Beyond Diabetes Management: Unraveling Metformin’s Long-Term Effects on Vitamin B12
Gurusha Bahl, Md Sadique Hussain, Nikita Saraswat, Mohit Agrawal

Effectiveness of Theory-Based Intervention on Knowledge Level, Psychological Constructs, Metabolic Index and Physical Activity Status in Patients with Type 2 Diabetes: Application of the Health Action Process Approach (HAPA) Model
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Prevalence of Musculoskeletal Manifestations in Type 2 Diabetes: A Single Centre, Cross-Sectional Study
Kushdeep Singh, Narender Pal Jain, Sandeep Chhabra, Prannav Jain, Deepanshu Goel, Namita Bansal, Suman Sethi, Parminder Singh

Prevalence and Severity of Chronic Obstructive Pulmonary Disease in People with Type 2 Diabetes: A Cross-Sectional Study
Mridul Bera, Amit Gupta, Rishad Ahmed, Arjun Baidya, Mrinal Kanti Guha
Contents

EDITORIAL
Beyond Diabetes Management: Unraveling Metformin’s Long-Term Effects on Vitamin B12
Gurusha Bahl, Md Sadique Hussain, Nikita Saraswat, Mohit Agrawal 279

RESEARCH PAPER
Knowledge and Attitude towards Risk Factors and Complications of Diabetes among Housekeeping Staff at a Tertiary Care Center in India
Sushma H. Nayak, Saleena Ummer Velladath, Kalaivani Manokaran, Venilla Jaganathan, Anju Muraleedharan 283

Effectiveness of Theory-Based Intervention on Knowledge Level, Psychological Constructs, Metabolic Index and Physical Activity Status in Patients with Type 2 Diabetes: Application of the Health Action Process Approach (HAPA) Model
Fatemeh Zanjanchi Neko, Isa Mohammadi Zeidi, Hadi Morshed, Banafsheh Mohammadi Zeidi, Mohammad Reza Maleki, Amir Pakpoor Hajia 290

Prevalence of Musculoskeletal Manifestations in Type 2 Diabetes: A Single Centre, Cross-Sectional Study
Kushdeep Singh, Narender Pal Jain, Sandeep Chhabra, Prannav Jain, Deepanshu Goel, Namita Bansal, Suman Sethi, Parminder Singh 301

Prevalence and Severity of Chronic Obstructive Pulmonary Disease in People with Type 2 Diabetes: A Cross-Sectional Study
Mridul Bera, Amit Gupta, Rishad Ahmed, Arjun Baidya, Mrinal Kanti Guha 308

OBSERVATION LETTER
The Effect of the COVID-19 Crisis on Metabolic Control of Patients with Type 2 Diabetes in Tunisia: A Cross-Section and Retrospective Cohort Study
Melika Chihaoui, Chayma Bel Hadj Sliman, Anis Grassa, Nadia Khessairi Fatma Chaker, Meriem Yazidi, Bessem Hammami, Moncef Feki, Ibtisssem Oueslati 315

Association between Random Glucose Level, HbA1c and COVID-19 Mortality: A Single Center, Cross-Sectional Study
Faizal Awaluddin, Husaini Umar, Sudirman Katu, Syakib Bakri, Andi Makbul Aman, Harun Iskandar, Arifin Seweng 318
Beyond Diabetes Management: Unraveling Metformin’s Long-Term Effects on Vitamin B12

Introduction

The use of metformin has been associated with potential vitamin B12 malabsorption and deficiency, which can exacerbate distal symmetrical, autonomic, and cardiac neuropathy in diabetic patients. Numerous observational studies and meta-analyses have highlighted a significant association between metformin use and vitamin B12 deficiency [1, 2]. Prolonged and high-dose metformin treatment has been shown to have an inverse relationship with vitamin B12 levels [3]. Patients undergoing metformin treatment exhibit reduced B12 absorption, resulting in decreased serum total vitamin B12 and transcobalamin II (TCII-B12 levels). This outcome is attributed to a calcium-dependent ileal membrane antagonism, which can be counteracted through calcium supplementation [4]. Based on these findings, it is highly recommended that individuals using metformin, especially vegetarians, given the scarcity of Vitamin B12 in plant based diets [5], and those undergoing treatment for over 5 years, undergo routine monitoring of their vitamin B12 levels. This precaution is essential because prolonged metformin use may deplete hepatic vitamin B12 reserves [1].

Mechanism of long-term metformin-induced vitamin B12 deficiency

The precise mechanism by which metformin induces vitamin B12 deficiency remains incompletely understood. However, a plausible explanation revolves around metformin’s potential interference with calcium-dependent membrane functions in the terminal ileum, where vitamin B12-intrinsic factor absorption takes place. This absorption process relies on the calcium-dependent uptake of the B12-intrinsic factor complex by ileal cell membrane receptors, and metformin has shown the ability to affect calcium-dependent membrane functions. One of the clearest mechanisms for reversing metformin-induced B12 deficiency involves the calcium administration. The uptake of the vitamin B12-intrinsic factor complex by ileal cell surface receptors naturally relies on luminal calcium concentration to facilitate this vital process. Metformin is thought to introduce a positive charge to the membrane’s surface, possibly displacing divalent cations such as calcium. This disturbance in calcium availability, attributed to metformin’s activity, consequently disrupts the calcium-dependent mechanism responsible for vitamin B12 absorption [6].

Initial clinical observations suggested the presence of vitamin B12 malabsorption in individuals receiving prolonged metformin therapy (Fig. 1) [7]. Subsequent investigations have confirmed these observations by demonstrating that metformin can lead to a significant reduction in serum vitamin B12 levels, ranging from 14% to 30%. Notably, patients displaying vitamin B12 deficiency tend to have a lengthier history of metformin usage (≥ 4 years) and were prescribed higher daily doses.
of metformin (> 1000 mg) compared to non-deficient patients [8].

From a clinical standpoint, vitamin B12 deficiency can present as changes in mental function, megaloblastic anemia, and neurological impairments. Notably, the symptoms of diabetic neuropathy, including paresthesias and compromised vibration sensation and proprioception, may overlap with those of peripheral neuropathy resulting from vitamin B12 deficiency. Consequently, peripheral neuropathy due to vitamin B12 deficiency can be mistaken for diabetic peripheral neuropathy or potentially exacerbate its symptoms. Timely identification and intervention through cobalamin supplementation can halt the progression of neurological damage associated with vitamin B12 deficiency. However, when misdiagnosed as diabetic neuropathy, this condition may lead to irreversible neurological impairments. It is worth noting that factors such as the daily dosage of metformin and the duration of treatment consistently emerged as significant risk factors for vitamin B12 deficiency [9].

Vitamin B12 deficiency can result in a diverse array of symptoms encompassing neurological manifestations such as tingling and numbness in the extremities, difficulties in maintaining balance, cognitive distress, including depression, confusion, dementia, compromised memory, as well as discomfort in the mouth or tongue. Additional indications might include fatigue, muscular weakness, constipation, diminished appetite, and weight loss [10]. Importantly, the symptoms associated with vitamin B12 deficiency tend to be broad and nonspecific, possibly not correlating with anemia or an elevated mean corpuscular volume [11]. It is noteworthy that these manifestations of vitamin B12 deficiency hold the potential for reversal with vitamin B12 supplementation [9, 11].

Left untreated, vitamin B12 deficiency can lead to severe and irreversible neurological impairment (Fig. 2), including peripheral neuropathy, cognitive decline, dementia, and psychiatric conditions like depression [12]. Additionally, vitamin B12 deficiency can result in hematologic anomalies, including the development of megaloblastic anemia [13]. In infants, neglecting vitamin B12 deficiency can contribute to developmental setbacks, movement irregularities, and failure to thrive. Importantly, symptoms associated with vitamin B12 deficiency have the potential to be reversed through the administration of vitamin B12 supplements [14, 15]. Therefore, a prompt diagnosis and effective management of vitamin B12 deficiency are of utmost importance in preventing prolonged complications.

Figure 1. Absorption of Vitamin B12 in Healthy Individuals and Long-Term Metformin Users
In long-term metformin users, metformin induces a wall like structure which blocks the absorption of Vitamin B12 from foods...
In summary, the link between metformin use and vitamin B12 deficiency, with potential implication for neuropathy and overall health, is a significant concern. Prolonged metformin therapy primarily impacts vitamin B12 levels by interfering with calcium-dependent processes in the ileal membrane. Calcium supplementation may potentially alleviate this issue. Clinical observations have indicated that a significant proportion of individuals on long-term metformin treatment may experience vitamin B12 deficiency, especially those with extended treatment durations and higher daily doses. Vitamin B12 deficiency can present with various neurological and general symptoms, sometimes resembling diabetic neuropathy. This underscores the importance of timely detection and intervention to prevent permanent neurological damage. It is important to note that the symptoms associated with vitamin B12 deficiency are multifaceted and non-specific, which can complicate diagnosis. Nevertheless, appropriate vitamin B12 supplementation typically leads to the reversal of these symptoms. Given these insights, it is highly advisable to regularly monitor vitamin B12 levels in all metformin users, particularly vegetarians, and those undergoing treatment for more than five years. This proactive approach can help prevent the depletion of hepatic vitamin B12 stores and mitigate potential long-term complications.

