables were compared with the Mann-Whitney test, and dependent variables with the Wilcoxon test. Fisher's exact test was used for comparison of proportions. Correlations were identified with the Pearson's correlation coefficient for parametric variables, and the Spearman's rank correlation coefficient for non-parametric variables. Multiple regression linear analysis was done to assess the relationship between lactation duration/intensity and both glucose and insulin response 18 months after delivery, with covariates such as: pregestational BMI, gestational weight gain and family history of DM. Statistical significance was defined as $p < 0.05$.

Results

Of all 144 women included in the study 68 participated in the follow-up visit and finally this group was taken into consideration in the analysis. 53 (78%) women breastfed more than 12 weeks, and 52 (76%)

Table 1. The characteristics of the study group at baseline visit in pregnancy week 26–30 according to the lactation duration

Parameters	Whole group (n = 68)	Lactation < 12 weeks (n = 15)	Lactation > 12 weeks (n = 53)	p
Age (years)	34.1 ± 4.3	35.3 ± 4.5	33.8 ± 4.8	0.297
Multiparity, n (%)	35 (51.5)	4 (26.6)	31 (58.5)	0.041
Smoking, yes, n (%)	15 (22.1)	3 (20.0)	11 (20.6)	0.761
Education				
Secondary, n (%)	29 (42.6)	8 (53.3)	21 (39.6)	0.386
Post secondary, n (%)	39 (57.4)	7 (46.7)	32 (60.4)	0.248
Family history of DM, yes, n (%)	37 (54.4)	6 (40.0)	31 (58.4)	
History of GDM, yes, n (%)	3 (4.4)	1 (6.7)	2 (3.7)	0.532
Maternal birth weight [g]	3212 ± 500	3212 ± 373	3245 ± 489	0.826
Prepregnancy weight [kg]	68.8 ± 15.5	68.0 ± 11.5	69.35 ± 15.56	0.771
Prepregnancy BMI [kg/m^2]	25.1 (CI 24.0–26.1)	25.3 (CI 22.4–28.6)	23.9 (CI 22.8–25.8)	0.604
Actual body weight [kg]	79.2 ± 16.2	77.0 ± 10.2	80.3 ± 16.9	0.502
Actual BMI [kg/m^2]	27.1 (CI 26.3–27.8)	27.1 (CI 24–28.4)	27.2 (CI 25.4–28.8)	0.915
OGTT result during pregnancy				
Fasting glucose [mg/dL], n = 68	86 ± 12	86 ± 15	85 ± 12	0.788
1-h post-OGTT glucose [mg/dL], n = 56	175 ± 27	176 ± 33	173 ± 28	0.725
2-h post-OGTT glucose [mg/dL], n = 68	155 ± 21	154 ± 26	152 ± 21	0.758
Time of GDM diagnosis (gestational week)	28.1 ± 2.4	27.46 ± 1.8	27.96 ± 2.78	0.746
Measurements between 26th and 30th gestational week				
Fasting glucose [mg/dL]	81 ± 11.8	80.36 ± 8.73	80.65 ± 13.7	0.947
Fasting insulin [μIU/ml]	16.6 ± 9.07	14.77 ± 5.86	13.57 ± 9.25	0.887
HbA_{1c} (%)	5.18 ± 0.34	5.25 ± 0.44	5.227 ± 0.34	0.807
hsCRP [mg/dL]	4.11 ± 3.04	3.67 ± 1.8	4.6 ± 3.4	0.241

CI — confidence interval; GDM — gestational diabetes mellitus; BMI — body mass index; OGTT — oral glucose tolerance test; hsCRP — high-sensitivity C-reactive protein

had intensive lactation. Only three women that attended the follow-up visit were not lactating at all. They were included in the group of shorter or less intensive lactation, respectively. The characteristics of the study groups according to lactation duration and intensity are presented in Table 1 and 2.

Majority of women breastfed longer than 12 weeks. In a group of subjects that were breastfeeding longer than 12 weeks there was a higher proportion of multipara (p = 0.041), and higher incidence of positive family history of DM (p = 0.021). However, both groups did not differ significantly in relation tobaseline variables such as age, history of GDM, anthropometric parameters, OGTT result and additional measurements performed at enrollment. Similarly, according to lactation intensity the women from both groups did not differ significantly in relation to baseline parameters during pregnancy. Women lactating more intensively tented to have lower prevalence of diabetes in the family and their educational level was frequently higher than secondary school, but these differences were insignificant.

The characteristics of women at the 18 months visit are presented in Tables 3 and 4.

18 months after delivery, the women lactating longer than 12 weeks had significantly higher body weight (p = 0.038) and BMI (p = 0.001) than the women lactating for a shorter period of time. Additionally, 2-h postload insulin concentration was one third lower in this group of women but this difference was not statistically significant. There was 3-fold higher number of women treated with insulin in the group lactating for a longer period of time (p = 0.038). The remaining parameters did not differ significantly according to lactation duration. The women lactating more intensively had significantly lower HOMA 2 IR (p = 0.019) compared to the women breastfeeding less intensively. They had also lower HOMA 2 %B, and this difference was approaching statistical significance (p = 0.05). The number of subjects with isolated impaired glucose tolerance was significantly higher in the women lactating less intensively (18.7% *vs.* 1.9%, p = 0.037). The remaining parameters did not differ significantly according to lactation intensity.

Table 2. The characteristics of the study group at baseline visit in pregnancy week 26–30 according to the lactation intensity

Parameters	Whole group (n = 68)	Lactation > 70% (n = 52)	Lactation < 70% (n = 16)	p
Age (years)	34.1 ± 4.3	34.1 ± 4.4	33.18 ± 3.7	0.439
Multiparity, n (%)	35 (51.5)	28 (53.8)	7 (43.7)	0.527
Smoking, yes, n (%)	15 (22.1)	11 (21.1)	4 (25.0)	0.739
Education				
Secondary, n (%)	29 (42.6)	20 (38.4)	9 (56.2)	0.257
Post secondary, n (%)	39 (57.4)	32 (61.6)	7 (43.8)	
Family history of DM, yes, n (%)	37 (54.4)	25 (48.0)	12 (75.0)	0.08
History of GDM, yes	3 (4.4)	2 (3.8)	1 (6.25)	0.552
Maternal birth weight [g]	3212 ± 500	3225 ± 519	3123 ± 484	0.473
Prepregnacy weight [kg]	68.8 ± 15.5	67.9 ± 14.4	67.0 ± 14.0	0.828
Prepregnancy BMI [kg/m^2]	25.1 (CI 24.0–26.1)	23.8 (CI 22.6–25.3)	25.3 (CI 21.8–26.3)	0.948
Actual body weight [kg]	79.2 ± 16.2	77.8 ± 14.8	78.1 ± 14.0	0.931
Actual BMI [kg/m^2]	27.1 (CI 26.3–27.8)	26.3 (CI 25.6–27.4)	27.9 (CI 24.7–29.5)	0.426
OGTT result during pregnancy				
Fasting glucose [mg/dL], n = 52	86 ± 12	86 ± 12	85 ± 14	0.780
1-h post-OGTT glucose [mg/dL], n = 49	175 ± 27	176 ± 28	174 ± 27	0.802
2-h post-OGTT glucose [mg/dL], n = 52	155 ± 21	154 ± 21	156 ± 19	0.735
Time of GDM diagnosis (gestational week)	28.1 ± 2.4	28 ± 2.4	28.5 ± 2.3	0.735
Measurements between 26th and 30th gestational week				
Fasting glucose [mg/dL]	81 ± 11.8	80 ± 9.5	80.5 ± 16	0.969
Fasting insulin [μIU/ml]	16.6 ± 9.07	12.5 ± 7.2	16.8 ± 12.2	0.260
HbA_{1c} (%)	5.18 ± 0.34	5.17 ± 0.31	5.18 ± 0.39	0.978
hsCRP [mg/dL]	4.11 ± 3.04	3.88 ± 2.97	5.19 ± 3.4	0.193

CI — confidence interval; GDM — gestational diabetes mellitus; BMI — body mass index; OGTT — oral glucose tolerance test; hsCRP — high-sensitivity C-reactive protein

A significant negative correlation between lactation duration and fasting glucose concentration ($r = -0.282$, $p < 0.05$) (Figure 1) as well as fasting insulin concentration ($r = -0.251$, $p < 0.05$) (Figure 2) was detected. Similar correlation was noticed as concerns 2-h post-load insulin concentration but this relationship had borderline significance ($p = 0.05$) (Figure 3). Moreover, a significant negative correlation between lactation intensity and fasting insulin concentration ($r = -0.251$, $p < 0.05$) was found (Figure 4). No other significant correlations were found according to lactation duration nor intensity.

In multiple regression model analysis, according to data suggested in literature, we used the following factors that might have impact on fasting and post-OGTT glucose and insulin concentrations as well as CRP concentration, lactation duration, lactation intensity, prepregnancy BMI, family history of DM, and gestational weight gain (Table 5). Covariates that were used in the analysis were the most frequently chosen in the analyses of other authors, as it was described in a recent meta-analysis [15].

Our model was correct for the influence on concentrations of CRP, fasting glucose, fasting insulin and 2-h post-load insulin and for the indices such as HOMA 2 %B and HOMA 2 IR. Prepregnancy BMI and gestational weight gain appeared to be the strongest factors influencing the obtained results. Neither lactation duration nor intensity appeared as the significant factors in the model.

Discussion

The aim of our study was to investigate the influence of lactation on insulin and glucose response 18 months after delivery in the group of women with previous GDM. The impact of lactation duration and intensity was analyzed. Results from our observation reveal that a vast majority of women (93.8%) with prior GDM breastfed their infant. In our trial this number was relatively higher that reported in other studies [9, 19], which may result from greater health awareness as our participants were educated regarding the advantages of breastfeeding. In our study the inci-

Table 3. The characteristics of the study group at the 18 month visit according to lactation duration

Parameters	Whole group (n = 68)	Lactation < 12 weeks (n = 15)	Lactation > 12 weeks (n = 53)	p
Actual body weight [kg]	67.8 ± 16.9	65.9 ± 14.5	71.2 ± 16.7	0.038
Actual BMI [kg/m^2]	24.4 (CI 23.0–25.8)	22.2 (CI 21.0–23.9)	25.5 (CI 24.3–31.1)	0.001
Gestational weight gain [kg]	9.5 ± 9.15	9.0 ± 5.9	11.0 ± 5.7	0.276
Insulin treatment in pregnancy, yes, n (%)	27 (39.7)	2 (26.6)	23 (43.4)	0.371
OGTT result				
Fasting glucose [mg/dL]	92 (CI 89–95)	93 (CI 88–98)	89.5 (CI 86–94)	0.38
2-h post-OGTT glucose [mg/dL]	107 (CI 101–113)	107 (CI 96–129)	104 (93–109)	0.40
Fasting insulin [μIU/ml]	9.63 ± 6.5	9.37 ± 4.32	9.66 ± 2.06	0.88
2-h post-OGTT insulin [uIU/ml]	50.1 ± 30.0	66.7 ± 41	46.4 ± 26.1	0.14
HOMA 2 IR	1.19 (CI 1.02–1.43)	0.92 (CI 0.38–1.54)	1.1 (CI 0.80–1.39)	0.430
HOMA 2 %S	117.6 ± 84.6	138.6 ± 97.5	103.5 ± 55.0	0.427
HOMA 2 %B	101.7 ± 41.5	95.4 ± 29.5	107.3 ± 41.5	0.506
QUICKI	0.66 ± 0.50	0.63 ± 0.32	0.67 ± 0.54	0.844
Isolated IFG, yes, n (%)	15 (22.1)	2(13.0)	13 (24.5)	0.492
Isolated IGT, yes, n (%)	5 (7.3)	1 (6.5)	4 (7.5)	1.0
IFG + IGT, yes, n (%)	1 (1.4)	0	1	–
HbA_{1c} (%)	5.16 ± 0.30	5.26 ± 0.41	5.11 ± 0.28	0.123
hsCRP [mg/dL]	1.97 (CI 1.03–2.35)	1.47 (CI 1.0–2.48)	1.02 (CI 0.83–1.7)	0.31

CI — confidence interval; BMI — body mass index; OGTT — oral glucose tolerance test; hsCRP — high-sensitivity C-reactive protein; HOMA 2 %S — homeostasis model assessment for insulin sensitivity index; HOMA 2 %B — homeostasis model assessment for β-cell function index; HOMA 2 IR — homeostasis model assessment for insulin resistance index; IFG — impaired fasting glucose; IGT — impaired glucose tolerance

dence of impaired glucose tolerance was significantly higher in the group of women lactating less intensively (p = 0.037). The results of other studies concerning this issue are still inconclusive. In the study of Kim et al., conducted in a group of Asian women 6–12 weeks after delivery, no protective effect of breastfeeding on the risk of developing diabetes was reported [8]. Although a retrospective observation of Stuebe et al. showed a beneficial effect of breastfeeding on the risk of developing diabetes, this observation was not confirmed in the subgroup of women after GDM [14]. On the other hand however, in a long-term observation of Ziegler et al. lactation after GDM pregnancy has been shown to delay diabetes by an average of 10 years (12.3 years *vs.* 2.3 years), with the lowest observed risk in women who have breastfed more than 3 months [13]. Similar conclusions come from another study, comprising 300 women with prior GDM, the prevalence of persistent hyperglycemia at 12 weeks after delivery was lower in subjects who lactated comparing to not lactating women [9]. Also, in the SWIFT study (Study of Women, Infant Feeding, and Type 2 Diabetes), performed 6–9 weeks after delivery, it was shown that the prevalence of diabetes and pre-diabetes were lower in the group of women who were breastfeeding exclusively or mainly [10]. However, in the Nurses' Health Study, longer lactation decreased the risk of type 2 diabetes in the group without GDM, while it did not in the women with previous GDM [14]. Like in Stuebe et al., in the Coronary Artery Risk Development in Young Adults Study longer lactation duration was associated with a lower incidence of the metabolic syndrome in the women with prior GDM during a 20-year observation [20]. Finally, in the recent systematic review, lactation of any intensity for more than 4 weeks to more than 12 weeks postpartum in the women with previous GDM was associated with significantly lower risk of type 2 diabetes mellitus in the long term. It is worth stressing that the impact of longer lactation was not obvious when diabetes was evaluated in early postpartum, but became more evident with longer follow-up. The possible explanation is that glucose disturbances prevalence after GDM pregnancy increases with time so it seems that at least several years of follow-up are required to objectively judge this effect.