Clinicians must maintain a high level of awareness since vitamin B12 deficiency can manifest with...
symptoms similar to diabetic neuropathy, emphasizing the importance of timely diagnosis and intervention. Additionally, factors including the daily metformin dosage and treatment duration significantly contribute to the risk of deficiency. The symptoms of vitamin B12 deficiency are wide-ranging, spanning neurological, cognitive, and physical aspects, all of which can be alleviated through cobalamin supplementation. Failure to promptly diagnose and treat this deficiency can result in severe and irreversible neurological damage, hematological irregularities, and developmental problems in infants.

Further research is imperative for a comprehensive understanding of the precise mechanism through which metformin hinders vitamin B12 absorption, providing insights for tailored interventions. Investigations should also focus on determining the optimal and cost-effective frequency for monitoring vitamin B12 levels in metformin users. Furthermore, researchers ought to explore genetic and dietary variables that may make individuals more susceptible to metformin-induced B12 deficiency, facilitating the creation of personalized preventative approaches. Equally important is the development of standardized treatment guidelines for addressing vitamin B12 deficiency in metformin users, considering the appropriate dosage and duration of supplementation.

Article information

Funding

None.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

Knowledge and Attitude towards Risk Factors and Complications of Diabetes among Housekeeping Staff at a Tertiary Care Center in India

ABSTRACT
Objective: This study aimed to assess the knowledge and attitude towards risk factors and complications of diabetes among housekeeping workers.
Material and methods: After obtaining institutional ethics approval, a cross-sectional survey was conducted among housekeeping staff working in a tertiary care center with an age group ranging from 18 to 60 years to assess knowledge and attitude towards risk factors and complications of diabetes. The correlation between knowledge and attitude scores was determined using Karl Pearson correlation coefficient analysis.
Results: A total of 287 housekeeping staff, with majority of females (73.9%) were included in the study. The average knowledge score was 16.24 ± 6.74, and the average attitude score was 7.22 ± 1.27. A weak correlation between knowledge and attitude scores was observed with a coefficient of 0.215 (p < 0.01). Multivariate linear regression analysis revealed that total knowledge and attitude scores and previously counseled people were statistically significant.
Conclusions: The findings revealed that the overall level of knowledge about diabetes among housekeeping staff is poor, but the overall attitude is positive. There was a weak correlation between knowledge and attitude scores. Coordinated educational initiatives focusing on lower socioeconomic background, rural, and less educated individuals are needed to avoid diabetes and its complications. (Clin Diabetol 2023; 12; 5: 283–289)
Keywords: knowledge, attitude, complications, diabetes, housekeeping workers

Introduction
Diabetes (DM) is one of the world’s fastest-growing public health emergencies in the 21st century [1]. The term diabetes consists of a group of metabolic illnesses that share the characteristic of hyperglycemia and are produced by a complicated combination of hereditary and environment [2]. It is caused by insulin deficiency or insulin resistance, or both. Insulin is a hormone produced by the pancreatic cells to regulate blood glucose levels [3]. Type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes mellitus (GDM) are the three primary categories of DM [1]. Ninety percent of all
diabetes cases are T2DM [4]. According to the International Diabetes Federation, global diabetes prevalence is 9.3 percent in 2019, rising to 10.2 percent by 2030 and 10.9 percent by 2045 [5]. Furthermore, the World Health Organization estimates that diabetes causes 3.2 million deaths per year, 8700 deaths per day, and six deaths each minute [6]. Diabetes was prevalent in 7.3 percent of Indians [7]. Males in Southern India and females in Northern India were found to have a higher prevalence of diabetes [8, 9]. Diabetes prevention requires understanding risk factors in the general population and high-risk groups. Genetic factors in specific ethnic communities, a family history of diabetes, and age (greater than 45) are unmodifiable risk factors. However, lifestyle factors such as poor diet, lack of physical activity, alcohol consumption, and smoking are the most common risk factors for diabetes epidemiology, leading to obesity, dyslipidemia, high blood pressure, and impaired glucose tolerance (IGT) [10]. DM that is not well controlled can cause life-threatening complications, including both microvascular and macrovascular problems [11]. DM will become a leading cause of illness and death in the future as its prevalence is increasing worldwide [2].

Diabetes treatment aims to reduce mortality and morbidity by returning blood glucose levels to normal. Diabetes patients can benefit from good eating habits, regular physical activity, and checkups. Due to their difficulty understanding and adhering to medical instructions, people with DM who lack health awareness and education are more likely to have poor blood glucose control and an elevated risk of complications [12]. The hospital’s housekeeping staff is in charge of keeping the facility clean and hygienic so that patients can receive quality care. The activities related to cleanliness, upkeep of the hospital environment, and adequate sanitation services to keep the premises free of pollution are included in the hospital housekeeping services. Innovative training methods are required for this category, especially when their level of education is below average. Increasing awareness and general knowledge of diabetes can benefit them in the healthcare field.

India is on track to become the world’s diabetic capital, resulting in 0.9 million deaths directly or indirectly. In the low and middle socioeconomic classes, where diabetes knowledge is lacking, 80% of all diabetes cases were found [7]. It is essential to understand the knowledge of housekeeping workers as they generally have low economic status and education level. Proper knowledge and the right attitude can assist them in determining their risk of diabetes, motivating them to seek proper treatment and care, inspiring them to take charge of their disease for the rest of their lives and reduce the financial burden caused due to treatment. There is a dearth of literature in the current study area. Therefore, we have conducted this survey to assess housekeeping employees’ knowledge and attitude regarding diabetes risk factors, complications, and prevention at a tertiary care center in India.

Materials and methods
Study design
A cross-sectional study was carried out between May 2022 and April 2023 using a questionnaire.

Study participants
Study participants were housekeeping staff working in a tertiary care center.

Study criteria
A total of 287 housekeeping staff working in a tertiary care center aged 18–60 years were included. Those who did not know how to read and write were excluded from this study, as a third party who comes to assist them will probably be biased. As a result, it is not a response based on the participant’s own knowledge.

Questionnaire design and validation
After reviewing the literature, the questions were collected and sorted under two domains: knowledge and attitude. The questionnaire was sent to five subject experts for validation. They assessed whether the questions effectively captured the topic under investigation and contained common errors such as double-barreled, confusing, or leading questions. After collecting responses from experts, the questionnaire was modified. A modified questionnaire, each of the English and Kannada versions, was sent to the housekeeping staff of another setting for further validation. Participants were asked to comment on the questionnaire’s clarity, format, and length. Responses from them were analyzed to check the efficacy of the questions. The Cronbach’s alpha coefficient for questionnaire reliability statistics was 0.807. After completion of validation, the questionnaire was used for the study.

Data collection
The study was carried out after approval from the Institutional Ethics Committee, Kasturba Hospital, Manipal (IEC2: 402/2022). The study’s objective was explained to every participant, and they were all given the assurance that their data would only be used for academic research and that it would be kept in strict confidence. Written informed consent was taken prior to the conduct of the study. The questionnaire was
distributed to all participants to measure their knowledge and attitude towards diabetic complications. The questionnaire (in English or regional language) form consists of “multiple choices” and “yes” or “no” questions pertaining to diabetes and its complications. The questionnaire was divided into three sections — Section 1 consisted of socio-demographic details. It included gender, age, educational status, family history of diabetes, duration of diabetes, and previously counseled about diabetes. Section 2 consisted of knowledge questions. A few questions will be given to evaluate their knowledge of diabetes, its risk factors, and complications. These questions are just intended to test their diabetes knowledge. Section 3 consisted of attitude questions. These questions were some statements about their feelings, thoughts, and opinions on diabetes and its complications. The participants were provided with the version of the questionnaire selected by them. The average time taken by participants to fill out the questionnaire was less than 10 minutes.

Statistical analysis
Data was entered in Microsoft Excel and analyzed using Excel EZR and Statistical Package for Social Science (SPSS) version 20. All categorical data were expressed in frequency and percentage. Mean and Standard Deviation were used to present knowledge and attitude levels. Karl Pearson correlation coefficient analysis was performed to find the correlation between them. Multivariable linear regression modeling was applied to determine the variable associated with diabetes-related knowledge and attitude. All associations were considered significant at the alpha level of 0.05.

Results
Characteristics of the study group
A total of 287 housekeeping staff working at the tertiary care center under the Quess Corp Limited (QUESS) department participated in the survey. Female participants were more predominant in the study (73.9%) than the male participants (26.1%). Most respondents (59.2%) were aged between 31 and 45. In our study, most of the participants were free from diabetes (88.9%). More than 50% of the study participants did not know that family history, high BP, mental stress, sedentary lifestyle, overweight, age (older than 45), alcohol consumption, and smoking were risk factors for diabetes. A maximum number of participants in the study were unaware that retinopathy, cataract, foot ulceration, neuropathy, nephropathy, hearing impairment, and skin lesions are the complications of diabetes. When compared to other diabetes control measures, the majority of the participants (84%) were aware of the significance of diet (Tab. 2).

Distribution of respondents based on knowledge of diabetes
In our study, 192 (66.9%) participants were aware that diabetes could affect the kidneys, and 150 (52.3%) knew that diabetes could affect the feet. However, more than half of the study participants were unaware that diabetes could affect the eyes, nerves, heart, lungs, and brain. Most respondents were aware that polyuria is a symptom of diabetes compared to other symptoms. More than 50% of the study participants did not know that family history, high BP, mental stress, sedentary lifestyle, overweight, age (older than 45), alcohol consumption, and smoking were risk factors for diabetes. A maximum number of participants in the study were unaware that retinopathy, cataract, foot ulceration, neuropathy, nephropathy, hearing impairment, and skin lesions are the complications of diabetes. When compared to other diabetes control measures, the majority of the participants (84%) were aware of the significance of diet (Tab. 2).
response/total potential correct response × 100% = 595/2009 × 100% = 29.6% (poor knowledge). The study respondents’ mean knowledge score was (16.24 ± 6.74). This suggests that the majority of respondents were unfamiliar with diabetes.

Distribution of respondents based on attitude toward diabetes

One hundred and sixty (55.7%) respondents agreed that eating sweets occasionally is all right, while 127 (44.3%) disagreed. Few (6.3%) believe that forgetting to take medicine is all right, while the majority (93.7%) disagree. 34.8% of respondents agreed that control of diabetes is difficult to achieve, but 65.2% of respondents disagreed. Most respondents (67.9%) agreed that using tobacco increases the complications of diabetes, while 92 (32%) disagreed. Diabetes being prevented through eating good green vegetables and fruits were agreed upon by 282 (98.3%) of respondents; avoiding extra cooking oil and fat in the diet was agreed upon by 239 (83.3%); using regular exercise was agreed upon by 277 (96.5%); and taking extra care of foot examination was agreed upon by 264 (92%).

Finally, 265 (92.3%) agreed that regular blood pressure checks can help avoid diabetes (Fig. 1).

The mean attitude score of the study participants was (7.22 ± 1.27). However, the respondents had a positive attitude toward the illness. Most respondents thought they were in charge of their own care, suggesting they were willing to change if properly motivated or educated.

A statistically significant weak correlation existed between knowledge and attitude score (p < 0.01). Multiple linear regressions for the total knowledge scores and total attitude scores on socio-demographic characteristics showed that the overall knowledge and attitude score was statistically significant, and the people who were previously counseled also showed statistically significant. Other characteristics showed that there was no statistical significance (Tab. 3).

Discussion

Diabetes knowledge and attitude are not constant subjects; they vary greatly from person to person based on socioeconomic conditions, cultural beliefs, educational level, and personal preferences. The gender distribution of study participants revealed that most study participants were females. The study included 73.9% females. Some similar studies on the prevalence of diabetes or its risk factors had a female predominance [13]. Most participants (59.2%) were between 31 and 45 years. A study conducted in Puducherry, India, which reports that age is one of the major concerns for the development of diabetes, reveals similar results [14]. According to the current study, most participants (48.8%) had primary education, and 40.8% had secondary education, with PUC and graduation accounting for 9% and 1%, respectively. A recent study found that twelve percent of the participants were uneducated or did not finish primary school, which contradicts our findings [15].

Table 2. Respondents Knowledge about Various Aspects of Diabetes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Category</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affected body parts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>Yes</td>
<td>192 (66.9%)</td>
</tr>
<tr>
<td>Feet</td>
<td>Yes</td>
<td>150 (52.3%)</td>
</tr>
<tr>
<td>Eyes</td>
<td>Yes</td>
<td>108 (37.6%)</td>
</tr>
<tr>
<td>Nerves</td>
<td>Yes</td>
<td>45 (15.7%)</td>
</tr>
<tr>
<td>Heart</td>
<td>Yes</td>
<td>87 (30.3%)</td>
</tr>
<tr>
<td>Lungs</td>
<td>Yes</td>
<td>32 (11.1%)</td>
</tr>
<tr>
<td>Brain</td>
<td>Yes</td>
<td>29 (10.1%)</td>
</tr>
<tr>
<td><strong>Symptoms of diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyuria</td>
<td>Yes</td>
<td>216 (75.3%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Yes</td>
<td>69 (24%)</td>
</tr>
<tr>
<td>Polyphagia</td>
<td>Yes</td>
<td>109 (38%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Yes</td>
<td>139 (48.4%)</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>Yes</td>
<td>50 (17.4%)</td>
</tr>
<tr>
<td>Mental confusion</td>
<td>Yes</td>
<td>49 (17.1%)</td>
</tr>
<tr>
<td><strong>Risk factors for diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>Yes</td>
<td>109 (38%)</td>
</tr>
<tr>
<td>High BP</td>
<td>Yes</td>
<td>119 (41.5%)</td>
</tr>
<tr>
<td>Mental stress</td>
<td>Yes</td>
<td>97 (33.8%)</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>Yes</td>
<td>73 (25.4%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>Yes</td>
<td>99 (34.5%)</td>
</tr>
<tr>
<td>Age (older than 45)</td>
<td>Yes</td>
<td>61 (21.3%)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Yes</td>
<td>73 (25.4%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
<td>74 (25.8%)</td>
</tr>
<tr>
<td><strong>Complications of diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Yes</td>
<td>160 (55.7%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>Yes</td>
<td>78 (27.2%)</td>
</tr>
<tr>
<td>Foot ulceration</td>
<td>Yes</td>
<td>130 (45.3%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Yes</td>
<td>39 (13.6%)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Yes</td>
<td>88 (30.8%)</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>Yes</td>
<td>18 (6.3%)</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>Yes</td>
<td>82 (28.6%)</td>
</tr>
<tr>
<td><strong>Diabetes management</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Yes</td>
<td>171 (59.6%)</td>
</tr>
<tr>
<td>Diet</td>
<td>Yes</td>
<td>241 (84%)</td>
</tr>
<tr>
<td>Exercise</td>
<td>Yes</td>
<td>287 (65.2%)</td>
</tr>
<tr>
<td>Regular checkup</td>
<td>Yes</td>
<td>145 (50.5%)</td>
</tr>
</tbody>
</table>


Our findings revealed that 11.1% of participants had been diagnosed with diabetes. In the current study, 3.5% of individuals had diabetes for less than a year, 5.9% for one to five years, 1.7% for five to ten years, and 0.7% for more than ten years. In another investigation, the distribution of participants based on how long they had been diagnosed with diabetes revealed that 30.9% had suffered from the disease for five to ten years [13], which was opposite to our study. 56.8% of those surveyed had undergone at least one diabetes counseling session from a healthcare provider in any context, and 43.2% were unaware of diabetes in general. They are unaware that this condition is linked to blood glucose levels. This shows that diabetes counseling provided by healthcare providers may help enhance public awareness of the disease [16].

In the current study, participants’ knowledge was assessed based on their comprehension of diabetes, which covered affected body areas, symptoms, risk factors, complications, along with care options. In our study, the overall knowledge score (32%) on the diabetes-affected body parts is low. The majority of those surveyed believed that diabetes most frequently affected the eye, according to Namperumalsamy et al. [17]. It is essential to understand how diabetes affects the body. It can assist us in adhering to our treatment plan and maintaining our health.

Excessive urination was identified as a diabetes symptom by a substantial proportion of respondents (75.3%) compared to other diabetes symptoms. The overall knowledge score (36.7%) on diabetes symptoms is low. In another investigation, only 62.5% were aware of the asymptomatic nature, and an almost identical proportion (63.5%) were aware of polyphagia as a symptom of T2D patients [18]. Our participants’ knowledge of risk factors was 30.7%; the majority did not recognize old age, obesity, high blood pressure, sedentary lifestyle, and a family history of diabetes as risk factors for diabetes.

Diabetes self-management requires a thorough understanding of the disease and its complications. It is essential for the decrease of inappropriate behaviors and the subsequent prevention and reduction of disease-related consequences. Most of the participants in this study had insufficient knowledge of diabetes complications. The overall knowledge score on diabetes complications is low (29.6%). The most common diabetes complications, according to

![Figure 1. Attitude of Respondents towards Diabetes Prevention and Cure](image-url)
a previous study by Sharma et al. in North India, were nephropathy (45.2%), retinopathy (47.3%), the heart (14.1%), the lungs (10.8%), the brain (8.3%), and the feet (5%) [16]. In our study, most participants (84%) understood the significance of diet, while 65.2% also knew the importance of exercise, 59.6% understood the significance of medication, and 50.5% understood the significance of routine checkups in preventing the development of diabetes.

The mean knowledge score of our study participants was 16.24 ± 6.74. This indicates that most respondents had limited knowledge of diabetes. This opposes the findings of other research carried out in South India by Hussain R et al. and Rani PK et al., who found that 40.7% and 49.9% of their individuals were knowledgeable [19, 20]. It is suggested that some standard diabetes awareness educational events be organized to raise public knowledge of this hidden and curable illness with numerous complications that exert significant pressure on the national healthcare system.

Individuals’ attitudes towards a particular subject are defined by whether they have preconceived ideas about it and how they indicate their knowledge in order to control that specific condition. The mean attitude score of our study participants was (7.22 ± 1.27). Most of our respondents had favorable attitudes towards diabetes prevention. It is unexpected that the knowledge score was low, but the attitudes were higher. Another similar study found that the average attitude of study participants was (3.29 ± 1.15). The patients’ attitudes towards balancing their diet, exercise, and medication control of diabetes and their approach to the doctor were also good [13].