We observed that women who breastfed longer had significantly higher body weight (p < 0.05) and BMI (p < 0.01) comparing to the subjects lactating for a shorter period of time. We found a significant negative correlation between lactation duration and both fasting glucose and insulin concentrations. Additionally, a negative correlation between lactation duration

Table 4. The characteristics of the study group at the follow-up visit according to lactation intensity

Parameters	Whole group (n = 68)	Lactation > 70% (n = 52)	Lactation < 70% (n = 16)	p
Actual body weight [kg]	67.8 ± 16.9	67.2 ± 15.2	68.5 ± 15.9	0.742
Actual BMI [kg/m^2]	24.4 (CI 23.0–25.8)	23.7 (CI 22.3–25.0)	25.1 (CI 21.3–29.0)	0.604
Gestational weight gain [kg]	9.5 ± 9.15	8.8 ± 9.3	11.1 ± 6.2	0.352
Insulin treatment in pregnancy, yes, n (%)	27 (39.7)	22 (42.3)	5 (32.2)	0.562
OGTT result				
Fasting glucose [mg/dL]	92 (CI 89–95)	92 (CI 86–97)	90 (CI 85–94)	0.769
2-h post-OGTT glucose [mg/dL]	107 (CI 101–113)	105 (CI 94–111)	102.5 (CI 92–121)	0.823
Fasting insulin [μIU/ml]	9.63 ± 6.5	9.68 ± 7.1	9.82 ± 4.42	0.987
2-h post-OGTT insulin [μIU/ml]	50.1 ± 30.0	50.3 ± 30.1	54.4 ± 29.4	0.677
HOMA 2 IR	1.19 (CI 1.02–1.43)	0.77 (CI 0.68–0.88)	1.12 (CI 0.90–1.66)	0.019
HOMA 2 %S	117.6 ± 84.6	139.7 ± 76.8	103.61 ± 74.81	0.09
HOMA 2 %B	101.7 ± 41.5	102.86 ± 31.89	133.45 ± 56.09	0.05
QUICKI	0.66 ± 0.50	0.70 ± 0.28	0.59 ± 0.24	0.144
Isolated IFG, yes, n (%)	15 (22.1)	12 (23.1)	3 (18.7)	1.0
Isolated IGT, yes, n (%)	4 (5.8)	1 (1.9)	3 (18.7)	0.037
IFG + IGT, yes, n (%)	1 (1.4)	1 (1.9)	0	–
HbA_{1c} (%)	5.16 ± 0.30	5.22 ± 0.32	5.27 ± 0.35	0.582
hsCRP [mg/dL]	1.97 (CI 1.03–2.35)	1.36 (CI 1.02–1.58)	1.94 (CI 1.32–2.45)	0.209

CI — confidence interval; BMI — body mass index; OGTT — oral glucose tolerance test; hsCRP — high-sensitivity C-reactive protein; HOMA 2 %S — homeostasis model assessment for insulin sensitivity index; HOMA 2 %B — homeostasis model assessment for β-cell function index; HOMA 2 IR — homeostasis model assessment for insulin resistance index; IFG — impaired fasting glucose; IGT — impaired glucose tolerance

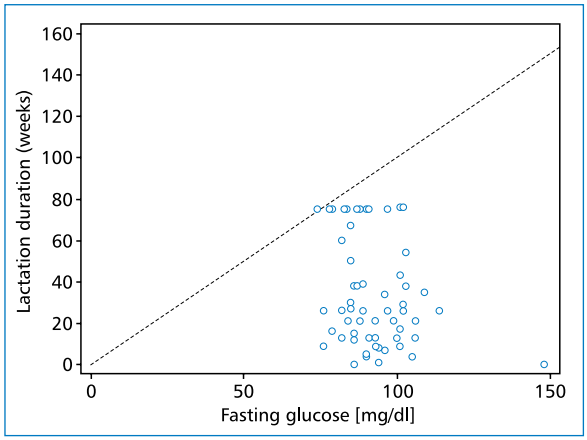

Figure 1. Correlation between lactation duration and fasting plasma glucose concentration at 18 month period

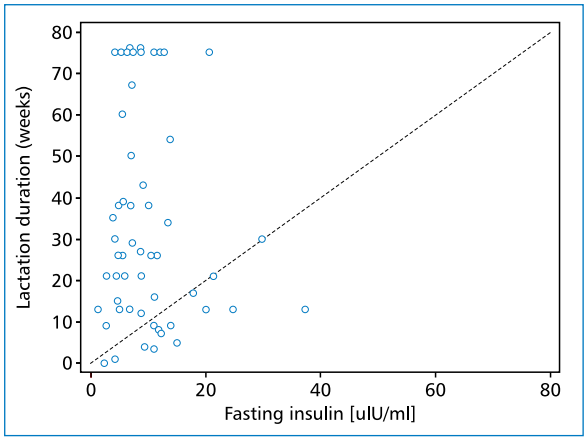

Figure 2. Correlation between lactation duration and fasting plasma insulin concentration at 18 month period

and 2-h post-load insulin concentration was noticed, approaching a level of significance (p = 0.05). Also, a significant negative correlation between lactation intensity and fasting insulin concentrations was recorded. In multiple regression model analysis however, neither lactation duration nor intensity were independent predictors of fasting and post-load glucose and insulin concentrations, which stays in line with some other observations [19]. Lactation duration appeared to affect 2-h post-OGTT insulin concentration, approaching but not reaching significance (p = 0.06). Similarly to our results, Ram et al. observed that lactation duration was inversely correlated with fasting insulin concentrations in a retrospective study comprising high number (2516) of women [12]. Additionally, other authors also showed that breastfeeding was inversely correlated

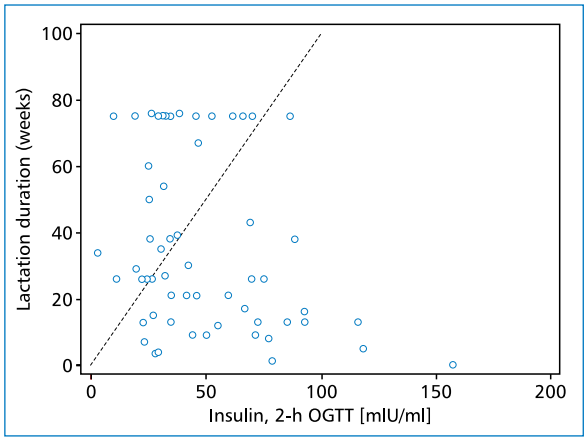

Figure 3. Correlation between lactation duration and 2-h post-OGTT insulin concentration at 18 month period

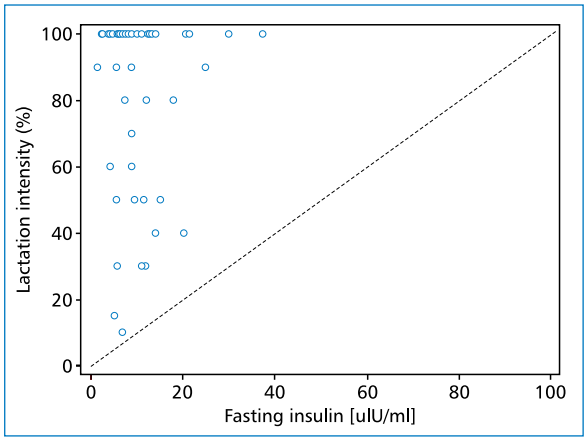

Figure 4. Correlation between lactation intensity and fasting plasma insulin concentration at 18 month period

with insulin response during OGTT [19, 21]. Also, in the SWIFT cohort, women who were breastfeeding exclusively or mostly had lower fasting insulin levels as well as reduced insulin response following a glucose challenge compared with formula feeding exclusive or mostly [10]. These results stay in line with our observations and suggest that lactation is associated with lower both fasting and post-load insulin concentrations. In our study longer lactation correlated with lower fasting glucose levels but not with 2-h post-load glucose values. Similarly, some studies have also shown improved insulin homeostasis but no changes in glucose tolerance among women who lactate, suggesting that lactation may be associated with post-load hyperinsulinemia thus maintaining normal glycemia [10, 21, 22].

Participants lactating more intensively in our study had significantly lower index of insulin resistance ($p = 0.019$) as well as insulin secretion ($p = 0.05$) compared to the women breastfeeding less intensively. The most probable explanation of these results is higher BMI and body weight in the women lactating more intensively, as these parameters were the strongest predictors of glucose and insulin response in a multivariate model. Tigas S et al., reported similar glucose results in OGTT, but in breastfeeding women post-load insulin levels were significantly lower, indicating higher insulin sensitivity [22]. In another study, higher insulin sensitivity in women who have been breastfeeding for more than 10 months have been demonstrated [19]. However, similarly to our results McManus et al. observed that insulin sensitivity was not significantly different in relation to lactation 3 months after delivery [11]. On the longer perspective, this relationship is also not so evident, as the results from the study performed 3 years after delivery did not show any association between lactation and insulin resistance [23]. Similarly, in a larger study of women with prior GDM (SWIFT), 522 subjects with prior GDM were tested shortly post partum (6–9 weeks after delivery). Intensive lactation (exclusive or almost exclusive) was associated with significantly lower HOMA-IR compared to no lactation, while no differences were found regarding the mixed or inconsistent lactation [10]. Similarly to our results, McManus has showed that in breastfeeding women, improvement in pancreatic β-cell function was observed. Also, a higher β-cell function was observed in 3 months after delivery, while there was no difference in insulin sensitivity [11]. In a study of Chouinard-Castonguay S et al., improved insulin secretion among women who lactated longer than 10 months was observed [19]. In a multiple regression model, however, lactation duration was no longer significant when other variables were included in the model.

Several hypotheses concerning potential mechanisms underlying a possible beneficial effect of lactation on glucose metabolism have been proposed. First, direct prolactin action which has been shown to stimulate insulin secretion through stimulation of β-cell proliferation by downregulating the expression of menin [24, 25]. Prolactin levels remain high during lactation, suggesting that this hormone may play a role in regulating insulin secretion and glucose homeostasis in the post partum period [26]. The similar role of oxytocin was also suggested [27]. Another suggestion is that glucose could be preferentially utilized in lactogenesis process (which is estimated for about 50 g of glucose per day) in an insulin-independent pathway, which in turn may unload the pancreatic β-cells and finally preserve long-term insulin production in lactating women [28]. Also, breastfeeding may affect

Table 5. Multiple regression linear analyses of the relationships between lactation duration and the glucose and insulin response 18 months after delivery (n = 68). Covariates included in the models were: pregestational BMI, family history of DM, parity and pregnancy weight gain

	β	p	Model r^2
Fasting glucose [mg/dL]			0.2219
Lactation duration	–0.08	0.209	
Lactation intensity	–0.036	0.526	
Prepregnancy BMI	0.610	0.108	
Family history of DM	–3.425	0.322	
Gestational weight gain	–0.251	0.0040	
2-h post-OGTT glucose [mg/dL]			0.111
Lactation duration	–0.071	0.589	
Lactation intensity	0.047	0.720	
Prepregnancy BMI	0.790	0.459	
Family history of DM	11.08	0.105	
Gestational weight gain	–0.338	0.139	
Fasting insulin [μIU/ml]			0.378
Lactation duration	0.038	0.895	
Lactation intensity	–0.04	0.179	
Prepregnancy BMI	0.978	0.0001	
Family history of DM	–2.129	0.328	
Gestational weight gain	–0.274	< 0.0001	
2-h post-OGTT insulin [μIU/ml]			0.310
Lactation duration	–0.207	0.155	
Lactation intensity	–0.057	0.687	
Prepregnancy BMI	3.618	0.0029	
Family history of DM	14.671	0.068	
Gestational weight gain	–0.94	0.0017	
HOMA 2 %S			0.100
Lactation duration	–0.723	0.123	
Lactation intensity	0.565	0.227	
Prepregnancy BMI	–5.392	0.154	
Family history of DM	4.054	0.864	
Gestational weight gain	1.343	0.092	
HOMA 2 %B			0.306
Lactation duration	0.244	0.228	
Lactation intensity	–0.237	0.242	
Prepregnancy BMI	5.426	0.0015	
Family history of DM	–11.14	0.282	
Gestational weight gain	–1.586	< 0.0001	
HOMA 2 IR			0.372
Lactation duration	0.0002	0.940	
Lactation intensity	–0.005	0.172	
Prepregnancy BMI	0.124	0.0002	
Family history of DM	–0.257	0.177	
Gestational weight gain	–0.03	< 0.0001	
QUICKI			0.055
Lactation duration	–0.003	0.232	
Lactation intensity	0.001	0.540	
Prepregnancy BMI	–0.017	0.320	
Family history of DM	-0.056	0.701	
Gestational weight gain	0.003	0.440	
CRP			0.2548
Lactation duration	–0.008	0.495	
Lactation intensity	0.0001	0.990	
Prepregnancy BMI	0.167	0.081	
Family history of DM	0.099	0.870	
Gestational weight gain	–0.060	0.0004	

BMI — body mass index; DM — diabetes mellitus; CRP — C-reactive protein; HOMA 2 %S — homeostasis model assessment for insulin sensitivity index; HOMA 2 %B — homeostasis model assessment for β-cell function index; HOMA 2 IR — homeostasis model assessment for insulin resistance index

adipocytes metabolism by mobilizing and redirecting lipids accumulated in hepatocytes and muscle cells into breast milk instead of adipocytes. Additionally, prolactin modulates the transcription factors such as STAT5 and PPARγ, and the expression of lipoprotein lipase, which are co-expressed in breast, adipose tissue, and skeletal muscle [29]. Thus, a non-lactating woman would be at higher risk of storing lipids in non-adipose tissues resulting in further imbalance between insulin secretion and sensitivity. In another study, it was observed that lactation affected both ghrelin and YY peptide concentrations, the hormones involved in hypothalamic appetite regulation, suggesting the impact of feeding on neuroendocrine pathways within the hypothalamus. A correlation between adiponectin concentration and breastfeeding duration was also noted in this study, while no relationship was found as concerns leptin concentrations. However, it should be stressed that women with prior GDM were excluded from this cohort [23].

There are some limitations of our current study that have to be addressed. First, only 68 of all 144 initially enrolled subjects attended the follow-up visit, which is relatively high proportion (in relation to the reported general follow-up rate, but still unsatisfactory in the light of statistical power. Secondly, the controlgroup of not lactating women was unavailable, which resulted from both insufficient follow-up attendance rate and the fact that the great majority of women lactated, leaving finally only 3 not lactating women of 68 subjects. However, all efforts were made to encourage the women to attend the visits, as every single participant was called by the investigator before the estimated date of the follow-up meeting. Furthermore, no control group with a negative history for GDM was available for comparison, but such methodology can be found in the literature concerning this issue [19]. There is a possibility that some confounding factors were not taken into consideration. The effect of unknown confoundings or reverse causation cannot be ruled out even in well designed and adequately analyzed studies. However, we were able to control for multiple potential confounders including age, education level, parity, family history of DM, BMI, OGTT result during pregnancy, time of GDM diagnosis, weight gain during pregnancy, maternal birth weight, and finally insulin use during pregnancy. Finally baseline data on the metabolic profile during pregnancy, as well as precise prepregnancy weight, were available in our study and these parameters did not differ between the analyzed subgroups thus allowing further objective comparison.

The strenghts of our study are that the subjects were enrolled during pregnancy, which enabled to collect all the relevant baseline data so that any information biases could be rather excluded. Secondly, initial metabolic profile could be then assessed and compared as the first blood sample was taken during the initial visit. The baseline metabolic profiles of the subjects seem to be comparable as the enrollment took place within a specified 4-week period between 26th and 30th gestational week. It is also worth mentioning that the study comprised the women with GDM diagnosed according to the current WHO diagnostic criteria, so it seems that the conclusions are rather universal and the results can be transmitted to all the countries where the new recommendations have been implemented. Additionally, the prospective design of the study gave us a certainty of obtaining detailed and accurate data. Moreover, every participant was informed before the follow-up visit on the conditions of the glucose challenge test to ensure that all the procedures will be standardized. Each OGTT was performed at one site and all the measurements were performed in the same laboratory, so there were no between-site or between-laboratory differences.

In conclusion, our data provide evidence that lactation may have favorable effects on insulin and glucose response after delivery among women with prior GDM who are at high future cardiometabolic risk. The effects seems to be more evident with longer lactation duration as well as higher lactation intensity. Therefore, our study supports a growing evidence on the health benefits of breastfeeding on maternal insulin and glucose metabolism later in life. As lifestyle modification is often difficult in real life settings, encouraging women to breastfeed may provide an important strategy for reducing the metabolic risk in the women with a history of GDM. It seems however, that further investigations, especially large scale, long-term and prospective are needed to clarify the mechanisms underlying this association.

Conflict of interest

The authors declare no conflict of interest.

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Rafał Maciulewski[1], Anna Zielińska-Maciulewska[1], Katarzyna Siewko[1], Gabryela Kozłowska[1], Danuta Lipińska[1], Anna J. Milewska[2], Maria Górska[1], Adam Krętowski[1], Małgorzata Szelachowska[1]

[1]Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Poland
[2]Department of Statistics and Medical Informatics, Medical University of Bialystok, Poland

Elevated levels of betatrophin in patients with newly diagnosed diabetes

ABSTRACT

Introduction. Betatrophin is primarily produced in the liver and regulates the metabolism of triglycerides. Its elevated concentration might be associated with an increased risk of type 2 diabetes. The aim of the study was to evaluate the impact of betatrophin on beta cell function and to compare the concentration of betatrophin in patients newly diagnosed with type 1 diabetes mellitus (T1DM including LADA), type 2 diabetes mellitus (T2DM) and a control group (CG) of healthy volunteers.

Patients and methods. The study included 210 patients with newly diagnosed diabetes (70 with T1DM, 140 with T2DM) and 70 CG. To evaluate the relationship between betatrophin and insulin secretion, a glucagon stimulation test was conducted.