Statistically significant mild correlations between knowledge and attitude scores were found despite this outcome. There is a weak but statistically significant association between participant knowledge and attitude scores ($r = 0.215$, $p < 0.01$). In another research study on diabetic KAP, it was discovered that knowledge as well as attitude had a strong correlation ($r = 0.5308$, $p < 0.01$) [21]. Regular medical education programs on diabetes should be conducted to keep people up to date on the disease so that they are better aware and educated.

**Limitation**

This study was conducted in a single center. The questionnaire form consists of multiple-choice questions. This does not provide an opportunity for the participant to think on their own, and they might choose random options.

**Conclusions**

This study found that housekeeping staff had a poor knowledge about diabetes but showed a positive attitude towards diabetes prevention. There was a weak correlation between knowledge and attitude scores. More research is required to explore the effect of cleaning staff members on the rate of diabetes, as well as the association between morbidity and mortality rates among housekeepers after increasing their performance.

**Article information**

**Data availability statement**

Data of the study will be available on request.

**Ethics statement**

The project was approved by the institutional ethics committee.

**Author contributions**

All authors are responsible for the study conception and design, data collection, analysis, interpretation of results and manuscript preparation.

| Table 3. Comparison of Knowledge and Attitude Scores with Socio-Demographic Characteristics |
|---------------------------------------------|----------|----------|
| **a. Knowledge and Attitude** | **F-value** | **P-value** |
| Gender | 0.759 | 0.469 |
| Age | 0.758 | 0.470 |
| Education | 1.236 | 0.292 |
| Family history of diabetes | 0.501 | 0.607 |
| Diabetes | 2.769 | 0.064 |
| Duration of diabetes | 1.591 | 0.206 |
| Previously counselled for diabetes | 12.847 | 0.000*** |

| **B. Knowledge** | **F-value** | **P-value** |
| Gender | 0.290 | 0.590 |
| Age | 0.270 | 0.603 |
| Education | 0.378 | 0.539 |
| Family history of diabetes | 0.956 | 0.329 |
| Diabetes | 1.242 | 0.266 |
| Duration of diabetes | 1.129 | 0.289 |
| Previously counselled for diabetes | 1.658 | 0.199 |

| **C. Attitude** | **F-value** | **P-value** |
| Gender | 0.943 | 0.332 |
| Age | 0.966 | 0.326 |
| Education | 2.395 | 0.123 |
| Family history of diabetes | 0.000 | 0.991 |
| Diabetes | 3.221 | 0.074 |
| Duration of diabetes | 1.391 | 0.239 |
| Previously counselled for diabetes | 25.738 | 0.000*** |

***$p < 0.05$ is statistically significant
**Funding**
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**Acknowledgements**
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**Conflict of interest**
The authors declare that there is no conflict of interest.

**REFERENCES**

Effectiveness of Theory-Based Intervention on Knowledge Level, Psychological Constructs, Metabolic Index and Physical Activity Status in Patients with Type 2 Diabetes: Application of the Health Action Process Approach (HAPA) Model

ABSTRACT
Objective: The aim of the study was to determine the effect of the educational intervention based on the health action process approach (HAPA) model on the level of knowledge, metabolic indicators, psychological constructs and physical activity status in type 2 diabetes (T2D) patients in 2022–2023.

Material and methods: The present study was a randomized controlled trial and 100 T2D patients were equally assigned to experimental and control groups using multi-stage random sampling. The educational program included six online sessions, targeted pamphlets, educational audio files and reminder messages. Data were collected before and 3 months after intervention with demographic items, awareness scale, constructs of HAPA model, IPAQ-s, HbA1c and fasting blood glucose (FBG). Data were entered to SPSS 25.0 and analyzed with chi-square, ANOVA and ANCOVA.

Results: After controlling the effect of the pre-test variable, the mean of the HAPA model constructs and mean of physical activity improved significantly in posttest. In addition, educational intervention explained 30.2%, 57.8%, 33.2%, 64.4%, 76.3%, 25.3%, 24.6%, 36.1% and 36.9% of the variance of health awareness, risk perception, outcome expectancy, action self-efficacy, maintenance self-efficacy, action plan, coping plan, behavioral intention and physical activity, respectively. In addition, the mean of FBG and HbA1c in the experimental group improved significantly after the intervention by controlling the pre-test effect (p < 0.001).

Conclusions: Providing theory-based educational interventions through the web and mobile can increasingly promote the effectiveness of cognitive behavioral interventions and facilitate the process of behavior change in T2D. (Clin Diabetol 2023; 12; 5: 290–300)

Keywords: diabetes, self-efficacy, mobile-based education, physical activity, HbA1c, risk perception
Introduction

Behavior change in people with chronic diseases can prevent serious complications and reduce mortality [1]. Type 2 diabetes (T2D) patients can effectively prevent short-term and chronic complications of diabetes by following a low-calorie diet, regular and sufficient exercise, and following a medication regimen [2]. The key role of regular physical activity in the management of T2D, reducing chronic consequences and improving quality of life has been proven [3, 4]. Despite the vital role of physical activity in controlling the complications of T2D, estimates indicate that 37–60% of T2D patients do not exercise, and this low amount worsens with age [5].

Diabetes self-management education is a cost-effective strategy and leads to an increase in the level of knowledge and improvement of psychological and clinical outcomes [6, 7]. Moreover, in most secondary prevention programs such as cardiac rehabilitation (CR), patient education is considered a central component and structural quality indicator [8]. Education can have a positive effect on health awareness, silent beliefs, perceived risk and self-efficacy [9]. There is a significant relationship between the effectiveness of educational interventions and the logical application of behavior change models [10]. One of the widely used behavior change model for planning effective educational interventions is the Health Action Process Approach (HAPA) model [11]. Based on HAPA model, it can be assumed that performing a specific behavior by people requires passing through two motivational and voluntary stages. In the motivational phase, risk perception, outcome expectancy and action self-efficacy affect behavioral intention. Subsequently, people prepare themselves to adopt a certain behavior and make decisions related to it. After the formation of behavioral intention, people enter the volitional stage, which consists of the constructs of action and coping plan, and maintenance and recovery self-efficacy [12, 13]. The HAPA model has been used many times to describe variables affecting physical activity in different groups such as patients with diabetes [14–16].

In addition to the application of the appropriate model, one of the main challenges facing health education experts is the preparation of health education programs based on needs assessment and appropriate to patients’ experiences and interests [17]. Indirect and virtual education is able to overcome the obstacles of face-to-face education, such as crowding of health care centers, different educational needs of patients, lack of diversity in educational programs, unfamiliarity with educational principles, lack of time, and insufficient response to the educational demands of patients along with irregular referrals [18, 19]. The findings of previous studies showed that mobile-based interventions can be used as a therapeutic strategy to optimize the management and treatment of diabetes [20].

Therefore, considering the increasing prevalence of T2D in Iran and its serious consequences, the importance of using behavior change models to design educational interventions, the efficiency of mobile-based educational programs on improving clinical indicators and preventing disease complications, the present study was designed with the aim of determining the effect of the educational intervention based on the HAPA model on the level of knowledge, metabolic indicators, psychological constructs and physical activity status in T2D patients in 2022–2023.

Material and methods

Study design

The current study was a randomized controlled trial that was conducted from June 2022 to February 2023 in Qazvin city (trial registration code IRCT20210509051229N1). Using a pretest-posttest design, the effectiveness of theory-based educational intervention was evaluated regarding the level of knowledge, metabolic indicators, psychological constructs, and physical activity status in T2D patients.

Study population

All adults with type 2 diabetes covered by the comprehensive health care centers of Qazvin city participated in the present study as the target population. The sample size was calculated using G*Power software, confidence level 95%, test power 80% and impact factor 0.5. Finally, 50 T2D patients were selected to participate in each of the experimental and control groups.

The inclusion criteria were: 1) having type 2 diabetes with a definitive diagnosis of more than 6 months; 2) age 18 to 60 years and living in the Qazvin city; 3) registration of fasting blood glucose (FBG) more than 140 mg % during of two visits at least a month apart; 4) not suffering from diabetic foot ulcer (grade 2 and higher based on Wagner criteria and clinic expert confirmation); 5) an ability to communicate, read and write the Persian (Farsi) language; 6) having active medical records in health care centers; 7) being able to use a mobile phone equipped with What’s App by the patient or close family members.

Family members participated in the research if they had the following characteristics: 1) living in the Qazvin city; 2) having enough time to help patients complete the questionnaire or participate in the online education process; 3) being a spouse, child, grandchild, sibling,
or friend, 4) the ability to use what’s App, and 5) aged 18 years or older. All people who were suffering from chronic and severe complications caused by diabetes or suffered from severe physical and mental disorders that might affect the results of the study were excluded from participating in the study.

The exclusion criteria were: Returning incomplete questionnaires or refusing to complete them, non-participation in training sessions (less than 50% of sessions), unwillingness to perform blood glucose and HbA1c tests, suffering from uncontrolled underlying diseases such as high blood pressure despite taking medication (90/160 mmHg), and severe disability such as blindness, limb amputation, cardiovascular diseases and renal failure, using any type of psychoactive drugs.

In order to evaluate the effect of the intervention on the knowledge level, psychological constructs, metabolic index and physical activity status in patients with type 2 diabetes in Qazvin city, a single-blinded randomized controlled trial was designed and implemented.