Results. Serum betatrophin concentrations were significantly elevated in T1DM and T2DM in comparison to the control group (3.47 [Q_1 = 2.28, Q_3 = 4.54] in T1DM *vs.* 1.81 [Q_1 = 1.04, Q_3 = 2.67] ng/ml in CG, $p < 0.001$; 3.12 [Q_1 = 1.89, Q_3 = 4.48] in T2DM *vs.* 1.81 [Q_1 = 1.04, Q_3 = 2.67] ng/ml in CG, $p < 0.001$). No statistically significant differences in betatrophin concentration were observed between the T1DM and T2DM groups. Significant correlations were established between betatrophin, triglyceride (TG) and high-density lipoprotein (HDL) levels in all study participants, and C-peptide in the T1DM group.

Conclusions. Betatrophin concentration was significantly elevated in patients with newly diagnosed T1DM and T2DM, compared to the control group and could be a biomarker of diabetes. Our study provided evidence which supports the impact of betatrophin on lipid metabolism. The positive correlation between betatrophin and C-peptide in the T1DM group suggests that betatrophin is associated with insulin secretion in T1DM. (Clin Diabetol 2019; 8, 2: 110–115)

Key words: betatrophin, C-peptide, glucagon stimulation test, newly diagnosed diabetes

Introduction

Betatrophin is a protein encoded by the chromosome 19 open reading frame 80 (C19orf80) gene [1] and is produced primarily in the liver and adipose tissue. Despite the fact that it was discovered in 2004, its mechanism of action has not been fully elucidated. As our knowledge about betatrophin evolved, the protein was given various names including hepatocellular carcinoma-associated protein (TD26) [2], angiopoietin-like protein 8 (ANGPTL8) [3], refeeding-induced fat and liver protein (RIFL) [4], and lipasin [5]. However, the best documented and most widely known effect of betatrophin is on lipoprotein lipase (LPL). Together with ANGPTL3 and ANGPTL4, betatrophin is involved in the regulation of fasting and postprandial triglyceride (TG) levels by inhibiting LPL activity. These mechanisms also impact on the distribution of fatty acids to muscle or adipose tissue depending on the individual's nutritional intake and physical activity.

Address for correspondence:
Rafał Maciulewski, MD
Klinika Endokrynologii, Diabetologii i Chorób Wewnętrznych
Uniwersytet Medyczny w Białymstoku
ul. Marii Skłodowskiej-Curie 24A, 15–276 Białystok
Phone: +48 85 8318239
Fax: +48 85 7447611
e-mail: rav-m@wp.pl
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Since the liver and adipose tissue are the two key organs involved in insulin resistance, the role of betatrophin in insulin resistance and type 2 diabetes mellitus (T2DM) has been investigated by a number of researchers. In the majority of published studies in diabetic and obese patients, betatrophin concentrations have been demonstrated to be elevated [6–8]. Furthermore, Abu-Farha et al. showed betatrophin to be an independent predictor of T2DM development. The risk of developing the condition was six times higher in patients with betatrophin concentrations in the highest, third tertile after taking into account the effects of multiple confounders such as age, sex, nationality and lipid profile [7]. A subsequent study by the same research team found that betatrophin concentrations were not associated with C-peptide levels in patients with T2DM, whereas in non-diabetic individuals a positive relationship between betatrophin and C-peptide concentrations was established [9]. An association between betatrophin, insulin resistance and beta cell function has been observed in other diseases such as polycystic ovary syndrome [10].

One of the aims of the study when it was initially designed was to explore the crucial issue regarding the potential role played by betatrophin in insulin secretion. However, a publication supporting the hypothesis that betatrophin was responsible for beta cell proliferation in mice had been retracted [11] since subsequent studies produced contradictory results [12–15]. Both Yi et al. and Cox et al. established that betatrophin did not contribute to pancreatic beta cell proliferation in animals [11, 13, 14].

The primary aim of the study was to assess the concentration of betatrophin in patients with newly diagnosed diabetes in comparison to a control group (CG). The secondary objective was to determine the relationship between betatrophin concentration, residual beta cell secretory capacity and lipid concentration.

Materials and methods

In total, 280 subjects recruited from the Diabetology Department and the Diabetology Outpatient Clinic of the Medical University of Bialystok participated in the study — 210 with newly diagnosed diabetes and 70 controls. All participants were interviewed by a doctor and their medical history, smoking status, and alcohol and drug use were assessed. Patients with diabetes secondary to another condition (e.g. steroid use, Cushing's disease, acute and chronic pancreatitis), liver cirrhosis, advanced renal failure, cancer, advanced heart failure (NYHA III–IV) or acute inflammation (based on CRP indication) were excluded from this study. Written informed consent was obtained from all participants. The study design was approved by the Local Ethics Committee of the Medical University of Bialystok, Poland.

Diabetes was diagnosed in accordance with the 1999 WHO criteria [16]. Patients with diabetes were divided into two groups: those with type 1 diabetes mellitus (T1DM including patients with latent autoimmune diabetes of adults [LADA]; 70 patients) and those with type 2 diabetes mellitus (T2DM; 140 patients). In the patients with T1DM and T2DM with high blood glucose levels, fasting blood sampling and a glucagon stimulation test (GST) were performed after prior metabolic adjustment (glycemic control, and fluid and electrolyte management). In the patients with T2DM without severe hyperglycaemia (i.e. those who did not require hospitalisation), blood samples were collected and a GST conducted prior to hypoglycaemic treatment. The control group was recruited (through advertising in the local community) from healthy volunteers with no family history of T1DM or other autoimmune diseases. Each candidate for the control group underwent an OGTT and routine blood tests (CRP, creatinine, and transaminase). Only individuals with normal test results were included in the control group. Fasting blood samples were collected from all study participants to determine the concentrations of betatrophin, glucose, C-peptide, total cholesterol, LDL, HDL, TGs, free fatty acids, CRP, creatinine, percentage of HbA_{1c}, activity of AST and ALT as well as titration of anti-glutamic acid decarboxylase (anti-GAD), anti-tyrosine phosphatase (anti-IA2) and anti-insulin antibodies. Subsequently, a GST was performed in which 1 mg glucagon was administered intravenously and the concentration of C-peptide was measured at 0 and 6 minutes after glucagon administration. Selected anthropometric measurements including weight (using electronic weigh scales), height, waist and hip circumference, and waist to hip ratio (WHR) were obtained from all study participants. BMI was calculated according to the standard formula (body weight in kg/height in meters squared).

Betatrophin concentrations were measured using a commercially available ELISA kit (USCN Life Science Inc., Wuhan, China) with both an intra- and inter-assay coefficient of variation (CV) of $< 10\%$. The assessment of serum fatty acids was conducted using a calorimetric measure of non-Estrified fatty acids (NEFA) (Zenbio, Research Triangle Park, North Carolina, USA). Anti-islet antibodies (GADA, IA-2A, IAA) were evaluated using ELISA kits (Euroimmun AG, Lubeck, Germany). C-peptide levels were analysed using an enzyme-amplified sensitivity immunoassay performed on a microtiter plate (DiaSource Europe SA, Ottignies-Louvain-La-Neuve, Belgium). Glycated hemoglobin (HbA_{1c}) was assessed using high-performance liquid chromatography (HPLC;

BIO-RAD Laboratories, Munich, Germany). Plasma glucose concentration was measured using an enzymatic method with hexokinase (Cobas c111, Roche Diagnostic Ltd, Basel, Switzerland). Total cholesterol, high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and TG concentrations were assayed using an enzymatic-colorimetric method (Cobas c111, Roche Diagnostic Ltd, Basel, Switzerland).

As regards the GST, the area under the curve of the C-peptide level (AUC) was calculated using the formula:

AUC = (fasting C-peptide × C-peptide after glucagon) × 3.

Statistical analysis

Data were analysed using the STATISTICA software, v. 12.5 (Stata Soft, Tulsa, USA) and STATA 12.0 software. Statistical significance was determined at $p < 0.05$. The Shapiro–Wilk normality test was used to evaluate data distribution. The data are presented as median and first–third quartiles (Q_1–Q_3) due to a lack of normal distribution of the tested parameters. To compare differences between groups, the Kruskal-Wallis test with a post-hoc analysis and the Mann-Whitney test were used. Correlations between betatrophin concentrations and biochemical variables were established using Spearman's correlations coefficient. A multivariate linear regression analysis was performed to evaluate which factors were independently associated with the serum betatrophin level.

Results

Serum betatrophin concentration was highest in patients with T1DM, with the levels being significantly higher than those in the CG (3.47 [$Q_1 = 2.28$, $Q_3 = 4.54$] ng/ml *vs.* 1.81 [$Q_1 = 1.04$, $Q_3 = 2.67$] ng/ml, respectively; $p < 0.001$), but not those in the T2DM group (3.12 [$Q_1 = 1.89$, $Q_3 = 4.48$] ng/ml). Similarly, in patients with T2DM, the concentration of betatrophin was significantly higher compared to that of the CG (Fig. 1). Despite the fact that patients with T1DM and the controls did not differ in terms of age and BMI, those with T2DM were older and had a higher BMI than those in the CG (see Table 1). Following adjustment for sex, age and BMI, differences in betatrophin concentration between the groups were still statistically significant ($p < 0.001$). There were no statistically significant differences in the concentration of betatrophin in smokers compared to non-smokers in either study group.

Table 1 presents the clinical and biochemical characteristics of the three study groups. In the T1DM group, a significant positive correlation between betatrophin levels and C-peptide following the GST was observed (Δ C-peptide; Table 2). A statistically significant positive correlation between the concentration of betatrophin and fasting C-peptide at the beginning of the GST (C-peptide 0') and 6 min after stimulation (C-peptide 6'), as well as the AUC of C-peptide in the GST (AUC GST; Table 3) was observed in the CG.

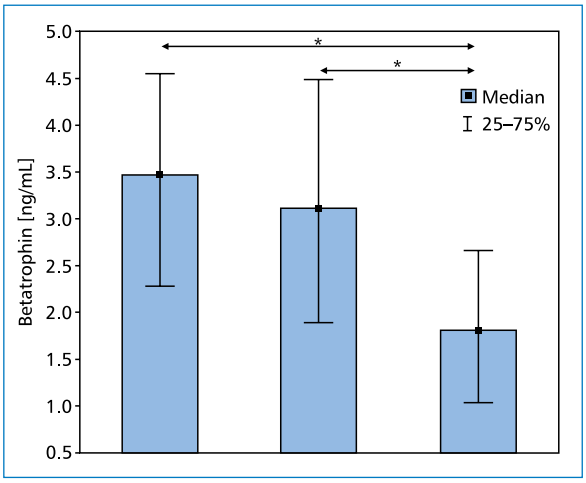

Figure 1. Significantly higher betatrophin concentrations were observed in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), compared to patients in the control group (CG). *$p < 0.001$ (*post hoc* analysis, Kruskal-Wallis test). T1DM: n = 70; T2DM: n = 140; CG: n = 70

In all subjects, a significant positive correlation between serum betatrophin and TG concentrations, as well as a significant negative correlation with HDL cholesterol, were observed (Table 4). In the T1DM group, a significant positive correlation between betatrophin and total cholesterol levels was observed (Table 2). In the T2DM group, the concentration of betatrophin was positively correlated with the concentration of LDL cholesterol (Table 5).

Using multivariate linear regression, independent predictors of betatrophin concentration in the T2DM group were demonstrated to include: fasting glucose ($\beta = -0.01$, $p < 0.001$), BMI ($\beta = -0.06$, $p = 0.04$) and total cholesterol ($\beta = 0.01$, $p = 0.016$); $R^2_A = 0.11$. In the T1DM group, multiple linear regression revealed that independent predictors of betatrophin concentration included C-peptide AUC ($\beta = 0.13$, $p = 0.029$), gender ($\beta = 0.86$, $p = 0.019$), and LDL-cholesterol ($\beta = 0.01$, $p = 0.039$); $R^2_A = 0.17$.

C-reactive protein was within the normal range in all the subjects since individuals with acute infections were excluded from the study. We found no statistically significant differences in total and LDL cholesterol between the groups, but we established significantly higher TG levels in T2D in comparison with T1D and CG. HDL cholesterol was significantly lower in T1D and T2D in comparison with CG.

Table 1. Characteristics of the study groups

	Type 1 diabetes	Type 2 diabetes	Control group	p value Kruskall-Wallis
N	70	140	70	
Age (years)	34.0 (26.0–43.0)[a]	54.0 (44.5–63.0)[c]	33.5 (27.0–50.0)	< 0.001
BMI [kg/m^2]	22.5 (20.8–25.8)[a]	29.8 (26.5–33.6)[c]	24.0 (22.0–27.9)	< 0.001
WHR	0.9 (0.8–0.9)[a]	1.0 (0.9–1.0)[c]	0.9 (0.8–0.9)	< 0.001
HbA_{1c} (%)	11.0 (9.4–12.9)[a, b]	8.0 (6.5–10.9)[c]	5.3 (5.0–5.4)	< 0.001
C-peptide 0′ [pmol/l]	0.3 (0.2–0.5)[a, b]	0.9 (0.6–1.3)[c]	0.5 (0.4–0.7)	< 0.001
C-peptide 6′[pmol/l]	0.5 (0.3–0.9)[a, b]	1.6 (1.2–2.3)	1.4 (1.0–1.8)	< 0.001
Δ C-peptide	0.2 (0.1–0.4)[a, b]	0.7 (0.4–1.0)	0.7 (0.5–1.1)	< 0.001
AUC C-peptide	0.5 (0.2–1.3)[a, b]	4.6 (2.3–9.3)[c]	2.1 (1.3–4.0)	< 0.001
Glucose 0′ [mg/dl]	146.5 (122.5–176.5)[b]	140.5 (115.5–163.5)[c]	88.0 (83.0–93.0)	< 0.001
Glucose 6′ [mg/dl]	164.0 (135.5–195.5)[b]	156.5 (131.5–179.0)[c]	106.0 (101.0–117.0)	< 0.001
Total cholesterol [mg/dl]	177.0 (154.0–208.0)	185.0 (161.0–223.0)	192.0 (170.0–222.0)	0.106
HDL cholesterol [mg/dl]	46.0 (36.0–60.0)[b]	44.0 (34.0–51.0)[c]	60.0 (51.0–74.0)	< 0.001
LDL cholesterol [mg/dl]	107.0 (83.1–131.1)	116.0 (88.0–148.0)	122.0 (91.6–140.0)	0.186
TG [mg/dl]	89.0 (66.0–145.0)[a]	148.0 (110.0–196.0)[c]	90.5 (61.0–117.0)	< 0.001
Free fatty acids [μM/ml]	1073.8 (849.3–1503.8)[b]	1174.4 (916.8–1565.9)[c]	893.7 (553.2–1070.2)	< 0.001
CRP [mg/dl]	0.9 (0.4–2.0)[a]	2.4 (1.0–5.6)[c]	0.6 (0.4–1.0)	< 0.001

Note: Values for median (first–third quartile) are presented. AUC — area under the curve; BMI — body mass index; CRP — C-reactive protein; HbA_{1c} — glycated hemoglobin; HDL — high-density lipoprotein; LDL — low-density lipoprotein; WHR — waist–hip ratio. Conversion factors to SI units are as follows: glucose, 0.05551; total cholesterol, 0.02586; LDL cholesterol, 0.02586; HDL cholesterol, 0.02586; triglycerides, 0.0114; Superscript letters indicate statistically significant ($p < 0.05$) differences between: [a]T1DM and T2DM; [b]T1DM and control group; [c]T2DM and control group

Table 2. Variables significantly correlated with betatrophin concentration in the T1DM group

	R	p value
Waist circumference	0.28	0.021
WHR	0.27	0.029
BMI	0.27	0.022
C-peptide 6′	0.24	0.049
Δ C-peptide	0.28	0.020
Total cholesterol	0.26	0.031

BMI — body mass index; WHR — waist–hip ratio

Table 3. Variables significantly correlated with betatrophin concentration in the control group

	R	p value
C-peptide 0′	0.39	< 0.001
C-peptide 6′	0.32	0.007
AUC C-peptide	0.37	0.002

AUC — area under the curve

Table 4. Variables significantly correlated with betatrophin concentration in the whole group

	R	p value
Age	0.12	0.040
Waist circumference	0.12	0.042
WHR	0.15	0.011
HbA_{1c}	0.24	< 0.001
Glucose 0′	0.19	0.001
Glucose 6′	0.17	0.004
HDL cholesterol	–0.17	0.006
TG	0.20	0.001

HbA_{1c} — glycated hemoglobin; HDL — high-density lipoprotein; TG — triglycerides; WHR — waist–hip ratio

Table 5. Variables significantly correlated with betatrophin concentration in the T2DM group

	R	p value
HbA_{1c}	–0.19	0.023
Glucose 0′	–0.23	0.005
Glucose 6′	–0.24	0.005
LDL cholesterol	0.20	0.019

HbA_{1c} — glycated hemoglobin; HDL — low-density lipoprotein

Discussion

To our knowledge, no comprehensive analysis of the concentration of betatrophin in patients with newly diagnosed T1DM and T2DM has been conducted to date. The majority of published papers on betatrophin are related to T2DM. No study evaluating the concentration of betatrophin in newly diagnosed T1DM is available in the literature and only one study

on the subject in newly diagnosed patients with T2DM has been published [14]. In our study, betatrophin concentration was demonstrated to be significantly higher in patients with newly diagnosed T1DM and T2DM compared to the CG.