Among the comprehensive health care centers of Qazvin city, in which diabetes education programs were not implemented, 5 centers were randomly selected. A list of all patients was prepared based on the inclusion criteria, and after obtaining their informed consent to participate in the trial, they were randomly assigned to control and experimental groups (ratio of 1:1). A matte envelope was prepared from a sequence of computer-generated random numbers to facilitate allocation. All participants signed a written consent form before starting the study and completing the questionnaires in the first phase. The research team provided full explanations about the objectives and the necessity of providing real answers and also completing all the items in the first phase of the trial and were excluded from the final study — were asked to complete the mentioned scales within two-week interval. The data included in the Supplementary Table 1 confirmed the validity and reliability of the HAPA related subscales.

E) International Physical Activity Questionnaire short (IPAQ-s): According to the IPAQ-s guideline, the total intensity of the physical activities performed by a person according to the energy consumed in the last 7 days is placed in one of three groups: light, medium and heavy. To calculate the total amount of physical activity per week, the amount of walking (metabolic rate × minutes × day) should be added to the amount of moderate and intense physical activity in the last week. The IPAQ-s has been used in many studies and its validity and reliability have been confirmed in Iranian studies [24]. The questionnaire was completed both online and in person by the T2D patients in approximately 35 to 40 minutes. The research team emphasized the importance of providing correct and accurate answers, the necessity of providing real answers and also completing all the items in the first phase of the trial and before completing the questionnaires. All participants answered the questions in two stages — before the theory based education and 3 months after the educational intervention.

Educational intervention program

Due to the conditions caused by the COVID-19 pandemic and to comply with health protocols, the educational program was designed using the capabilities of mobile phones and its applications. After forming virtual groups of 6–9 people on what’s App, educational content based on the constructs of the
HAPA model was presented in 6 online sessions for 6 weeks. The time (day and hour) of all the educational sessions was set with the coordination and opinion of the majority of the participants and was informed to all the T2D patients by phone call a week ago. In addition, two text messages (one day and one hour before the online educational session) were also sent to each patient to remind them of the time and purpose of the session. The duration of the training sessions — with the exception of the last session — was approximately 45 minutes, which sometimes lasted up to an hour due to the questions and answers at the end of the sessions. In each session, the educators presented a short speech of 10–15 minutes focusing on the general and specific goals. Then, the speaker presented main topics and then, the participants were asked to express their opinions about it. A summary of the educational content presented at the end of the training session and possible ambiguities were resolved using the question-answer method.

The content of each session was recorded and placed in the virtual group immediately after each session. A targeted training pamphlet along with an educational audio file was also considered for further training for each session. Five educational messages — which were summaries of the content presented in each session — were also presented to each participant in the interval between the sessions. The objectives of the sessions were as follows:

**The first session:** increasing knowledge (regarding diabetes risk factors, the causal relationship between diabetes and physical activity, the role of physical activity in regulating metabolism), **the second session:** the perceived risk and consequences expectancy (physical, psychological and social consequences of diabetes, positive consequences of adequate physical activity, reduction of negative emotions and replacement of positive thoughts and emotions). **The third and fourth sessions:** action and maintenance self-efficacy (identification of individual, environmental and motivational factors affecting the continuation of physical activity, expressing the successful experiences of patients, verbal encouragement from significant others, improving coping skills appropriate to an inactive lifestyle), **the fifth session:** action and coping plan (providing an action plan for physical activity for the elderly with diabetes and personalizing it, methods for assessing physical activity status, identifying barriers to regular physical activity and providing solutions. **Sixth session:** individual ten-minute face-to-face or online consultation (expressing problems, progress rate, providing feedback, strengthening individual motivations and providing environmental stimuli).

During the online training program, no specific training program was considered for the control group. Nevertheless, to comply with research ethics, an intensive training program including two online training sessions along with all training content was presented to the control group after the 3-month follow-up phase. The steps of conducting the study are shown in the consort Figure 1.
Statistical analysis

The data were entered into SPSS 25.0 and the Kolmogorov Smirnov test was used to evaluate the normality of data distribution. Chi-square test, independent t-test, one-way ANOVA, and ANCOVA tests were used to compare the difference between the two groups and also the effect of the educational intervention on the psychological variables, FBG and physical activity by controlling the pre-test effect. The significance level was considered less than 0.05 in the current study.

Ethical considerations

All stages and processes of the research, from data collection to the implementation of interventions, have been approved by the Ethics Committee of Qazvin University of Medical Sciences (IR.QU.MS.REC.1400.029). The study has been approved by TCTR Committee on 30 August 2022. The TCTR identification number is IRCT20210509051229N1. Voluntary participation in the research, anonymity of the questionnaires, confidentiality of all information and other rights of the participants were explained to them before the study.

Results

The mean age of the participants was 54.3 ± 10.33 years and 69% of the patients were women. Respectively, 93% and 28% of the T2D patients were married and employed, and 40% had a family history of diabetes. Comparison of demographic characteristics did not show significant difference between the two groups before the theory-based educational intervention. More information is shown in Table 1.

The findings related to the comparison of the mean of the HAPA model constructs in the pre-test stage and 3 months after the theory-based educational intervention in the experimental and control groups are shown in Table 2. The results indicate that there was no significant difference between the two groups before the theory-based educational intervention, but the results of the paired t-test showed a significant increase in the mean of the HAPA model constructs in the experimental group after the educational intervention (p < 0.001). In addition, the comparison of the physical activity status of T2D patients participating in the experimental and control groups before and after the theory based educational intervention is shown.

### Table 1. Comparison of Demographic Characteristics between Patients Participating in the Experimental (n = 50) and Control (n = 50) Groups before the Educational Intervention

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Control group frequency (%)</th>
<th>Experimental group frequency (%)</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td></td>
<td>55.7 (12.3)</td>
<td>54.6 (10.6)</td>
<td>0.335</td>
</tr>
<tr>
<td>BMI' [kg/m²]</td>
<td></td>
<td>27.34 (3.46)</td>
<td>27.86 (3.78)</td>
<td>0.426</td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
<td>(6.85) 7.13</td>
<td>(7.00) 7.26</td>
<td>0.511</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Male 14 (28.0)</td>
<td>17 (34.0)</td>
<td>0.644</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female 36 (72.0)</td>
<td>33 (66.0)</td>
<td></td>
</tr>
<tr>
<td>Economic status</td>
<td></td>
<td>Excellent 6 (12.0)</td>
<td>4 (8.0)</td>
<td>0.356</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good 11 (22.0)</td>
<td>9 (18.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medium 23 (46.0)</td>
<td>25 (50.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 10 (20.0)</td>
<td>12 (24.0)</td>
<td></td>
</tr>
<tr>
<td>Marriage status</td>
<td></td>
<td>Married 47 (94.0)</td>
<td>46 (92.0)</td>
<td>0.822</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single, divorced, others 3 (6.0)</td>
<td>4 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Job</td>
<td></td>
<td>Employed 13 (26.0)</td>
<td>15 (30.0)</td>
<td>0.650</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Housewife 31 (62.0)</td>
<td>30 (60.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unemployed 6 (12.0)</td>
<td>5 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td>Elementary and mid school 11 (22.0)</td>
<td>13 (26.0)</td>
<td>0.493</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High school and diploma 32 (64.0)</td>
<td>31 (62.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>University 7 (14.0)</td>
<td>6 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Family history of T2D</td>
<td></td>
<td>Yes 28 (56.0)</td>
<td>26 (52.0)</td>
<td>0.818</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No 22 (44.0)</td>
<td>24 (48.0)</td>
<td></td>
</tr>
<tr>
<td>Treatment type</td>
<td></td>
<td>Hypoglycemic drugs 24 (48.0)</td>
<td>26 (52.0)</td>
<td>0.577</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin 14 (28.0)</td>
<td>11 (22.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoglycemic drug + insulin 12 (24.0)</td>
<td>13 (26.0)</td>
<td></td>
</tr>
</tbody>
</table>

BMI — body mass index; T2D — type 2 diabetes
in Table 2. Although there was no significant difference between the two groups before the educational intervention, the results of the paired t-test showed a significant increase in the mean of physical activity after the theory-based educational intervention in the experimental group (p < 0.001).

The results of the analysis of covariance regarding the effect of the educational intervention based on the HAPA constructs by controlling the effect of the pre-test are showed in Table 3. The findings have shown that by controlling the effect of the pre-test variable, the mean of the HAPA constructs and mean score of physical activity improved significantly after the theory-based educational intervention. In addition, based on the Eta coefficient, it can be concluded that the educational intervention explained 30.2%, 57.8%, 33.2%, 64.4%, 76.3%, 25.3%, 24.6%, 36.1% and 36.9% of the variance of health awareness, risk perception, outcome expectancy, action self-efficacy, maintenance self-efficacy, action plan, coping plan, behavioral intention and physical activity, respectively.

Table 4 shows the results related to the comparison of FBG and HbA1c in experimental and control group patients before and after theory-based educational intervention. The results showed that there was no significant difference between the two groups in terms of the mentioned metabolic indicators before the educational intervention; however, the results of the paired t-test showed a significant decrease in mean of FBG and HbA1c after the theory-based educational intervention in the experimental group (p < 0.001).
Discussion
The current study was conducted with the aim of investigating the effectiveness of the theory-based educational intervention regarding using the HAPA model constructs on the health knowledge, metabolic indicators, and physical activity status in T2D patients. The results of the study showed the positive effect of theory-based educational intervention on psychological constructs such as risk perception, outcome expectation, self-efficacy, action and coping planning, knowledge level, metabolic indicators and physical activity level in T2D patients.

Most of behavior change models emphasize on increasing the amount of knowledge, improving awareness, access to information and proper risk perception. In fact, raising knowledge level is the first steps in changing behavior process. In the present study, the level of knowledge of T2D patients in the experimental group improved significantly after the theory-based educational intervention, which was in line with the findings of previous studies [25–27].

Table 3. The Results of the Analysis of Covariance Regarding the HAPA Constructs in the Post-Test Phrase

<table>
<thead>
<tr>
<th>Constructs</th>
<th>Sources</th>
<th>Type III sum of squares</th>
<th>df</th>
<th>Mean square</th>
<th>F</th>
<th>Sig</th>
<th>Partial eta squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health awareness</td>
<td>pre</td>
<td>427.378</td>
<td>1</td>
<td>427.378</td>
<td>42.978</td>
<td>p &lt; 0.001</td>
<td>0.259</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>529.195</td>
<td>1</td>
<td>529.195</td>
<td>53.217</td>
<td>p &lt; 0.001</td>
<td>0.302</td>
</tr>
<tr>
<td>Risk perception</td>
<td>pre</td>
<td>3789.392</td>
<td>1</td>
<td>3789.392</td>
<td>636.848</td>
<td>p &lt; 0.001</td>
<td>0.838</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>1001.022</td>
<td>1</td>
<td>1001.022</td>
<td>168.233</td>
<td>p &lt; 0.001</td>
<td>0.578</td>
</tr>
<tr>
<td>Outcome expectancy</td>
<td>pre</td>
<td>2146.929</td>
<td>1</td>
<td>2146.929</td>
<td>486.627</td>
<td>p &lt; 0.001</td>
<td>0.796</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>270.586</td>
<td>1</td>
<td>270.586</td>
<td>61.332</td>
<td>p &lt; 0.001</td>
<td>0.332</td>
</tr>
<tr>
<td>Action self-efficacy</td>
<td>pre</td>
<td>1782.043</td>
<td>1</td>
<td>1782.043</td>
<td>328.824</td>
<td>p &lt; 0.001</td>
<td>0.728</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>1207.897</td>
<td>1</td>
<td>1207.897</td>
<td>222.882</td>
<td>p &lt; 0.001</td>
<td>0.644</td>
</tr>
<tr>
<td>Maintenance self-efficacy</td>
<td>pre</td>
<td>574.524</td>
<td>1</td>
<td>574.524</td>
<td>206.867</td>
<td>p &lt; 0.001</td>
<td>0.627</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>1099.557</td>
<td>1</td>
<td>1099.557</td>
<td>395.915</td>
<td>p &lt; 0.001</td>
<td>0.763</td>
</tr>
<tr>
<td>Action plan</td>
<td>pre</td>
<td>434.781</td>
<td>1</td>
<td>434.781</td>
<td>63.711</td>
<td>p &lt; 0.001</td>
<td>0.348</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>273.210</td>
<td>1</td>
<td>273.210</td>
<td>40.035</td>
<td>p &lt; 0.001</td>
<td>0.253</td>
</tr>
<tr>
<td>Coping plan</td>
<td>pre</td>
<td>489.200</td>
<td>1</td>
<td>489.200</td>
<td>67.343</td>
<td>p &lt; 0.001</td>
<td>0.335</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>286.615</td>
<td>1</td>
<td>286.615</td>
<td>41.622</td>
<td>p &lt; 0.001</td>
<td>0.246</td>
</tr>
<tr>
<td>Behavioral intention</td>
<td>pre</td>
<td>320.512</td>
<td>1</td>
<td>320.512</td>
<td>122.518</td>
<td>p &lt; 0.001</td>
<td>0.499</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>181.494</td>
<td>1</td>
<td>181.494</td>
<td>69.377</td>
<td>p &lt; 0.001</td>
<td>0.361</td>
</tr>
<tr>
<td>Physical activity</td>
<td>pre</td>
<td>1455.602</td>
<td>1</td>
<td>1455.602</td>
<td>73.851</td>
<td>p &lt; 0.001</td>
<td>0.372</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>1438.548</td>
<td>1</td>
<td>1438.548</td>
<td>71.010</td>
<td>p &lt; 0.001</td>
<td>0.369</td>
</tr>
</tbody>
</table>

DF — degrees of freedom; sig — significance

Table 4. Results of the Effect of Mobile-based Educational Intervention on FBG and HbA1c in the Experimental and Control Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Baseline Mean ± SD</th>
<th>Post-intervention Mean ± SD</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBG</td>
<td>Control</td>
<td>157.8 ± 55.46</td>
<td>150.7 ± 50.45</td>
<td>0.119</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>161.3 ± 59.82</td>
<td>118.1 ± 23.45</td>
<td>p &lt; 0.011</td>
</tr>
<tr>
<td></td>
<td>**P-value</td>
<td>0.275</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>Control</td>
<td>7.46 ± 1.85</td>
<td>7.53 ± 1.94</td>
<td>0.277</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>7.23 ± 1.74</td>
<td>6.20 ± 1.12</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>**P-value</td>
<td>0.303</td>
<td>p &lt; 0.011</td>
<td></td>
</tr>
</tbody>
</table>

*P-value: between control and experimental group; ** P-value: pre-post intervention; FBG — fasting blood glucose; HbA1c — glycated hemoglobin; SD — standard deviation
In line with previous researches, the results of the present study showed the improvement of FBG and Hba1c levels in the experimental group after the theory-based educational intervention [25–28]. Abaza and Marschollek (2012) emphasized that SMS based education to promote self-management caused a 1% decrease in Hba1c in middle and low-income patients [27]. Chen (2019) also emphasized that the use of a mobile app led to the improvement of self-care behaviors and a reduction in the severity of diabetes in the elderly [29]. The study of the effect of mobile-delivered diabetes prevention program on long-term weight loss and blood glucose levels by Toro-Ramos et al. (2020) showed a 0.28 percent reduction in blood glucose in patients with pre-diabetes [30]. These results confirm that providing a theory-based educational program using mobile phone capabilities can have positive effects on patients’ Hba1c control. The main goal of treating patients with diabetes is to achieve optimal control (Hba1c less than 7%), which is related to the reduction of morbidity and mortality. In addition, blood glucose control has a significant relationship with better quality of life, and poor blood glucose control in T2D patients is considered a form of stress that has an adverse effect on the quality of life of these patients. In addition, considering that a 1% increase in this variable causes a 12% increase in coronary artery diseases, therefore, the reduction of this index should be considered by all health care personnel in various counseling programs and cognitive behavioral interventions. Clinical indicators such as Hba1c and FBG have a significant relationship with LDL, HDL, BMI and the amount of physical activity, and adding a regular physical activity program and weight loss program can significantly increase the effectiveness of interventions.

The significant improvement of the mean of outcome expectancy in the T2D patients is another important finding of the current study, which was consistent with the results of previous studies [22, 29, 31]. The results of Aliabad et al. (2014) research with the aim of evaluating the effect of the intervention based on the HAPA model and family support in maintaining physical activity capacity in coronary heart patients after discharge showed an improvement in the mean of outcome expectancy and other HAPA related constructs [22]. Outcome expectancy — which is also called behavioral beliefs, decisional balance and perceived barriers/benefits in some studies — is considered as a person’s perception that is the result of a specific behavior and emphasizes the possibility of performing a behavior based on its various consequences Positive consequences (such as improving physical and mental health) and negative consequences (such as the possibility of injury and being time-consuming). Moreover, the predictive feature of physical activity by the outcome expectancy has been emphasized in the meta-analysis of Bohlen et al. (2022) [32]. The emphasis of cognitive behavioral interventions should be on the importance of assessing the benefits and barriers of physical activity in the T2D patients and clarifying the social, physical and mental consequences and providing frequent and diverse emotional feedback through mobile phones can be effective in strengthening behavioral intention and adjusting physical activity.

Another finding of the current research was a significant improvement in the mean score of the social support in the T2D patients, which was consistent with the findings of Liang et al. (2022), and Baillot et al. (2022) [33, 34]. Social support can directly and indirectly strengthen behavior. Direct social support is related to doing physical activity together or performing household tasks such as caring for family members to create opportunities for the individual to be physically active. Indirect support is defined as activities such as encouraging a family members or friends to start an exercise program. Social support has a positive and constructive effect on encouraging people to participate in the changing behavior and improving lifestyle by strengthening self-efficacy [35]. Providing the opportunity to exchange opinions, participation of family members along with their encouragement through the formation of virtual friendly groups in What’s App should be considered as a part of the educational program aimed at preventing and controlling the complications of T2D.