Similar observations were made by Hu et al., who showed that patients with newly diagnosed T2DM had higher betatrophin concentrations in comparison with the control group [17]. Despite the fact that a number of studies have demonstrated betatrophin concentrations to be higher in patients with T2DM [6, 18–20], conflicting data exist on the subject [21]. A study conducted by Yamada and colleagues [22], for instance, which included 34 patients with T1DM and 30 patients with T2DM, demonstrated that betatrophin levels were significantly higher in diabetic patients compared to the control group (12 individuals). The authors also reported that the concentration of fasting C-peptide correlated significantly with betatrophin levels in patients with T1DM but not in those with T2DM, which was also confirmed by our results. Our study revealed positive correlations between C-peptide and betatrophin levels in T1DM and the CG but no such correlations were observed in the study participants with T2DM. A study conducted by Abu-Farha and colleagues, which included a larger group of patients with T2DM (556 subjects), did not establish a correlation between betatrophin levels and fasting C-peptide [7]. Interestingly, and in contrast to the findings presented above, Tokumoto and colleagues [23] observed a negative correlation between betatrophin and C-peptide concentration in the GST in patients with T2DM. Unlike the study by Tokumoto et al., we performed the test in patients with T1DM and in the CG. To the best of our knowledge, the present study is the first to use glucagon to assess beta cell reserve and compare it to betatrophin concentration in T1DM patients. We demonstrated a significant correlation between betatrophin and C-peptide 6′ and ΔC-peptide in those patients and observed similar correlations in the CG. The mechanism responsible for this effect has not yet been elucidated. The results of our research alone do not allow us to determine why the concentration of betatrophin is not associated with beta cell reserve in patients with T2DM, unlike in patients with T1DM and the CG. To date, no evidence concerning the impact of betatrophin on the number of pancreatic beta cells in patients with T1DM, T2DM or healthy individuals has been published. Therefore, studies utilising the GST assessing beta cell function in patients with T1DM are needed.

Another aspect of our research was the contribution of betatrophin to lipid metabolism. The results of a number of recent studies confirm that betatrophin, together with ANGPTL3 and ANGPTL4, is involved in the regulation of TG and HDL cholesterol levels by affecting lipoprotein lipase (LPL) [6, 24–26]. During fasting LPL activity is inhibited in white adipose tissue and increased in the myocardium and skeletal muscles to provide energy in the form of fatty acids. Following a meal, LPL activity in white adipose tissue increases, allowing fatty acids to be stored in adipocytes. By contrast, in muscles, under the influence of betatrophin and ANGPLT3, LPL activity is inhibited. ANGPTL4 is responsible for the inhibition of LPL activity in white adipose tissue during times of fasting and exercise. An increase in the amount of the above ANGPTLs (3, 4, 8) results in an increase in the concentration of TG in the serum while a reduction in any of these ANGPTLs decreases the levels of TG in the blood. Understandably, the distribution of fatty acids in the corresponding tissues is different, but each of these ANGPTLs is an inhibitor of LPL and therefore, the effect on the concentration of TG in the blood is the same [25]. The present study demonstrated a positive correlation between betatrophin and TG, and a negative correlation between betatrophin and HDL cholesterol, which may be evidence in support of the impact of betatrophin on lipid metabolism described above.

The situation is different in the case of patients with T1DM. In our study, this group was observed to have significantly higher concentrations of betatrophin in comparison with the CG, despite having similar levels of lipids. A potential explanation for this could be the effect of insulin deficiency in patients with T1DM. The results of a study conducted by Haridas and colleagues demonstrated that insulin reduced the concentration of circulating ANGPTL3 while increasing betatrophin expression in white adipose tissue, but not in the blood [27].

In conclusion, our study demonstrated betatrophin concentration to be significantly higher in patients with newly diagnosed T1DM and T2DM in comparison with the control group, which could potentially make it a biomarker of diabetes. Furthermore, it produced evidence supporting the impact of betatrophin on lipid metabolism. It also established that betatrophin concentration was associated with insulin secretion in T1DM, unlike in T2DM. Further research on the impact of betatrophin on insulin secretion in T1DM is needed.

Conflict of interest

The authors declare no competing interests.

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Debmalya Sanyal[1, 2], Sandip K Batabyal[3], Subrata Maity[3], Sudip Chatterjee[1, 3]
[1]Ramkrishna Mission SevaPrathisthan (RKMSP), India
[2]KPC Medical College, Kolkata, India
[3]Park Clinic, Kolkata, India

Changing profile of GAD and IA-2 antibody positivity in Indian children with recently diagnosed type 1 diabetes mellitus

ABSTRACT

Introduction. Published literature on type 1 diabetes (T1DM) patients from India suggests that a substantial number of them are negative to GAD 65 and IA-2 antibodies. Antibody positivity rates have been linked to dietary and socio-economic factors and more recently, to changes in the enterobiome. Our anecdotal evidence indicated that antibody positivity rates among newly diagnosed T1DM children were rising. In this presentation we have formally collated our data on these antibodies, a first, we believe, in the Indian pediatric population.

Material and methods. T1DM was diagnosed by standard clinical criteria advocated by American Diabetes Association including in all patients, the presence of diabetic ketoacidosis (DKA). We used plasma blood glucose rather than A1C to diagnose the acute onset of type 1 diabetes in individuals with symptoms of hyperglycemia. All patients with this diagnosis had GAD (glutamic acid decarboxylase) and IA-2 (insulinoma antigen 2) antibodies measured as a routine procedure from 2007. Data on patients between the ages of 1 and 16 years as on 31st August 2016 were collected for this study. The antibodies were measured by standard RIA kits from the same manufacturer and performed in the endocrinology laboratory of one of the institutions.

Results. We included 694 T1DM cases from 2007 till 2016, out of which 296 were antibody positive. A total of 172 were GAD antibody positive, 62 were IA-2 antibody positive and 90 exhibited dual antibody positivity (GAD positive + IA-2 positive). The chi-square test for trend analysis showed a significant rising trend for IA-2 antibody alone positive ($p < 0.001$, chi-square for trend = 17.437, df = 1) and either antibody positive percentages ($p < 0.001$, chi-square for trend = 22.71, df = 1), but not in the GAD antibody positivity ($p = 0.059$, chi-square for trend = 3.567, df = 1) and in dual antibody positive percentages ($p = 0.486$, chi-square for trend = 0.485, df = 1) over a period of 9 years i.e. from 2007 to 2016.

Conclusion. Antibody positivity rates in recently diagnosed T1DM children have changed fairly rapidly over the last nine years. This surge in autoimmunity may also be a significant contributing factor towards the recent increased incidence of T1DM in India. (Clin Diabetol 2019; 8, 2: 116–120)

Key words: type 1 diabetes mellitus, autoantibody, children, India

Introduction

Type 1 diabetes mellitus (T1DM) is a disease caused by an autoimmune destruction of β-cells, and is clinically manifest when almost 90% of pancreatic islet β-cells are destroyed [1, 2]. It is a T-cell — mediated disease caused predominantly by CD4 positive cells. Islet cell antibodies (ICA), glutamic acid-decarboxylase (GAD65) antibodies, and insulin auto antibodies (IAA) are positive at diagnosis in over 85 % of Western T1DM patients [3–7]. The incidence of T1DM is growing at a rate of 3–5% every year [8, 9]. Of the world wide estimate of 490,000 children with T1DM, 24% are in the European

Address for correspondence:
Debmalya Sanyal
36 Block H New Alipore Kolkata
West Bengal, India, Zip code: 700053
Mobile: 0091-9830118388
e-mail: drdebmalyasanyal@gmail.com,
dr_debmalya@hotmail.com
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region and 23% in the South East Asian region [10]. There are an estimated prevalence of 97,700 children with T1DM in India with an annual incidence of 3 new patients with T1DM per 100,000 children over a period of 13 years from 1995 to 2008 in the age group 0–16 years. Patients from India account for most of the pediatric prevalence of T1DM in South East Asia [11]. It has been hypothesized that environmental and microbial factors play a role in the rising incidence of T1DM [12]. Alterations in the composition of the enterobiome have been experimentally linked with the development of T1DM. In Non-Obese Diabetic (NOD) mice, a standard model of T1DM, the males have a lower incidence of T1DM than females. If the enterobiome of the male is altered to the female pattern, the incidence of T1DM rises to the female rate [13–16].

Historically, more than 40% of T1DM patients in India were antibody negative [17]. There are no significant studies from India tracing the change in auto-antibody positivity in recently diagnosed T1DM. We wanted to determine whether the antibody positivity of newly diagnosed T1DM children patients have changed since 2007, i.e. since the time we have been performing antibody measurements.

Materials and methods

The current study was a retrospective study, performed in two secondary referral endocrine clinics. The protocol was presented to the Ethics Committees of the two centers who felt that given the retrospective chart review nature of the study, informed consent is not neccesary We used plasma blood glucose rather than A1C to diagnose the acute onset of type 1 diabetes in individuals with symptoms of hyperglycemia. Patients with DKA and typical clinical features of T1DM as per the American Diabetes Association (ADA) position statement of 2017 and aged 1–16 years were included in the study [18]. In this retrospective chart review, we have only included patients with a confirmed diagnosis of type 1 diabetes, diagnosed by standard clinical criteria advocated by American Diabetes Association. All our patients had confirmed diagnosis of diabetic ketoacidosis (DKA) along with ketonuria. This finding strengthened the clinical diagnosis of T1DM in our patients and ensured that young type 2 diabetes patients were excluded.

Patients with pancreatitis, any feature suggestive of type 2 diabetes (T2DM), and diabetes from secondary causes were excluded from the study. Neonatal diabetes was excluded by age as the lower age limit for inclusion in the study is one year. Patient records meeting the eligibility criteria were evaluated from January 2007 to 31st August 2016. Blood samples were collected for estimation of glucose, C-peptide, GAD and IA-2 autoantibody in all patients. Venous blood sampling was done once the acute metabolic crisis was over and before oral feeding was allowed, in one center and after discharge in the other center. Lipemic or grossly haemolysed samples were discarded and the test repeated. The kits used came from the same manufacturer all through and the tests were done in one center. Antibodies to glutamic acid decarboxylase (GAD) and insulinoma antigen-2 were measured in all newly diagnosed T1DM patients' (n = 692). Serum C-peptide values were required to be below the reference range. The samples were centrifuged at 2000 r.p.m. (at room temperature) for 15 min to separate the plasma. Plasma was decomplemented by heating at 56°C for 30 min and stored in aliquots at –20° C with 0.1% sodium azide as preservative. Serum GAD-Ab and IA-2 Ab titers were measured by I^{125} RIA technique (DLD DIAGNOSTIKA, GmBH, GERMANY) and C-peptide was estimated by RIA (IMMUNOTECH, FRANCE) [19]. For GAD and IA-2 antibody a titer $\leq$ 1.0 U/ml was considered normal while for C-peptide a fasting value $\geq$ 1.1 ng/ml was considered normal. Precision within the assay series was evaluated by processing 10 serum replicates. For GAD-Ab, IA-2Ab and C-peptide the results were mean 5.1 ± 0.96 U/ml (%CV 3.9), mean 3.6 ± 0.85 U/ml (%CV 2.7) and mean 1.05 ± 0.14 ng/ml (% CV 0.8) respectively. The assay sensitivities for GAD-Ab, IA-2Ab and C-peptide were 0.21 U/ml, 0.19 U/ml and 0.036 ng/ml respectively, as obtained from kit literature. It may be noted that the ADA does not advise measurement of C-peptide, thyroid function tests or screening for celiac disease during the initial metabolic crisis [20, 21]. This is because C-peptide values can be excessively depressed at this time, while thyroid function tests can be vitiated due to sick euthyroid syndrome and celiac screening affected by the lack of usual oral intake of gluten.

Statistical methods

Descriptive statistical analysis were carried out with SAS (Statistical Analysis System) version 9.2 for windows, SAS Institute Inc. Cary, NC, USA and Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for windows, SPSS, Inc., Chicago, IL, USA, with Microsoft Word and Excel being used to generate graphs and tables. Results on categorical measurements are presented in Number (%). Significance is assessed at a level of 5%.

Results

Auto-antibody positivity to β-cell antigens over a period of ten years i.e. from 2007 to 2016 is shown in Table 1. We included 694 T1DM cases from 2007

Table 1. Pattern of number of autoantibodies to β-cell antigen in the study sample

Year	Total number of cases N = 694	GAD antibody positive N = 172	IA-2 antibody positive N = 62	Both antibodies positive N = 90	Both antibodies negative N = 371	Total positive cases N = 296
2007	29	6 (20.67)	1 (3.45)	4 (13.79)	18 (62.07)	11 (37.93)
2008	54	10 (18.52)	0	7 (12.96)	37 (68.52)	17 (31.48)
2009	70	12 (17.14)	4 (5.7)	7 (10)	47 (67.14)	23 (32.86)
2010	91	17 (18.68)	1 (1.09)	15 (16.48)	58 (63.74)	33 (36.26)
2011	97	38 (39.18)	2 (20.62)	11 (11.34)	46 (47042)	51 (52.57)
2012	64	14 (21.87)	9 (14.06)	6 (9.38)	35 (54.69)	29 (45.31)
2013–2014	203	53 (26.11)	31 (15.27)	19 (9.36)	101 (49.75)	102 (50.25)
2015–2016	86	22 (25.58)	14 (16.28)	21 (24.42)	29 (33.72)	57 (66.28)

GAD — glutamic acid decarboxylase; IA-2 — insulinoma antigen 2. Numbers in brackets denotes percentage

till 2016, out of which 296 were antibody positive. A total of 172 were GAD antibody positive, 62 were IA-2 antibody positive and 90 exhibited dual antibody positivity. The chi-square test for trend analysis showed a significant rising trend for IA-2 antibody alone positive ($p < 0.001$, chi-square for trend = 17.437, df = 1) and either antibody positive percentages ($p < 0.001$, chi-square for trend = 22.71, df = 1), but not in dual antibody positive percentages ($p = 0.486$, chi-square for trend = 0.485, df = 1) and in GAD antibody positivity ($p = 0.059$, chi-square for trend = 3.567, df = 1), though the p value for GAD antibody positivity fell in the range of suggestive significance.

Discussion

For reasons unknown, low rates of antibody positivity are found in T1DM patients in Asia in comparison to their Western counterparts [4]. Prevalence of 26 to 61% of antibody positivity in T1DM patients has been reported from North India [3, 5]. Tandon et al. have reported a 26% prevalence of GAD and/or IA-2Ab in T1DM patient with disease duration greater than 5 years in north India. They found a 14% GAD positivity and 15% IA-2Ab positivity [4]. Some other studies [4] have reported higher rates of antibody positivity. Overall, variable antibody positivity rates have been reported from India, but were substantially lower than the 85–95% GAD positivity reported in Western populations [15–17].

Our study traced the autoantibody positivity of recently diagnosed T1DM patients over ten years in an East Indian pediatric population and found a secular trend of increased prevalence of antibody positivity (Table 1). Similar results were demonstrated by Ahmed et al. in 2008 where the authors found a prevalence of 47% of auto antibodies in their T1DM population. GAD65 antibody was positive in 41.2% and IA-2 in 20.6%. A total of 14.7% TIDM subjects showed both GAD65 plus IA-2 autoantibody positivity [19].

There is a rising incidence of T1DM worldwide, and global estimates show significant increases of 4.0% in Asia, 3.2% in Europe and 5.3% in North America. The average annual increase in incidence of T1DM was 2.4% (95% CI 1.3–3.4%) during 1990–1994, and a higher increase of 3.4% (95% CI 2.7–4.3%) was recorded in the period 1995–1999. There is a suggestion in the Indian literature that the incidence of T1DM has been raising in the recent years [22]. Around 78,000 children under 15 years of age are estimated to develop T1DM annually worldwide. An estimated 18,000 children under the age of 15 were newly diagnosed with T1DM in 2011 in India [23]. In south India, the Karnataka Type 1 Diabetes Registry reported an incidence of 3.7/100,000 in boys' and 4.0/100,000 in girls, over 13 years of data collection [23]. Recently Kalra et al. reported a high prevalence (10.20/100,000 population) of T1DM in Karnal district in north India [24].

Wilkins had postulated an accelerator hypothesis where he linked weight gain with autoimmunity in T1DM in developed countries [25]. India being a fast developing country, has witnessed a rise in childhood obesity. Recently Jagadesan et al. had estimated 21.4% prevalence of childhood obesity among private school students in southern India [26]. Patterson and associates had further found a directly proportional relationship between national prosperity and childhood onset T1DM, which fits the data from India [27]. The hygiene hypothesis proposed by Gale and McKinney et al. which goes hand in hand with Patterson's hypothesis could also be one of the reasons for increases autoimmunity in our study sample [28, 29]. This recent surge in autoimmunity of T1DM could be triggered by a change in the enterobiome of the population. A decade ago, in an Indian study of newly diagnosed T1DM,

Balasubramanium and colleagues demonstrated mono GAD antibody positivity of 42% and IA-2 positivity of 33%. Considering the absence of GAD and IA-2 Ab's in around 45% of the recently diagnosed Indian T1DM subjects, Bhatia postulated idiopathic (type 1B) patients to be substantially more frequent in the Indian population as compared to the Caucasian [30].

Conclusion

Our study traces the autoantibody positivity of recently diagnosed T1DM children over past ten years in an East Indian population and found a significant increase of autoantibody positivity over time. As this was an observational retrospective study, we could not assign any definite cause to this increase in autoimmunity. This surge in autoimmunity may be a significant contributing factor towards the recent reported increased incidence of TIDM in India.

Limitations

We have not included ZnT8 in our analysis since it is recently added in the panel of auto-antibodies for screening of T1DM from 2012 onwards. Since, we have included T1DM patients diagnosed from the year 2007; we wanted to maintain uniformity of the tested antibody in the study. Hence the antibody ZnT8 was not tested.

Conflict of interest

The authors declare no conflicts of interest in relation to this article.

Author contributions

D.S and S.C. was involved in designing the study, data collection, data entry and writing of manuscript. S.M. and S.B. were involved in data collection and biochemical and pathological investigations. All authors reviewed the manuscript.

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Oskar Kublin, Mariusz Stępień
Unit of Military Internal Medicine, Department of Nephrology and Hypertension, Military Medical Faculty, Medical University of Łodz, Poland

Measurement of glucose concentration in interstitial fluid — an alternative or a supplement to conventional blood glucose monitoring?

ABSTRACT

The paper describes currently available interstitial glucose monitoring systems and discusses their advantages and disadvantages in comparison with conventional blood glucose measurements using glucose meters. Furthermore, it describes clinical trials assessing these systems in terms of their usefulness, safety and influence on therapeutic management in diabetes. (Clin Diabetol 2019; 8, 2: 121–126)

Key words: interstitial glucose levels, diabetes, self-monitoring of glycemia, CGM, FGM

Introduction

Glucose monitoring is an integral part of an effective diabetes treatment. It has been proven that patients who perform regular glucose level measurements achieve better metabolic control of diabetes [1]. The Diabetes Poland recommends adjusting the number of blood glucose measurements during the day to specific groups of patients with diabetes [2]. In the light of these recommendations, those who are treated with diet only can measure blood glucose least often. In this group of patients it is recommended to perform a 4-point blood glucose profile once a month (fasting and 2 hours after the main meals) and weekly blood glucose measurements at different times of the day. Patients on oral antidiabetic agents and/or GLP analogs should perform a 4-point blood glucose profile once a week and daily blood glucose measurements at different times of a day. Patients on insulin therapy are advised to measure blood glucose more often. Patients treated with fixed doses of insulin should perform 1–2 blood glucose measurements daily, and additionally 4-point blood glucose profile once a week and 7-point blood glucose profile once a month. The most frequent measurements are recommended for patients treated with multiple insulin injections. These patients should measure blood glucose at least 4 times daily. It is recommended that these patients should measure blood glucose both before and after meals and additionally at bedtime, before physical activity, when suspecting hypoglycemia, and also when performing activities during which hypoglycemia may be particularly dangerous. In addition, all patients, regardless of the treatment used, should monitor blood glucose levels more frequently in case of feeling unwell or sudden deterioration of their health status.

Regular self-monitoring of blood glucose (SMBG) should help in achieving good glycemic control. A general glycated hemoglobin (HbA_{1c}) target for diabetic patients is ≤ 7%, which translates into an average

Address for correspondence:
lek. Oskar Kublin
Zakład Interny Wojskowej, Katedra Nefrologii i Nadciśnienia Tętniczego
USK im. WAM — Centralny Szpital Weteranów
Uniwersytet Medyczny w Łodzi
ul. Żeromskiego 113, 90–549 Łódź
Phone: 694 502 829
e-mail: oskar.kublin@gmail.com
Translation: lek. Małgorzata Kamińska
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plasma glucose level of 154 mg/dL [3]. In patients with type 1 diabetes, the individualized HbA_{1c} target of ≤ 6.5% is recommended, if this can be achieved without significant decrease in life quality and increased risk of hypoglycemia. Fasting and preprandial glucose levels should be within the range of 80–110 mg/dL, and 2-hour postprandial blood glucose should not exceed 140 mg/dL. The glycated hemoglobin target of ≤ 6.5% is also recommended in patients with type 2 diabetes of short duration, in children and adolescents, regardless of the type of diabetes, and in women with pregestational diabetes who are planning to become pregnant. However, in the second and third trimester of pregnancy more stringent metabolic control is indicated and HbA_{1c} should be targeted at < 6%, providing that this does not lead to frequent hypoglycemic episodes. In elderly patients with macroangiopathic complications and multiple comorbidities HbA_{1c} levels higher than 7.0% but not exceeding 8.0% are acceptable [4].

Blood glucose monitoring

It is recommended that diabetic patients perform SMBG using personal glucose meters. They should be taught how to use glucose meter and interpret SMBG data. The current European standard (EN ISO 15197:2015) includes requirements for blood glucose meters and outlines the following acceptable minimum accuracy criteria: 95% of the results must be within ± 15 mg/dL for blood glucose values < 100 mg/dL or less than 15% for blood glucose values ≥ 100 mg/dL [5]. Currently available blood glucose monitoring devices use the electrochemical or spectrophotometric method. More frequently used is the electrochemical method that involves the measurement of electrons released during the reaction between glucose in a blood sample and the reagent contained in the test strip. The spectrophotometric method consists in measuring the amount of a colored product of the enzymatic reaction of glucose with the appropriate reagents. This method is associated with a larger measurement error resulting from possible contamination of the sample.

Nowadays, there are many types of glucometers available on the market. They differ in weight, size of the device, size of the screen, memory (data storage), the possibility of removing a test strip after measurement without touching it, measurement time, volume of blood sample and the range of blood glucose values evaluated. Some glucose meters, in addition to the measurement of glycemia, allow the determination of ketone and cholesterol in the blood. Newer devices also have the ability to connect to a computer or smartphone and send measurement results wirelessly.

Measurements of interstitial glucose

Continuous glucose monitoring (CGM) and flash glucose monitoring (FGM) systems are becoming more and more popular. They enable glucose measurements to be made with an electrode immersed in interstitial fluid. This may cause a slight delay in relation to the conventional method of glucose measurement, because the concentration of glucose first changes in the blood, and subsequently in the interstitial fluid. This should be taken into account during rapid blood glucose fluctuations and additional verification of the results obtained using the conventional method of measuring blood glucose should be made. Table 1 presents key differences between the two methods of blood glucose monitoring.

Currently, the most popular CGM systems in Poland are Medtronic Enlite, Dexcom G4 Platinum from Willcare and the recently available Eversense system from Roche. There is also an FGM system — Libre from Abbott. CGM systems measure interstitial glucose every 5 minutes. In the Libre system, the measurement is made while the reader is placed over the sensor, which results in the inability to trigger alarms in the event of hypo- or hyperglycemia. On the other hand, it should be noted

Table 1. Comparison of two methods of glucose monitoring

Feature compared	Conventional blood glucose monitoring	Interstitial glucose monitoring
Costs	Low	High
Availability	Available at every pharmacy	Not readily available — few pharmacies, online orders
Pain associated with measurement	During finger pricking	Painless or minimal pain during implantation
Traumatization	Fingertip injury	Possible allergic reaction in the sensor application site
Number of available devices	Many types	Several types
Measurement result	Individual glycemic values	Individual values with trends

that the Libre system has precalibrated sensors, while the other CGM systems require additional calibration.

Characteristics of currently available systems for measuring interstitial glucose

Enlite

This system uses a glucose sensor that can be worn for up to 6 days. It works in conjunction with the Guardian 2 Link transmitter, which has a range of less than 2 meters. The user can connect the device wirelessly with Medtronic pumps to take full advantage of their functions. Medtronic Veo pump automatically suspends insulin delivery when glucose level is low. Another insulin pump from Medtronic, MiniMed 640G, thanks to the SmartGuard function, can predict hypoglycemia and suspend insulin infusion until blood glucose normalization. It is worth noting that patients treated with multiple insulin injections also can use the Enlite sensors with Guardian Real-Time — a stand-alone CGM system [6, 7].

Dexcom G4 Platinum

The system consists of a sensor, a transmitter and a receiver. It differs from the Enlite device by a much larger range — the maximum distance between the transmitter and the receiver is 6–7 meters. The sensor remains on the skin for 7 days. This system can be used both by patients treated with personal insulin pumps and those on multiple insulin injections [8].

Eversense

This is a new CGM system, available in Poland since October 2017. It consists of a sensor, a transmitter and an Eversense CGM application. The sensor (size: 3.5 mm × × 18.3 mm) is implanted subcutaneously, and the transmitter that connects wirelessly to the smartphone is fixed to the skin with an adhesive right above the sensor. Two types of sensors differing in terms of time of use have been designed: a 90-day sensor and a 180-day sensor. However, currently only 180-day sensors are available on the market. After this time, the sensor should be removed [9].

Libre

This is the only flash system. The result is obtained when the sensor is scanned. The system differs from previously described systems by the lack of alarms and the fact that it is precalibrated. The system consists of a reader and a 14-day sensor attached to the skin with an adhesive. The site recommended by the manufacturer for placing the sensor is the back of the arm. Additionally, Libre reader can be used to measure glucose and ketone bodies in the blood. During the congress of the European Association for the Study on Diabetes, which was held in Berlin in October 2018, Abbott presented a new version of the device — the FreeStyle Libre 2 system. It enables wireless Bluetooth communication between the sensor and the reader, so that it will be possible to receive notifications when the glucose value is outside the normal range [10]. It is worth noting that FreeStyle Libre, which is not designed as a CGM system, can also be used as such system with a special supplementary device. Currently, there are two available devices: MiaoMiao and Blucon from Ambrosia. These small transmitters read the FreeStyle Libre sensor and pass data to smartphone via Bluetooth every 5 minutes [11, 12]. However, it should be borne in mind that these devices have not been evaluated in clinical trials.

Table 2 present basic parameters of interstitial glucose monitoring systems and differences between these systems.

Table 2. Characteristics of currently available interstitial glucose monitoring system

Feature compared	Enlite Medtronic	Dexcom G4 Platinum	FreeStyle Libre	Eversense
Time of use	6 days	7 days	14 days	90 or 180 days
Insertion site	Skin — abdomen, alternatively upper buttocks	Adults: skin — abdomen Children: skin — abdomen or upper buttocks	Skin — back of the arm	Subcutaneously — back of the arm
Users approved	Adults and children	From 2 years of age	From 4 years of age	From 18 years of age
Calibration	Yes	Yes	No	Yes
Alarms	Yes	Yes	No	Yes
Connection between a sensor and a reader	Wireless, radio waves, range: 1.8 meters	Wireless, range: 6 meters	Wireless, NFC, a few centimeters	Wireless, the reader should be placed right above the implantation site
MARD	9.1%	Adults 9% Children 10%	9.4%	8.5%

MARD — mean absolute relative difference

Among the above-described CGM systems, only Medtronic and Willcare devices are subject to reimbursement by the National Health Fund. However, they are available only to a small group of patients. The reimbursement is limited to type 1 diabetes patients under 26 years of age with impaired hypoglycemia awareness, who are treated with insulin pumps. Patients are entitled to purchase 12 Enlite sensors or 9 Dexcom sensors once every 3 months and 1 transmitter every 8 months after paying 30% of the device retail price [13].

CGM systems and conventional blood glucose measurements

The first difference noticed by patients during the use of CGM systems is the fact that they do not need to perform multiple punctures of the fingertips in order to measure blood glucose, which increases the patient's comfort. This is evidenced by the results of a multicenter randomized study. The study showed an increase in treatment satisfaction among patients using the FreeStyle Libre system, which, however, did not translate into an improvement of the quality of life [14].

The usefulness of continuous glucose monitoring systems in the treatment of diabetes was confirmed in the GOLD study [15]. It was a randomized clinical trial lasting 26 weeks. The study included a group of 161 patients with type 1 diabetes treated with multiple insulin injections. There was a greater reduction in HbA_{1c} in patients using CGM (Dexcom G4 Platinum) compared with the conventional method. Additionally, the use of CGM system was associated with a shorter time spent in hypoglycemia and a lower number of severe hypoglycemic episodes compared with conventional glycemic monitoring.

Similar conclusions were reached by the authors of the systematic review and meta-analysis of 14 studies including a total of 1,268 patients with type 1 diabetes [16]. Included in the analysis were trials lasting at least 12 weeks, in which CGM systems were compared with the conventional method of glucose measurement using glucose meters. Reduction in HbA_{1c} by 0.25% in children and adolescents and 0.33% in adults using CGM systems has been demonstrated. In addition, in the group of CGM system users, significantly more patients achieved target HbA_{1c} values and a smaller number of hypoglycemic episodes were observed.

The analysis of data of 17,731 patients with type 1 diabetes showed better metabolic control among patients using CGM systems as compared with conventional glycemic measurements [17]. In the analyzed group, 35% of patients used multiple insulin injections, 50% used insulin pumps, 13% — personal insulin pumps paired with the CGM system, and 2% — multiple insulin injections together with the CGM system. Regardless of the type of insulin therapy, patients using the CGM system achieved better metabolic control of diabetes. In subjects using insulin pumps paired with the CGM system, HbA_{1c} was 7.7%, whereas in users of the CGM system treated with multiple insulin injections HbA_{1c} was 7.6%. It is worth noting that among patients who did not use the CGM system, those treated with personal insulin pumps had HbA_{1c} value of 8.3%, whereas in patients treated with multiple insulin injections, the HbA_{1c} value was 8.8%.

In the COMISAIR study, lasting 12 months and including 65 patients with type 1 diabetes, a greater reduction in HbA_{1c} was observed in the group using the CGM system compared with the group using conventional methods of blood glucose measurement [18]. Improvement in metabolic control in the group using the CGM system was greater both in patients treated with multiple injections of insulin and in those using personal insulin pumps.

Another study evaluated the usefulness of CGM systems (Dexcom G4 Platinum) in patients aged 65 years or older [19]. The 6-month study included 296 patients with diabetes. The control group consisted of patients using the conventional method of blood glucose measurements. It has been shown that CGM use was associated with a reduction in hypoglycemic episodes, frequency of visits related to hypoglycemia, and severe hypoglycemia (requiring the assistance of another person). Furthermore, patients using CGM systems declared less fear of hypoglycemia and less diabetes-related distress.