In accordance with the findings of previous researches, the results of the present study also showed a significant increase in the mean of the action and maintenance self-efficacy constructs in the T2D patients after participating in the mobile-based educational program based on the HAPA model [36–38]. People who have strong beliefs about their abilities show more effort and persistence in doing tasks than people who doubt their abilities, and as a result, their performance in doing tasks is better. Human success requires commitment, cooperation and perseverance, which are achieved through self-efficacy [38]. Educational interventions should strengthen self-efficacy by using strategies such as verbal persuasion, self-encouragement, modeling, and using informational feedback. Therefore, health education experts should consider the identification of barriers, facilitators and factors affecting self-efficacy as an important step in increasing the probability of success in achieving predetermined educational goals when designing cognitive behavioral interventions.
Another important result of the current study was the significant improvement of the mean of the action and coping planning in the T2D patients after participating in the mobile-based educational program regarding the HAPA model, which were consistent with the findings of Okati Aliabad et al. (2022), Labudek et al. (2022), and Schröe et al. (2022) [22, 39, 40]. Planning is a prospective self-regulatory strategy that connects individual responses and anticipated situational guiding factors. When interventions are designed, health education experts can reduce the intention-behavior gap by improving self-regulation skills and encourage clients to think about the conditions affecting physical activity. Action planning acts as a reminder to perform a behavior, and even when self-regulation skills and memory capacity are low, planning can play a constructive role in forming healthy behavioral habits [41]. Goal setting, complete description of behavioral goals, describing the steps or processes necessary to achieve the goals, determining the necessary resources, determining the criteria for measuring progress, various solutions to deal with obstacles are part of the strategies used in online training were aimed at strengthening “action and coping planning” to improve physical activity in the T2D patients.

Finally, the results of the present study emphasized the improvement of the physical activity status in the T2D patients participating in a theory-based online educational intervention, which was in line with the results of previous studies [33, 36, 37]. A systematic review of 52 studies focusing on web-based behavior change interventions by Lin et al. (2022) indicated that providing strategies such as self-monitoring of behavior, problem solving, while significantly increasing the mean of the HAPA model constructs and Self-regulation, led to an improvement in the level of physical activity in patients with chronic diseases [36]. Electronic self-care education and telephone follow-up have been introduced as one of the standard programs for continuous and regular patient’s education. Moreover, one of the common instructions to promote a healthy lifestyle is continuous access to up-to-date educational resources, which should be focused on general knowledge of diabetes, self-control of blood glucose, and self-care education [17, 30]. T2D patients can get essential health information without leaving home, save time and money, and communicate effectively with health experts [42]. In addition, inadequate education, irregular follow-ups and age restrictions in the T2D patients are considered effective factors in promoting lifestyle and self-care behaviors, which can be resolved through web-based or mobile-phone based cognitive-behavioral interventions. Considering the importance and acceptability of social networks in strengthening social mobilizations and transferring information, the increasing capabilities of mobile phone applications and sending large volumes of educational text, photos, audios and videos, it is recommended to use this communication channel to increase access to educational resources and facilitate the process of behavior change.

Conclusions

The findings of the study showed that mobile-based educational intervention using HAPA model framework could improve the knowledge level, psychological constructs, Hb1Ac, FBG and the physical activity status in T2D patients. Therefore, considering the importance and acceptability of social networks it is recommended to use the capacities of mobile phones and its applications such as what’s App in the design, implementation and evaluation of theory-based educational interventions.

Strengths and limitations

The strengths of the current study included the design of the educational program based on the HAPA model, mobile-based education, and the randomization of the participants. Nevertheless, the present study also contains limitations, which include: A) the follow-up was done only 3 months after the intervention. Therefore, regular follow-ups at intervals of 6 months and 1 year after the theory-based intervention will make it possible to evaluate the stability of the effect of the educational intervention. B) Only patients from Qazvin city participated in the present study, which prevents the generalization of the results to the T2D patient’s society. Therefore, random selection of T2D patients from rural health centers or other cities will increase the generalizability of the results. C) The results of the educational intervention based on the HAPA model were compared with the control group (lack of training). Therefore, future studies can consider more groups in the trial design to compare different behavior change models or various intervention methods.

Article information

Supplementary materials

The Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/96203#supplementaryFiles

Data availability statement

Upon request, the authors can offer onsite access to external researchers to the data analyzed at Qazvin University of Medical Sciences, Isfahan, Iran.
Ethics statement

The ethics committee of Qazvin University of Medical Sciences approved the present study (IR. QUMS.REC.1400.029). In addition, all participants were aware of the voluntary participation in the research and signed the voluntary participation form. All questionnaires were anonymous and were assured that the information included in the questionnaires would remain confidential.

Authors’ contributions

All authors contributed to this work and commented on the manuscript at all stages, and the last version was approved for publication.

Funding

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Acknowledgments

We would like to thank the participants for their cooperation in this study and to the managers of Qazvin Health care centers for their generous cooperation.

Conflicts of interest

The authors declare that there is no conflict of interest.

REFERENCES


Prevalence of Musculoskeletal Manifestations in Type 2 Diabetes: A Single Centre, Cross-Sectional Study

ABSTRACT
Objective: The study was aimed to evaluate the prevalence of musculoskeletal manifestations in patients with type 2 diabetes (T2D).

Materials and methods: In this single center, cross-sectional study, 300 patients with clinically documented T2D were recruited from the outpatient clinic. Demographics, diabetes history, family history, treatment modalities, musculoskeletal symptoms were self-reported by participants. Anthropometric measurements and musculoskeletal examination were conducted by investigators. Complete blood count, fasting and postprandial plasma glucose, glycated hemoglobin (HbA1c), urine analysis, and X rays of the symptomatic joints were performed.

Results: Of 300 patients with T2D, musculoskeletal manifestations were observed in 50.7%. Osteoarthritis of the knee was the most common manifestation (20.3%) followed by carpal tunnel syndrome (10.7%), adhesive capsulitis (8.3%), diffuse idiopathic skeletal hyperostosis (7.3%), diabetic cheiroarthropathy (6.0%), flexor tenosynovitis (2.3%), and Dupuytren’s contracture (0.7%). Age (p = 0.001), T2D duration (p = 0.004), BMI (p = 0.031) and HbA1c (p= 0.006) were associated with increased prevalence of musculoskeletal manifestations.

Conclusions: Prevalence of musculoskeletal manifestations is higher in people with T2D. Advanced age, longer duration of disease, overweight and high HbA1c levels are associated with increased prevalence of musculoskeletal manifestations. (Clin Diabetol 2023; 12; 5: 301–307)

Keywords: type 2 diabetes, musculoskeletal manifestations, adhesive capsulitis of shoulder, osteoarthritis of knee, carpal tunnel syndrome, diffuse idiopathic skeletal hyperostosis, diabetic cheiroarthropathy

Introduction
Type 2 diabetes (T2D) is an increasing global health problem. In contrast to microvascular complications of diabetes; musculoskeletal manifestations of diabetes are often overlooked, misdiagnosed or managed sub-optimally. These complications may lead to physical disability and impair quality of life. Musculoskeletal manifestations are classified into four broad categories: those that are intrinsic to the disease, those that are...
related to metabolic abnormalities, those that share similar etiological mechanisms, and those that are more prevalent in the patients with diabetes [1, 2].

The exact etiology of diabetes associated with musculoskeletal disorders remains unknown. Evidence indicates that hyperglycemia may accelerate nonenzymatic glycation and abnormal collagen deposition in periarticular connective tissues. The structural matrix and mechanical properties of the musculoskeletal tissues are altered and lead to diffuse arthrofibrosis and stiffness [3].

Studies exploring the prevalence and associated factors of musculoskeletal manifestations of diabetes from India are limited. Therefore, we aimed to evaluate the distribution of different musculoskeletal manifestations in the Indian patients with T2D and the factors associated with them.

**Materials and methods**

**Study design**

In this single-center, cross-sectional study, adults (age 18 and above) with clinical diagnosis of T2D attending the outpatient clinic of Dayanand Medical College and Hospital, a tertiary care center in North India, between January 1, 2020 to June 30, 2021 were invited to participate in this research project. The ethical review board of the institution approved the study. The clinical diagnosis of diabetes was defined as per American Diabetes Association 2007 guidelines; fasting plasma glucose ≥ 126 mg/dL, postprandial plasma glucose ≥ 200 mg/dL, or symptoms of diabetes plus random plasma glucose ≥ 200 mg/dL [4].

Patients with other forms of diabetes such as monogenic diabetes [5], latent autoimmune diabetes in adults (LADA) [6], musculoskeletal manifestations due to non-rheumatological causes (e.g., cerebrovascular accident with frozen shoulder, Dupuytren’s contracture due to alcoholism), pre-existing CKD based on eGFR [7], and history of trauma-related musculoskeletal morbidities were excluded from the study.

The following criteria were used to define the musculoskeletal manifestations:

- Adhesive capsulitis (frozen shoulder): Pain in shoulder for at least 1 month, an inability to lie on the affected shoulder and limitation of active and passive range of movement greater than 25% in both abduction and external rotation compared to the other shoulder [8].

- Carpal tunnel syndrome: Positive Tinel test — tingling sensation in the distribution of the nerve on light percussion over median nerve at flexor retinaculum. Positive Phalen test — tingling and numbness over median nerve distribution on flexion of wrist at 90 degrees angle for 30–60 seconds [9].

- Dupuytren’s contracture: Pitting and thickening of the palmar skin with a firm, painless nodule, fixed to the skin and deep fascia with contracture of the ring and little finger [10].

- Diabetic cheiroarthropathy (limited joint mobility): Positive Prayer sign — Inability to touch the palmar surface of the interphalangeal joints together with the fingers fanned and the wrist maximally extended [11].