Similar results were obtained in the IN CONTROL study, which was conducted among patients with impaired awareness of hypoglycemia, treated with personal insulin pumps connected to the CGM system (Medtronic MiniMed Paradigm® Veo™ system) [20]. There was a 2-fold reduction in the time spent in hypoglycemia and a 3-fold reduction in the number of hypoglycemic episodes in the CGM group compared with those using the conventional method of SMBG.

In a randomized clinical trial conducted on a group of 129 patients with good glycemic control, i.e. with HbA_{1c} values < 7.0%, the use of the CGM system was found to reduce the time spent in hypoglycemia compared to the conventional method [21]. In the group using the CGM system, the mean time in glycemia ≤ 70 mg/dL was 54 minutes/day, while in the group using the conventional method it was longer and amounted to 91 minutes/day. The time spent in glycemia ≤ 60 mg/dL in the CGM group was almost two time shorter than in the conventional SMBG group (18 minutes/day *vs*. 35 minutes/day).

When CGM was paired with an insulin pump with a predictive suspend feature (Medtronic MiniMed 640), the hypoglycemic episodes were of shorter duration and less troublesome for patients compared with the group using CGM with a pump without this option. The duration of hyperglycemia was also reduced [22].

The authors of the GLADIS study [31] point out that the use of CGM system is associated with longer time spent in blood glucose range of 70–180 mg/dL. It was a 100-day, randomized, controlled study in which 160 patients with type 1 or type 2 diabetes participated. The subjects were divided into 3 groups: patients using the CGM system with alarms, patients using the CGM system without alarms and patients using the conventional method of blood glucose monitoring. Time spend outside the normal blood glucose range was 9.7 h/day in the group using the CGM system with alarms, 9.9 h/day in the group using the CGM system without alarms and 10.6 h/day in the group not using the CGM system.

Future perspectives

Continuous development of CGM systems leads to the increased accuracy of measurements, which is expressed by the mean absolute relative difference (MARD). The smaller the value of this parameter, the greater the reliability of the results. Of the systems described, Eversense from Roche is a clear leader. According to the manufacturer of this system, the MARD value is 8.5% [24]. The PRECISE II study showed that the MARD value when using a 90-day sensor was 8.8% [25]. In the PRECISE I study, which assessed a 180-day sensor, the MARD value was 11.1% [26]. The MARD value of another CGM system, Dexcom G4 Platinum with the new 505 software, is 9% in adults and 10% in children [27, 28]. It is worth noting that in previous studies this value was shown at 13%. Medtronic declares that the MARD value for MiniMed systems is 9.1% [29], whereas the MARD value for FreeStyle Libre system, according to Abbott, is 9.4% [10].

Which of the CGM systems is the best?

Most of the trials performed to date compared CGM systems with conventional blood glucose measurements. However, there are only few trials comparing specific CGM systems. The I HART study (performed in August 2018) compared the FreeStyle Libre system with the Dexcom system [30]. After 2 weeks of using blinded CGM, participants were randomly assigned to flash (Libre) or real-time continuous glucose monitoring (RT-CGM) (Dexcom) for 8 weeks. Then, all participants were offered to continue the study with RT-CGM. In the group switched from flash to RT-CGM, the percentage time in hypoglycemia decreased from 5% to 0.8% and the percentage time in normoglycemia increased from 60% to 67.4%.

In a study comparing three CGM systems: Dexcom G4 Platinum, Enlite and FreeStyle Navigator (not available on the Polish market), it was found that the Dexcom system is the most accurate [31]. However, one should bear in mind that this study was performed in 2014, and currently used devices allow for obtaining better results.

Summary

The continuous development of technologies enabling monitoring glucose levels in blood and interstitial fluid has a positive effect on both metabolic control and the quality of life of patients with diabetes. Numerous clinical trials have demonstrated the beneficial effect of CGM systems on the reduction of glycated hemoglobin, longer time in normoglycemia, and decrease in the duration and the number of hypoglycemic episodes. Newer versions of glucose monitoring systems are characterized by greater accuracy of measurements. More advanced systems for monitoring glucose levels in interstitial fluid are emerging on the market. They are becoming more and more popular because they offer convenient and less invasive measurements. A greater selection of devices can be found among CGM than FGM systems, but the advantage of the latter is a significantly lower cost of use. Currently Eversense is the most accurate CGM system. Besides accuracy of measurements, an additional advantage of this device is that the sensor is implanted subcutaneously, which prevents its accidental removal. The implantation and removal procedure, however, requires the incision of the skin. The advantage of Medtronic CGM systems is compatibility with Medtronic insulin pumps.

It is worth noting that the choice of a specific device should be made according to patient's individual needs, bearing in mind the type of insulin therapy used, obligatory calibration, the way the sensor is implanted, and the financial capability of the patient. The introduction of interstitial glucose monitoring systems in patients with diabetes gives hope for more effective control of this disease, but at the moment we cannot conclude that the interstitial glucose monitoring is an alternative to conventional methods of measuring blood glucose. However, it seems that it can be a valuable supplement to it.

Conflict of interest

None declared.

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REVIEW ARTICLE
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Lidia Witek[1], Irina Kowalska[2], Agnieszka Adamska[3]
[1]Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok Clinical Hospital, Poland
[2]Department of Internal Medicine and Metabolic Diseases, Medical University of Bialystok, Poland
[3]Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Poland

The association between depression and diabetes — the role of the hypothalamo--pituitary-adrenal axis and chronic inflammation

ABSTRACT

Depression and diabetes belong to the most common diseases in the human population. Mood disorders are often diagnosed in patients with chronic diseases, including type 1 and type 2 diabetes. Patients suffering from both diseases have been observed to have poorer blood glucose control, an increased risk of complications and mortality compared to the group with diabetes alone. The association between diabetes and depression is complex. Their frequent co-occurrence may be influenced by psychological factors, hormonal and immunological disorders. In depression, hypothalamo-pituitary-adrenal axis dysregulation is observed, which causes peripheral hypercortisolemia. The excess of cortisol leads to hepatic glycogenolysis and reduction in insulin sensitivity of peripheral tissues. It has been proven that depression is accompanied by chronic subclinical inflammation. In this review we present the data regarding the relation between hypercortisolemia, subclinical inflammation and depression in patients with type 1 and type 2 diabetes. (Clin Diabetol 2019; 8, 2: 127–131)

Key words: depression, diabetes, hypercortisolemia, inflammation

Address for correspondence:
lek. Lidia Witek
Klinika Endokrynologii, Diabetologii i Chorób Wewnętrznych
Uniwersytecki Szpital Kliniczny
ul. Marii Skłodowskiej-Curie 24a, 15–276 Białystok
Phone: 85 746 86 07, 85 746 82 39
e-mail: lidiawitek@tlen.pl
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Introduction

DAWN (Diabetes Attitudes, Wishes and Needs) and DAWN 2 belong to the largest international psychosocial research studies on diabetes [1, 2]. The aim of the projects was to provide new information on the feelings and needs of patients, as well as to determine the direction of changes in health policy. The first edition of the study took place in 2001. The participants were randomly selected from 13 countries, including those suffering from type 1 and 2 diabetes (5104 patients), but also primary care physicians, endocrinologists, diabetologists and nurses (3827 people). Forty-one percent of respondents had poor psychological well-being, only 9% of patients with type 1 diabetes and 12% with type 2 diabetes reported receiving psychological treatment in the past 5 years. Only 42% of health care providers declared that they were able to identify and assess psychological needs of patients and meet those requirements [1]. The DAWN 2 study was conducted in 2011 in 17 countries. The questionnaire was completed by people suffering from diabetes (8596 people), health care workers, but also family members. The influence of diabetes on particular areas of life was evaluated. Over 62% of respondents declared negative effects on physical health, 44.0% on financial situation, 20.5% on relations with family, friends and peers, 38.2% on leisure activities, 35.4% on work or studies, 46.2% on emotional well-being. Over 13% of participants were likely to have depression (WHO-5 Well-Being Index, WHO-5 score $\leq$ 28) [2]. People from Poland also took part in the both studies. According to data from the DAWN 2 study, 19.2% people suffering from diabetes were likely to have depression. Only 8% assessed the organization of healthcare in Poland as good [2, 3].

The conclusions from the above-mentioned studies have contributed to the improvement of the situation of patients with diabetes in countries included in the project, also in Poland.

Since 2006, the guidelines of the Polish Diabetes Association have accentuated the influence of the mental state on therapeutic management in patients with depression and diabetes. Noncompliance with medical recommendations is often associated with psychological problems. Mental condition of a patient should be assessed during every medical visit. The authors of the guidelines suggest that as screening tests, doctors can use two online questionnaires: Well-being index (WHO-5) or Patient Health Questionnaire 9 (PHQ-9), or ask two important questions: "Did you often feel depressed or hopeless during the last month? Did you often lack interest in undertaking various activities or a feeling of pleasure during these activities?". A positive answer to one of the questions has a sensitivity of 97% and a specificity of 67% for the recognize of depression. In case of suspected depression, the patient should be referred for psychiatric consultation [4, 5].

Depression and diabetes

Depression and diabetes are among the most common diseases in the human population. According to the WHO report, in 2015 the proportion of the global population with depression was estimated to be 4.4%. The prevalence rates depend on age, peaking in older adults, and gender (5.1% among women and 3.6% among men) [6]. The exact number of people suffering from mental illness is difficult to assess. According to the literature, only 15% to 26% of depression cases are diagnosed [7]. Mental disorders often co-occur with chronic diseases such as diabetes, arthritis, asthma, chronic obstructive pulmonary disease, ischemic heart disease, and stroke [8]. The prevalence of depression is more than three-fold higher in people with type 1 diabetes and nearly twice as high in people with type 2 diabetes, compared to the general population [9]. The relationship between the diseases is bidirectional. Despite many studies, it is not yet explained whether depression is a consequence of diabetes or mood disorders are a risk factor for the onset of diabetes. A depressive episode is associated with a 60% increased risk of type 2 diabetes [10]. People with mood disorders are mostly characterized by low physical activity, which predisposes to obesity. It has been observed that depression is significantly associated with the occurrence of metabolic syndrome (in particular abdominal obesity) in people aged 60 years or over [11]. According to a meta-analysis by Luppino et al., obese persons had a 55% increased risk of developing depression, and depressed persons had a 58% increased risk of becoming obese [12]. Older people with depressive symptoms and prediabetes have an increased risk of developing overt diabetes, compared to those with only one disease [13]. People with type 2 diabetes have a 24% higher probability of developing a mental disorder compared with non-diabetic controls. A history of a depressive episode and the occurrence of diabetes-related complications are additional risk factors for the development of mood disorders. Among people with diabetes and major depressive disorder, episodes last longer and are more recurrent than in people without glucose metabolism disorders [14]. In patients with type 1 diabetes, it was observed that depression was associated with an 86% increased risk of severe hypoglycemic events and more than doubled the risk of severe hyperglycemic events causing hospital admission or emergency room care [15]. It was shown that depressed mood, sleeping difficulties, problems with appetite and suicidal ideation were significantly associated with higher glycated hemoglobin (HbA_{1c}) values [16]. In the South London Diabetes (SOUL-D) study, people with diagnosed type 2 diabetes were followed for two years. Patients suffering from depression and diabetes were more likely to have macrovascular complications, mainly coronary heart disease (measured by the number of myocardial infarctions and coronary artery bypass graft), and stroke, carotid/limb revascularization or amputations [17]. The coexistence of the two diseases was associated with increased mortality, compared to the group with diabetes alone [18].

It is possible that depression and diabetes are causally related. The coexistence of diseases may result from hormonal and immune system disturbances.

Dysregulation of the hypothalamo-pituitary-adrenal axis

Chronic stress in depression causes hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis. As a result, it leads to excessive production of corticotropin-releasing hormone (CRH) by hypothalamus and then to secretion of adrenocorticotropin (ACTH) by pituitary gland and consequently, peripheral hypercortisolemia is observed. Physiologically, glucocorticosteroids affect the functioning of many tissues, but are also responsible for the feedback inhibition of the HPA axis — they inhibit the synthesis and release of CRH in the paraventricular nucleus and the secretion of ACTH by the pituitary gland, via glucocorticoid receptors (GR). The negative feedback is disturbed in depression. This phenomenon, called glucocorticoid resistance, is associated with GR dysfunction [19, 20]. A meta-analysis by Stetler and Miller showed that in patients with depres-

sion, especially in older people, cortisol and ACTH levels are increased [21]. The normal HPA axis diurnal rhythm consists of high morning and low afternoon-evening cortisol levels. Mood disorders are associated with flattening of the diurnal cortisol curve [22]. About 64% of people with psychotic depression and 41% of patients with nonpsychotic depression showed non-suppression of cortisol secretion in the low-dose dexamethasone test [23]. Exposure to cortisol promotes differentiation and proliferation of human adipocytes. The receptors for glucocorticoids are more plentiful in visceral than in subcutaneous tissue. This contributes to increased fat accumulation in visceral area, activates lipolysis and release of free fatty acids into the circulation [24]. Triglycerides and nonesterified fatty acids can accumulate in the pancreas and induce beta-cell failure. In addition, chronic exposure to glucocorticosteroids cause insulin resistance in skeletal muscle and hepatic tissues [25]. In a study by Oltmanns et al., a positive relationship between metabolic disturbances and salivary cortisol concentrations in patients with type 2 diabetes was found. Hormone levels were positively related to fasting and postprandial blood glucose and HbA_{1c} [26]. In the group of men and women aged between 26 and 36 years it was found that a depressive disorder was significantly related to insulin resistance as indexed by HOMA-IR [27]. Hormonal dysregulation may lead to disorders in metabolism of carbohydrates. Alterations in the HPA system can be reversed by successful antidepressant therapy [28].

The inflammatory theory of depression

Scientific evidence supports the role of the immune system in the etiology of depression. Chronic low-grade systemic inflammation can be reflected by increased concentrations of circulating inflammatory markers such as interleukin 6 (IL-6), interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α) and high sensitivity C-reactive protein (hsCRP). Inflammatory cytokines influence the metabolism of neurotransmitters, activation of the HPA axis and an increase in oxidative stress, which is responsible for degeneration of nerve cells, reduction in synaptic plasticity and activation of microglia [29]. Elevated levels of inflammatory markers are associated with somatic symptoms of mental disorders (fatigue, lack of energy, sleep disorders, changes in appetite) [30].

According to the results of the SOUL-D study, in a group of patients with newly diagnosed type 2 diabetes, symptoms of depression were associated with high concentrations of hsCRP, IL-1β, interleukin-1 receptor antagonist (IL-1RA), monocyte chemoattractant protein 1 (MCP-1) and leukocytes in the blood [31]. The results of a study by Herder et al. have shown that higher levels of hsCRP and IL-1RA in type 1 and 2 diabetes were associated with an increase in depressive symptoms. In addition, higher interleukin-18 (IL-18) levels and lower adiponectin levels were linked to the greater severity of mood disorders in type 2 diabetes. The associations were not found for IL-6 [32]. The results of another study proved that depression is associated with activation of proinflammatory cytokines, but also with endothelial dysfunction. It has been shown that depression in people with type 1 diabetes is associated with elevated levels of soluble intercellular adhesion molecule (sICAM-1) in the blood, and with elevated levels of hsCRP and increased ratio of high-molecular-weight/total adiponectin in the blood in patients with type 2 diabetes [33].

In addition, it is important to underline that the cytokines affect the HPA axis. Interleukin-1 increases the secretion of CRH and ACTH and leads to impairment of GR activation and translocation from the cytoplasm to the nucleus, resulting in reduced expression of GR. Antidepressants increase GR activation and function [19, 20, 34]. Not all depressed patients have increased inflammatory markers, but a group of severely depressed inpatients with treatment-resistant depression have been shown to have high IL-6, TNF-α and cortisol levels [20, 35]. In type 1 diabetes, a higher baseline level of hsCRP was associated with worse patient response to treatment (sertraline or cognitive-behavioral therapy) during the 3-month and 15-month follow-up [36]. Measurement of inflammatory markers may help in the choice of treatment method. Some antidepressants (escitalopram and fluoxetine) reduce CRP levels [37].

Conclusion

Depression and diabetes often co-occur. Mental state has a significant impact on treatment of diabetes. Episodes of depression in patients with diabetes are often long-term, difficult to treat and recurrent. Patients suffering from both diseases have an increased risk of the occurrence of diabetes-related complications, including coronary heart disease. Data from literature review suggest that the co-occurence of depression and diabetes result in dysregulation of the HPA axis and chronic subclinical inflammation. Health care providers who care for people with diabetes should know how to recognize depression. Individual approach to each patient is a very important element of successful therapy.

Conflict of interest

The authors declare no conflict of interest.

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Diabetes expert (in alphabetical order):
prof. dr hab. n. med. Grzegorz Dzida[1], prof. dr hab. n. med. Piotr Fichna[2], prof. dr hab. n. med. Przemysława Jarosz-Chobot[3], prof. dr hab. n. med. Tomasz Klupa[4], prof. dr hab. n. med. Maciej Małecki[4], prof. dr hab. n. med. Wojciech Młynarski[5], dr hab. n. med. Agnieszka Szadkowska[5]

[1]Department of Internal Medicine, Medical University of Lublin, Poland
[2]Department of Pediatric Diabetes and Obesity, Poznań University of Medical Science, Poland
[3]Department of Pediatric Diabetology, Faculty of Medicine, Medical University of Silesia, Katowice, Poland
[4]Department of Metabolic Diseases, Collegium Medicum, Jagiellonian University, Kraków, Poland
[5]Department of Pediatrics, Oncology, Hematology and Diabetology, Medical University of Łódź, Poland

Expert Opinion: Recommendation of diabetes experts on the use of FreeStyle Libre in diabetic patients in Poland

Introduction

The primary goal of diabetes treatment is to prevent the development of chronic complications of diabetes, which can be attained by, among other things, maintaining blood glucose values within the target range. Glycated hemoglobin (HbA_{1c}) is a commonly used risk marker for diabetes complications; however, this parameter has major limitations.

Hemoglobin A_{1c} value, reflecting blood glucose levels during the 3 months preceding the measurement, averages all episodes of hyperglycemia and hypoglycemia. This parameter does not reflect the variability of glycemia and does not provide precise information about the time spent in the target range of blood glucose. Patients with diabetes, especially those with type 1 diabetes, may experience considerable glycemic variability, with blood glucose levels changing rapidly from hyper- to hypoglycemia and vice versa.

Hypoglycemia not only causes acute neurovegetative and neuroglycopenic symptoms, but also is associated with the risk of falls, injuries, loss of consciousness or even death. In addition, it can lead to long-term consequences, which include cardiovascular events, and sometimes to episodes of depression. Rapid fluctuations in blood glucose are also associated with displacement of water in the body — dilution or increased concentration of fluids of various compartments and rapid changes in concentrations of substances other than glucose, which also carries a risk for the patient.

Current glucose monitoring has been integral part of adequate diabetes treatment for decades. Proper self-monitoring of blood glucose (SMBG) requires regular patient education in this regard, with particular emphasis on the frequency of blood glucose measurements and the interpretation of the results. Measured blood glucose values provide the basis for day-to-day modification of nutrition, physical exercise and insulin dose. Patients treated with multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII) should perform a daily blood glucose profile, which means for many of them performing 10 or more measurements a day. These procedures are time-consuming, invasive, painful and causing discomfort in everyday life.

The FreeStyle Libre system is an excellent solution to these problems. It offers continuous glucose monitoring using a sensor-based technology to measure glucose level in interstitial fluid. When the patient scans the sensor to obtain glucose values, he or she simulta-

Address for correspondence:
prof. dr hab. n. med. Maciej Małecki
Katedra i Klinika Chorób Metabolicznych
Collegium Medicum
Uniwersytet Jagielloński w Krakowie
e-mail: malecki_malecki@yahoo.com
Translation: lek. Małgorzata Kamińska
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neously receives a retrospective analysis of the glucose levels in the form of a continuous record. Information about the trends of glycemic variability presented by the device provides additional benefits related to improved effectiveness and safety of the therapy. Thanks to the possibility of generating an Ambulatory Glucose Profile (AGP), this system allows to precisely assess the level of metabolic control over the 90 days preceding the measurement, which corresponds to the period covered by HbA_{1c} value. The accuracy of the system allows for the current calculation of the HbA_{1c} value corresponding to the laboratory measurement of this parameter. This means that the useful, although imperfect, parameter which is HbA_{1c} can be monitored on an ongoing basis and integrated with the patient's SMBG.

Flash Glucose Monitoring

FreeStyle Libre is a Flash Glucose Monitoring (FGM) system. It is designed to measure glucose level in the interstitial fluid in patients with diabetes aged ≥ 4 years, also in pregnant women. It can also be used in other patients, without diabetes, who are at risk of glycemic disorders, e.g. in patients with prediabetes or recurrent hypoglycemia caused by hormonal or metabolic disorders.

The system consists of a reader, a device for wireless retrieval of data regarding glucose levels, and a sensor measuring the level of glucose in interstitial fluid of the subcutaneous tissue, which is worn on the skin.

The system converts the result of the measurement to the corresponding blood glucose value. It does not require user verification with blood glucose values.

Therapeutic benefits for patients

— The sensor continuously measures the glucose level for 14 days;
— Glucose monitoring without finger pricks translates in clinical practice into considerably more frequent measurements of glucose levels and more than 90% reduction in the number of blood glucose test strips (the IMPACT trial);
— The system does not require finger prick calibration;
— Computer software enables generating reports (glucose history), including AGP reports;
— Trend arrows indicates whether glucose level is increasing or decreasing and show trend dynamics, which significantly facilitates assessment of the risk of hypoglycemia in the next few hours (thanks to these data patients also learn how their body reacts, for example, to a specific diet or exercise; therefore, the system plays educational role as well);
— It is also possible to measure the level of glucose and ketones with the reader directly from the blood using test strips that are available and reimbursed in Poland;
— Readings can be obtained in a discreet way, through clothing. It is a comfortable solution, meeting the expectations of patients and their families — it allows for avoiding the violation of privacy and stigmatization of patients;
— Use of the system is easier and more convenient compared with test strips; therefore, it promotes more frequent measurements (more than 3-fold increase in the number of measurements performed) and improved glycemic control. Additionally, awakening the patients (e.g. a child) by a caregiver at night can be avoided;
— Full service for patients using FreeStyle Libre system (warranty/replacement, toll-free helpline).

Benefits demonstrated in clinical trials

Data from clinical trials indicate that the FreeStyle Libre system improves the effectiveness and safety of therapy in patients with type 1 and type 2 diabetes. It has been observed that the use of FreeStyle Libre decreased not only the number of hypo- and hyperglycemic episodes, but also reduced time spent in hypo- and hyperglycemia, including nocturnal episodes. It should be emphasized that hypoglycemia not only is a life-threatening condition (severe hypoglycemia) and decreases the patient's quality of life, but also is an important risk factor for the development of chronic, especially macroangiopathic, complications of diabetes. At the same time, the use of the FreeStyle Libre system resulted in extend time in the target glucose range, i.e. 70–180 mg/dL. Favorable changes were observed almost immediately after the readings from the device were opened to its users. Importantly, these changes were sustained and persisted for 6 months of follow-up (the IMPACT trial). The reduction of the time and number of hypoglycemic episodes has been achieved without insulin dose reduction or increase in HbA_{1c}. Extended time in normoglycemia with the reduction of the risk of hypo- and hyperglycemic episodes was also associated with a decrease in glycemic variability, a parameter now considered as an integral element in the evaluation of metabolic control of diabetes and an important prognostic factor for the development of diabetic complications. It is worth noting that glycemic variability is calculated automatically, similarly to the estimated HbA_{1c} ($eHbA_{1c}$), a parameter which in turn shows a far-reaching correlation with the biochemically determined HbA_{1c} value and can be obtained immediately after scanning FreeStyle Libre sensor without

having to waiting for a biochemical test result. The use of the FreeStyle Libre also allowed for a significant reduction in the number of test strips used, compared with using only the traditional method (a glucose meter). Several studies indicate that the FreeStyle Libre system provides glycemic monitoring that is accurate and consistent with the reference measurements for 14 days without the need to calibrate the device.

Surveys conducted among users have shown that patients appreciate the ease and convenience of measurements with the FreeStyle Libre system. It has been also observed that these patients more often follow the guidelines for glycemic monitoring than in the case of measurements performed using the conventional method. In the IMPACT trial, patients with type 1 diabetes using the FreeStyle Libre system measured glucose levels on average 15.1/day, which is much more often than in patients in the glucose meter group (5.6 measurements/day). The results of this survey and questionnaires assessing the quality of life also highlight the importance of the painlessness of measurements and a greater amount of information on glycemic variability, which allows patients to optimize their blood glucose levels. Ease of measurement and access to information also translated into clear preferences of patients, over 90% of whom declared that they prefer FreeStyle Libre rather than the traditional SMBG based on a glucose meter. Participants of the study also pointed to the increased awareness of the risk of hypoglycemia, security and privacy offered by the FGM device and the fact that it did not hinder usual daily-life activities, and even facilitated them by improving diabetes safety. The opinions of FreeStyle Libre users were similar regardless of the age of the respondents.

Patient register (Real World Data) — a confirmation of clinical data

Data from real-world medical practice confirm the above conclusions from clinical trials: the FreeStyle Libre system allows improving glycemic control. Particular attention is paid to the results of Dunn 2017 analysis, covering almost 51 thousand readers (about 280,000 sensors), indicating the relationship between the frequency of scans and the improvement in glycemic parameters. These results are all the more important because the frequency of scans in this analysis was even higher (an average of 16.3/day) than in the IMPACT study (an average of 15.1/day).

Interpretation of trends

Patients for whom the basis for glucose control is SMBG using a glucose meter make their therapeutic decisions based on the real-time but single blood glucose value. Lack of information about the rate and direction of glycemic changes makes it difficult for patients to determine correctly the dose of insulin.

The FreeStyle Libre system provides two very important pieces of information beyond the current glucose level. The reader screen displays a graph showing the results of glycemia from the last 8 hours and trend arrows indicating the direction and rate of changes in the glycemic level. The patient should immediately modify his or her therapy taking into account this information.

In patients treated with functional intensive insulin therapy, modifications of therapy based on glycemic trends should include:

— change of meal-time and correction doses of insulin;
— intake of fast-acting carbohydrates or skipping a meal;
— considering physical activity.

Patients treated with personal insulin pumps may additionally modify the basal rate of insulin infusion and consider earlier replacement of infusion set.

Proper interpretation of trends by patients results in the reduction in the incidence of hypo- and hyperglycemia, decreased glycemic variability and improved time in target range. The use of glycemic trends should translate into a reduction in the incidence of acute diabetic complications and a reduction in the risk of development and progression of chronic diabetic complications. This information is also very useful for patients driving vehicles.

Considering all the above factors, patients should be educated on how to interpret glycemic trends. Currently, guidelines are being developed regarding proposed modifications of therapeutic decisions depending on the rate and direction of glycemic changes. The current interpretation of glycemic trends by patients will add a new dimension to diabetes self-control.

Ambulatory Glucose Profile: benefits for doctors

FreeStyle Libre enables performing systemic evaluation of the therapeutic process and treatment outcomes regarding blood glucose control in diabetic patients. FreeStyle Libre is the only system available on the Polish market which presents data using internationally recognized standardized approach to the analysis of glucose data — Ambulatory Glucose Profile (AGP) — both directly in the device and in the available computer software.

AGP provides a visualization of changes in glucose levels in the patient's averaged day of life. It is created on the basis of a daily chart summing up the results of glycemic measurements from many days or weeks

in one 24-hour chart. AGP shows averaged daily glycemic variability for the 10th, 25th, 50th, 75th and 90th percentiles (the graph is generated with 5 percentile lines). Generated in this way and superimposed glucose curves show how often the glucose values are outside the target range (low or high values) and how often they fall within the target range. The visualization of the AGP reveals the tendencies to hypo- and hyperglycemia that could not be detected based on HbA_{1c} value. Scientific reports emphasize the need to prevent significant fluctuations of blood glucose, because it is considered as the most important factors contributing to the early onset of serious complications of diabetes. These goals cannot be achieved by assessing the level of glycemic control using only HbA_{1c} monitoring, and AGP provides a very valuable supplement. Ambulatory glucose profile facilitates detecting hypo- and hyperglycemic trends, which allows the identification of glycemic patterns and proper patient education. Reports from clinical trials indicate that AGP has introduced an effective standard for analyzing glucose data and provides clinically relevant information about the patient's condition. The FreeStyle Libre® system due to its functionality (the device stores the reading every 15 minutes; it stores 90 days of glucose data) enables widespread use and practical application of the AGP protocols.

Summary of this section:

— a glucose graph and trend arrows showing blood glucose changes in the last few hours provide the basis for making therapeutic decisions;
— the system offers the analysis of standardized AGP, which enables:
  • identification of glycemic patterns and adequate patient education (it helps patients to understand how daily activities impact blood glucose levels);
  • more detailed evaluation of the therapeutic process by the healthcare professionals.

New standard of glucose monitoring supplemented by SMBG

The FreeStyle Libre system, if it is permanently used by the patient, can replace the conventional glucose meter-based SMBG. This applies to patients with type 1 and type 2 diabetes treated with intensive insulin therapy except for the situations listed below.

In the following situations current readings from FreeStyle Libre should be verified with the finger prick test using a blood glucose meter:

— if hypoglycemia or impending hypoglycemia is reported by FreeStyle Libre;
— if the symptoms do not match the FreeStyle Libre system readings; symptoms that may be caused by low or high blood glucose must never be ignored.
— during times of rapidly changing glucose levels when interstitial fluid glucose levels may not accurately reflect blood glucose levels; when blood glucose decreases rapidly, sensor reading may be higher than blood glucose level; and conversely, when blood glucose increases rapidly, sensor readings may be lower than blood glucose level.

Indication for use (patient groups)

FGM is indicated for use in the following groups of patients:

— patients with diabetes treated with intensive functional insulin therapy (multiple daily insulin injections, insulin pump therapy), regardless the type of diabetes;
— pregnant women with diabetes;
— patients with diabetes treated with conventional insulin therapy (2–3 injections daily), who are able to adjust insulin doses.

Other special groups of patients with an indication for the use of FGM:

— diabetic patients with the fear of needles or fear of hypoglycemia;
— patients with diabetes who drive the vehicles, leading an active lifestyle, working in shifts;
— patients with diabetes who require constant care (children, people with physical or mental disabilities);
— patients with diabetes and visual impairment or blindness (text-to-speech option)
— elderly patients with diabetes (FGM systems are easy to operate), also in senior care facilities and nursing homes.

Potential limitations of the system and their importance

FreeStyle Libre is similar in many respects to other interstitial-glucose-monitoring systems, but it also has some unique features. The FreeStyle Libre sensor is a transmitter that connects wirelessly to the reader; it does not have to be recharged and can be worn on the skin for 14 days.

Exceptionally high accuracy of measurements and trend indications without calibration as well as 14-day life span of a sensor are advantages obtained at the expense of limiting energy expenditure, resulting mainly from the lack of continuous transmission of data and audible alarms. On the other hand, this solution is simple from a technical point of view and can be easily integrated in the system as it is successively improved. Another feature simplifying the use of the

FreeStyle Libre system is FreeStyle LibreLink application which enables the caregivers to trace the patient's blood glucose readings and support the patient in daily diabetes control. This is particularly important for remote parental control over children with diabetes or for caregivers of elderly patients.

Noteworthy is the fact that glucose measurements are automatically registered every 15 minutes, which is less frequently than in continuous glucose monitoring (CGM) systems, but the time interval is similar to that of natural changes of glucose concentration in interstitial fluid (where the measurement is actually performed) in response to blood glucose fluctuations. This can also result in higher accuracy of the measurement and more reliable prognosis of glycemic changes (trend), because the device analyzes a 15-minute periods rather than, for example, 5-minute periods. In addition, this automatic registration does not exclude much more frequent measurements made by the patient by scanning the sensor, even every 1 minute, which is not possible when using CGM systems. Frequent (every few minutes) monitoring of glucose levels may be useful in special situations.

There is only one site for administration of the FreeStyle Libre sensor recommended by Abbott — on the back of the arm. This is important for optimal accuracy of measurements, because this location was associated with the best results in manufacturer's quality tests. On the one hand, this can be considered as a limitation, although the use of sensors inserted subcutaneously do not cause significant tissue injury and therefore the limitation of rotation areas, even for smaller children, is not a problem. On the other hand, placing sensor within previously examined areas of the body, with known characteristics of vascularization and involvement in the glycemic balance, results in greater accuracy and repeatability of measurement results. If the user, in spite of Abbott's suggestions, places the sensor in another area for important reasons, the sensor will still work, although more frequent verifications of obtained readings with the result of the glucose meter measurements are required, especially in the case of abnormal blood glucose values.

FreeStyle Libre also stands out from other CGM systems due to its flat sensors with rounded edges, well-fitting to the body. Thanks to all these features the sensor is better secured on the skin and less susceptible to accidental detachment when, for example, caught by clothes, etc.

The biggest limitation preventing the widespread use of the system is the lack of reimbursement for patients, which limits its availability. The reimbursement would be, at least partially, offset by reducing the cost of test strips for glucose meters. The example of patients already using FreeStyle Libre shows that the use of strips for glucometers decreases about 10 times. They are not needed for FreeStyle Libre calibration, and are used, along with reader's indications, only in the specific situations listed above. Moreover, the Libre reader not only can be used as a glucometer using glucose strips (Optium Xido), but also can measure ketones (β-hydroxybutyric acid) in the blood (Optium Xido β-ketone strips), which allows determination of significant hazards for the patient. In addition, there is still a need to improve diabetes control and reduce the costs resulting from the development of complications and acute, transient, often life-threatening conditions (costs of outpatient visits and hospitalizations). Currently in Poland, the reimbursement of CGM systems is limited to type 1 diabetes patients in a specific age range who are users of personal insulin pumps. It also requires meeting additional criteria related to diabetes control. These conditions discriminate against patients with type 1 diabetes who have poor metabolic control or do not have (for various reasons) a personal insulin pump. They also discriminate against patients with type 2 diabetes treated with insulin, usually injected with pens. It should be remembered that many patients with type 2 diabetes are also treated intensively with insulin and they also require continuous monitoring of therapy.

Software

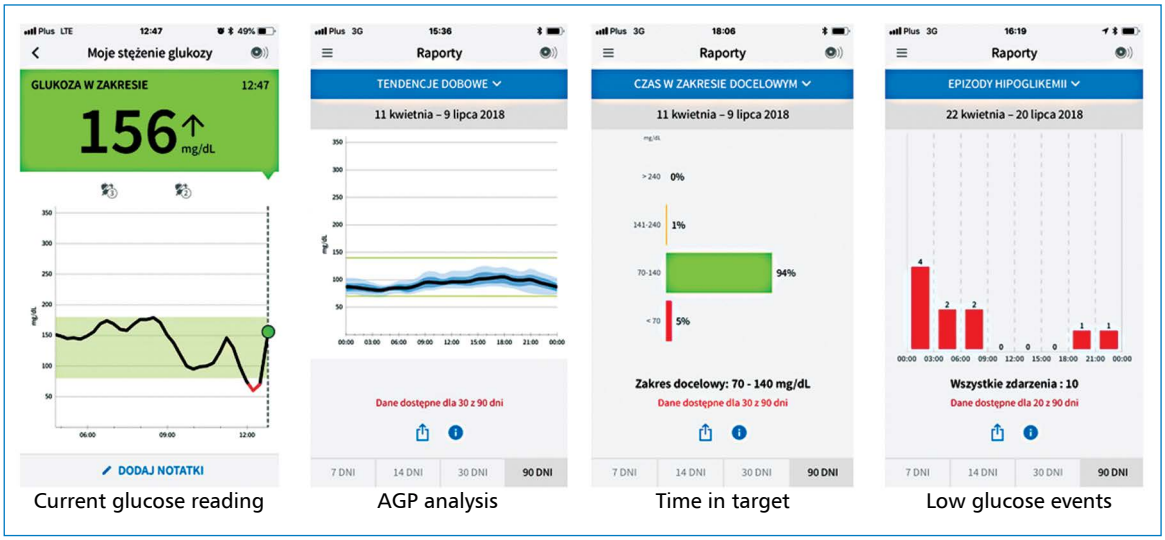
Since the second half of 2018, patients using FreeStyle Libre in Poland can use innovative digital solutions: FreeStyle LibreLink and LibreLinkUp applications available on Android and iOS systems as well as the LibreView system allowing for comprehensive data analysis and on-line access to glucose data.

Below are the features of these applications and the system:

The **FreeStyle LibreLink application** allows users of the FreeStyle Libre system to scan the sensor using a smartphone, providing greater convenience and discretion. It also allows the patient to reduce the cost of blood glucose monitoring, because there is no need to use a separate reader to monitor glucose.

The benefits for patients resulting from using this application:

— patients can use FreeStyle LibreLink on their smartphone instead of or simultaneously with the FreeStyle Libre reader;
— rich patient interface is available from a large high-resolution touch screen;
— patients can easily add notes to track meals, insulin doses, exercise and other events;



Current glucose reading | AGP analysis | Time in target | Low glucose events

Figure 1. Some examples of reports available to the patient using the FreeStyle LibreLink application

— cooperation of FreeStyle LibreLink with LibreLink-Up enables connection with caregivers;
— text-to-speech option converts glucose readers into spoken audio, which is important for users who are blind or have impaired vision.

Some examples of reports available to the patient using the FreeStyle LibreLink application are presented in Figure 1.

LibreLinkUp is a mobile application that allows parents and caregivers to remotely monitor glucose readings in patients who scan the sensor using the FreeStyle LibreLink application.

Figure 2 shows an example screenshot from a smartphone used by a caregiver working with the FreeStyle LibreLinkUp application.

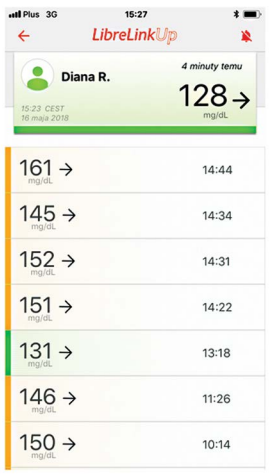


Figure 2. Example screen available to a caregiver using the LibreLinkUp application

LibreView is a cloud-based diabetes control system offered by Abbott and Newyu, Inc. LibreView provides a secure data repository for the FreeStyle LibreLink application and enables easy sharing of glycemic data with health care professionals or other people. The data is automatically sent to the LibreView system when the phone is connected to the Internet.

The main benefits of using this system are:
— glucose data can be simply uploaded from the reader via a computer and accessed from anywhere from any internet-connected device;
— the glucose data of patients using FreeStyle LibreLink application will be automatically transferred to their LibreView account each time the FreeStyle Libre sensor is scanned;
— clear, easy-to-read reports which allow the patient to discover glucose patterns and trends immediately;
— optimization of treatment plans thanks to remote patients monitoring and cooperation with a healthcare team.

Using the above-described applications and the system allows for remote control of glycemia with tools perfectly matching the concept of telemedicine, which not only significantly increases patient safety, but also reduces direct and indirect expenses by the public payer. Additionally, this technology provides real-world data showing actual effects of the use of a specific medical technology.

Education

Type 1 diabetes results from destruction of pancreatic beta cells. These cells are the source of insulin and a perfect natural regulator of its presence and access

to all cells in various organs. The beta cells precisely regulate insulin secretion according to the changing needs of the body. During the initial stage of type 2 diabetes, beta cells produce insulin in excessive amount. The progression of the disease is characterized by a disturbed profile of and a progressive decrease in insulin secretion. Thus, in the treatment of both type 1 and type 2 diabetes, it is necessary not only to supplement insulin, but also replace the lost regulatory function of the beta cells.

The way to improve this situation is proper education of the patients and/or their caregivers so that they understand the role of insulin and can predict the effects of its administration, in particular in relation to meals and physical exercise. It is also important to anticipate a change in insulin requirements during additional illness or in special situations. A particular difficulty in good diabetes therapy is associated with individual differences in the course of the disease and various life situations.

In practice this means that diabetes education, which is an integral part of the treatment of a patient with diabetes, must also be individualized. The patients actively participate in treatment, because they ultimately make therapeutic decisions. Their task is to observe their bodily reactions to meals, physical activity and, finally, insulin dosing, and sometimes also effects of other drugs influencing glycemia. These observations as well as drawing conclusions from them and constant modification of the therapy are based largely on glucose monitoring. The patient has to verify the recommendations received from the therapeutic team in real life, which is done by assessing the glycemic effects of the therapy. In healthy people, pancreatic beta-cells control glycemia and constantly regulate insulin secretion. In diabetes, FreeStyle Libre allows the user to imitate the natural mechanism of glycemic control. Indeed, it supports the patient's therapeutic decisions. FreeStyle Libre, by displaying real-time glycemic values, indicating the anticipated glycemic trends, storing these data in memory and offering the possibility of reviewing data from the past few hours, 24 hours or many days allows the patient to successively adjust his or her self-management and constantly improve glycemic control. This applies to evaluation of the risk of hypo- and hyperglycemia episodes, their amplitude and timing, identification of repeating patterns of normal and abnormal blood glucose values.

Patient self-education activity aiming at expanding their knowledge about diabetes is also needed. It involves arranging situations that are associated with changes in insulin dosing, diet or physical activity in order to carefully observe glycemic effects and evaluate the sensitivity to insulin, calculate insulin/carbohydrate ratio, assess the hypoglycemic effect of exercise etc. Thanks to the FreeStyle Libre system, diabetic patients can easily track glycemic changes even in very narrow time intervals, store them in the system's memory, and then draw conclusions about modifications or continuation of therapy i.e. insulin dosing, diet and physical activity.

The FreeStyle Libre system also allows the calculation of the corresponding HbA_{1c} value based on numerous glucose readings recorded by the sensor; its high accuracy has been confirmed by laboratory tests. The educational value of this efficient HbA_{1c} calculation is to indicate whether the therapeutic goal expressed by this parameter is achieved. It allows the patient to understand the relationship between the calculated HbA_{1c} value and his or her glucose profile — its amplitude, episodes of hypo- and hyperglycemia, etc. This makes the interpretation of HbA_{1c} parameter more valuable and informed.

Summary

On the basis of clinical trials, scientific evidence and experience from everyday practice, the use of FreeStyle Libre is recommended as a glucose monitoring system in patients with type 1 and type 2 diabetes treated with intensive insulin therapy. FreeStyle Libre supports treatment and can contribute to:

- improvement in diabetes control by decreasing mean blood glucose levels and HbA_{1c};
- reduction of the number of hypoglycemic episodes and time spent in hypoglycemia; it is particularly relevant to patients with frequent hypoglycemic episodes and hypoglycemia unawareness;
- reduced glycemic variability;
- potential decrease in long-term complications of diabetes;
- improved patient quality of life and safety.

We express the opinion that the FreeStyle Libre system should be widely available, also taking into account its affordability, for Polish patients with type 1 and type 2 diabetes treated with intensive insulin therapy.

The Expert Group was established by Abbott Laboratories Polska to express the above opinion as part of the meeting of the Advisory Committee, which was held in Warsaw on November 21, 2017 and on March 23, 2018.

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1st Forum of Modern Diabetology

The 1st Forum of Modern Diabetology and its closing event, the 2nd Debate "Diabetes Innovations Day" (DID), which took place on November 23–24, 2018 at the Congress Center, Poznań International Fair is already over, but this meeting has become the basis for further activities promoting the use of new technologies and modern solutions in the treatment of diabetes.

The Organizers of the Forum were the University and Hospital Department of Internal Medicine and Diabetology, Poznań University of Medical Sciences and the casusBTL Group, a team of specialists dealing with marketing communication in the medical industry. The patronage was provided by the Diabetes Poland and the Polish Diabetes Association, and the honorary patrons were the Marshal of the Wielkopolska Province Marek Woźniak, the President of Poznań Jacek Jaśkowiak and the Rector of Poznań University of Medical Sciences, Prof. Andrzej Tykarski.

The theme of the Forum was new technologies used in diabetes management. Nowadays, rapid technological progress enters the daily practice of diabetes care, helps to better understand diabetes and allows insulin therapy to mimic physiological insulin secretion. Thanks to their increasing availability, these new technologies can be widely used, but they require us to constantly improve our knowledge and skills in this area.

The Forum of Modern Diabetology was a scientific meeting of therapeutic teams, lecturers and experts in the topics presented, practitioners with extensive experience, but also software engineers and developers, medical educators and diabetic nurses, as well as representatives of many patient organizations offering support to diabetics and their families. The first day of the Forum started with a workshop for patients, during which innovative technological solutions supporting diabetics in their everyday active life were presented. Patients had the opportunity to learn about the functionality and benefits of modern applications, the use of which helps to make therapeutic decisions and increases involvement in managing diabetes.

During the workshop, the functionality of the new software (which is already available in Poland) for users of insulin pumps and continuous glucose monitoring (CGM) systems was presented and the advantages of applications supporting the improvement of glycemic control in patients with diabetes were demonstrated in practice. The latest advances in modern insulin therapies were also discussed.

The workshop also included the presentation by the NightScout Polska community #WeAreNotWaiting. Nightscout is a project that allows remote real-time access to glucose readings from the following systems: FreeStyle Libre, Medtronic Minimed 640G, Paradigm VEO, Paradigm 722, Dexcom G4, and Dexcom G5, using a smartphone, a tablet, or a SmartWatch. The open source project was originally created by parents to supervise children with type 1 diabetes. The system is also used by adult patients due to the benefits from its use.

During the inaugural lecture on the closed loop system, Adrian Tappe (Austria) and Miloš Kozak (Czech Republic), software engineers and developers working on open source software, appealed to doctors to support similar projects by providing scientific evidence confirming the effectiveness of applied solutions for glycemic control.

Presented and discussed topics show how important today are activities promoting modern therapies for type 1 diabetes. Ideas and plans regarding the possibility of continuous glycemic monitoring and automated insulin dosing according to the body's needs, which were dreams yesterday, are becoming real solutions today.

On the second day of the Forum there was a scientific session during which researchers from all over Poland presented the results of their studies, and practitioner-experts shared their experiences with diabetes patients. The topics that were discussed by the speakers were the necessity of using continuous glucose monitoring systems in the treatment of patients using personal insulin pumps and the impact of diabetes education and re-education on treatment effectiveness and self-control in patients during therapy.

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The Forum and program of Modern Diabetology is the result of cooperation of many people and their personal involvement.

Activities under the Modern Diabetology project are to contribute to the improvement of care for patients with diabetes in Poland. The implementation of this objective is based on the use of new advanced technologies. Wisdom and prudence as well as enthusiasm and joy of work are needed to turn words into deeds. We work as a team with multi-faceted and multi-center approach in order to change the existing situation for the better.

The dialogue from last year was continued in Poznań. During the 2nd DID Debate, solutions were sought to optimize the use of new technologies and new tools in the education of patients and their families and therapeutic teams. The technological revolution in diabetology provides new possibilities that will lead to better management of diabetes.

The motto of the debate was: "Let's replace the phrase 'should be done' with 'how to do it?' — from idea to realization".

During the debate, the most discussed topics were those related to patient education in the context of using new technologies, e-learning, and ordering or creating an effective certification system for educators. It was emphasized how important it is to involve the family in the education process. Considering the availability of various information on diabetes therapy on the Internet, it is necessary to evaluate and verify its content.

There is a need to develop tools and create a diabetes education workshop, which over time could be widely used, with the support of the authorities such as the Diabetes Poland.

Thank you to all involved in the Modern Diabetology project, Lecturers and Participants of the 1st Forum of Modern Diabetology and the 2nd DID Debate, and we invite you to the Second Forum of Modern Diabetology to be held in November 2019 in Poznań.

On behalf of the Organizers
Aleksandra Araszkiewicz
Andrzej Gawrecki
Dorota Zozulińska-Ziółkiewicz

Department of Internal Medicine and Diabetology
Poznań University of Medical Sciences