- Flexor tenosynovitis (trigger finger): Presence of a palpable nodule, usually in the area overlying the meta-carpophalangeal joint (MCP), thickening along the affected flexor tendon sheath on the palmar aspect of the finger and hand, occurrence of locking phenomenon with either active or passive finger flexion [12].

- Diffuse idiopathic skeletal hyperostosis (DISH): Radiographic finding of calcification of at least four contiguous vertebrae of thoracolumbar spine, with preservation of the intervertebral disc space and absence of sacroiliitis [13].

- Osteoarthritis: Altman’s clinical criteria of radiographic osteophytes along with one of the four criteria: pain, crepitus, morning stiffness < 30 min, age > 60 years [14].

- Rheumatoid arthritis (RA): EULAR/ACR classification criteria for rheumatoid arthritis [15].

**Study procedure**

A detailed medical history, general physical and musculoskeletal examination was done after obtaining informed written consent. Data collected included age, sex, duration of diabetes, mode of treatment, musculoskeletal symptoms and their duration (pain, restriction of movement, swelling of the joint), family history of diabetes. The anthropometric measurements taken were weight (kilogram), height (meter), body mass index (weight in kilogram/height in meter squared), waist and hip circumference (cm). Investigations done were complete blood count, fasting and postprandial plasma glucose (by hexokinase method in venous blood), glycated hemoglobin (by High Performance Liquid Chromatography), urine analysis, X-rays of the involved joints when indicated.

Data were described in terms of range; mean ± standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate. The Chi-square (χ²) test was used to compare categorical data, and exact test was used when the expected frequency was less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS version 21 (SPSS Inc., Chicago,
Results

The mean age of the study participants was 58.8 ± 10.1 years (range: 32–88 years), with the age at T2D onset of 49.8 ± 7.9 years and mean T2D duration of 8.9 ± 5.8 years. The mean BMI of the study participants was 24.2 ± 0.08 kg/m² (range: 18.9–44.20 kg/m²). One hundred fifty one (50.7%) patients had abnormal waist-to-hip ratio (> 1.0) and the mean waist-to-hip ratio was 0.9 ± 0.08. The mean fasting plasma glucose, postprandial plasma glucose and HbA1c were 137.3 ± 43.7 mg/dL, 199.1 ± 70.3mg/dL and 8.1% ± 1.9%, respectively. A history of hypertension was found in 30.3% of participants, 3.3% had a history of coronary artery disease, 2.7% had hypothyroidism and 0.3% had undergone knee replacement in the past.

Table 1 shows the distribution of subjects in various groups and their association with musculoskeletal manifestations. In our study, musculoskeletal manifestations were seen in 152 people with T2D (50.7%). Most of the study participants (54.7%) had diabetes for 5 to 10 years, followed by 19% who had duration of diabetes less than 5 years.

Table 2 shows the association of musculoskeletal manifestations with different variables. In the study population, 21.6% of cases had a family history of diabetes mellitus. Joint pain was present in 27.3%, joint swelling in 7.3%, restriction of movements at the joints in 18.3% and Tinel/Phelan test was positive in 10.7% cases. Insulin therapy was used by 13.7% of the participants, and 98% were taking oral hypoglycemic agents for the treatment of T2D.

Musculoskeletal disorders (one or more) were seen in 50.7% of our patients. This finding is in accordance with previous reports — 52.9% [16], and 53.3% [17]; but higher than the prevalence reported by other authors (27–42%) [18–21]. This discrepancy may be due to the larger sample size in this study compared with those mentioned above, and the fact that there were more people with T2D at advanced ages, which may have increased the likelihood of having more than one musculoskeletal manifestation at one time.

In this study, people with T2D aged above 60 years were found to have more such disorders. These findings are in accordance with previous studies [21–23] which showed that the duration of the disease is directly related to its complications. Moreover, a majority of the study participants (54.7%) in this study had diabetes for 5 to 10 years followed by those who had duration of T2D less than 5 years (19%). This is consistent with Kumar and Das [17] who observed that the odds of having musculoskeletal manifestations was 1.48 times higher in the study participants who had a duration of diabetes of more than 5 years as compared to those who had a duration of diabetes of less than 5 years.

The most common manifestation in this study was osteoarthritis of the knee (20.3%). This may be because the incidence of osteoarthritis is reported to increase with age [24], and there were 79% participants of more than 50 years in this study. The results were comparable to the studies conducted by Sarkar et al. [16] and Mathew et al. [25] who showed the prevalence of osteoarthritis of the knee to be 20.4% and 22.5%, respectively.

The prevalence of osteoarthritis and adhesive capsulitis in this study was lower than that reported by Kumar and Das (45.31%) [17], but comparable to Kannan et al.’s (11%) [19]. This inconsistency may be due to the regional differences in the incidence of these degenera-
Table 1. Distribution of Subjects and Association with Musculoskeletal Manifestations

<table>
<thead>
<tr>
<th>Total</th>
<th>Adhesive capsulitis</th>
<th>Carpal tunnel syndrome</th>
<th>Dupuytren’s contracture</th>
<th>Diabetic cheiroarthropathy</th>
<th>Flexor tenosynovitis</th>
<th>DISH</th>
<th>Osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
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<td>N (%)</td>
<td>N (%)</td>
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<td>p value</td>
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<tr>
<td>Age [years]</td>
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<td></td>
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<tr>
<td>&lt; 50</td>
<td>63 (21%)</td>
<td>3 (4.8%)</td>
<td>9 (14.3%)</td>
<td>1 (1.6%)</td>
<td>1 (1.6%)</td>
<td>3 (4.8%)</td>
<td>2 (3.2%)</td>
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<tr>
<td></td>
<td>0.27</td>
<td>0.27</td>
<td>0.46</td>
<td>0.01*</td>
<td>0.34</td>
<td>0.13</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>51–60</td>
<td>104 (34.6%)</td>
<td>12 (11.5%)</td>
<td>13 (12.5%)</td>
<td>0 (0.0%)</td>
<td>3 (2.9%)</td>
<td>2 (1.9%)</td>
<td>6 (5.8%)</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>133 (44.3%)</td>
<td>10 (7.5%)</td>
<td>1 (7.5%)</td>
<td>14 (10.3%)</td>
<td>2 (1.5%)</td>
<td>14 (10.5%)</td>
<td>41 (30.8%)</td>
</tr>
<tr>
<td>Mean/SD</td>
<td>58.4/8.9</td>
<td>56.4/8.6</td>
<td>51.5/19.1</td>
<td>66.6/8.4</td>
<td>54.9/14.3</td>
<td>62.5/9.5</td>
<td>63.7/8.5</td>
</tr>
</tbody>
</table>

Duration of diabetes [years]

|       |                     |                        |                         |                           |                     |               |               |
| < 5   | 57 (19.0%)          | 6 (10.5%)              | 5 (8.8%)                | 0 (0.0%)                  | 1 (1.8%)            | 1 (1.8%)| 6 (10.5%)    |
|       | 0.62                | 0.25                   | 0.61                    | 0.13                      | 0.71                | 0.07   | 11 (19.3%)   |
| 5–10  | 164 (54.7%)         | 14 (8.5%)              | 23 (14%)                | 1 (0.6%)                  | 8 (4.9%)            | 5 (3%)  | 9 (5.5%)     |
| > 15  | 40 (13.3%)          | 1 (2.5%)               | 1 (2.5%)                | 5 (12.5%)                 | 0 (0.0%)            | 0 (0.0%)| 13 (32.5%)   |
| > 20  | 24 (8.0%)           | 2 (8.3%)               | 0 (0.0%)                | 3 (12.5%)                 | 1 (4.2%)            | 3 (12.5%)| 41 (37.1%)   |
| Mean/SD | 264/6.11           | 24/0.21                | 22.7/1.7                | 24.7/2.4                  | 23.9/1.2            | 25.3/2.7| 24.9/3.5    |

BMI [kg/m²]

|       |                     |                        |                         |                           |                     |               |               |
| 18.9–22.9 | 100 (33.3%)      | 4 (4.0%)               | 8 (8.0%)                | 1 (1.0%)                  | 6 (6.0%)            | 1 (1.0%)| 7 (7.0%)     |
|       | 0.01*               | 0.23                   | 0.60                    | 0.47                      | 1.0                 | 0.10   | 17 (17.7%)   |
| 23–24.9 | 101 (33.6%)         | 6 (5.9%)               | 15 (14.9%)              | 1 (1.0%)                  | 4 (4.0%)            | 5 (5.0%)| 19 (18.8%)   |
| > 25  | 99 (33%)            | 15 (15.2%)             | 9 (9.1%)                | 0 (0.0%)                  | 8 (8.1%)            | 1 (1.0%)| 12 (12.1%)   |
| Mean/SD | 26/4.61            | 24/0.21                | 22.7/1.7                | 24.7/2.4                  | 23.9/1.2            | 25.3/2.7| 24.9/3.5    |

FPG [mg/dL]

|       |                     |                        |                         |                           |                     |               |               |
| < 127 | 177 (59%)           | 13 (7.3%)              | 9 (5.1%)                | 0.01*                     | 0 (0.0%)            | 14 (7.9%)| 0.09         |
|       | 0.45                | 0.23                   | 0.08                    | 0.09                      | 1 (0.6%)            | 0.01*   | 7 (4.0%)     |
| > 127 | 123 (41%)           | 12 (9.8%)              | 23 (18.7%)              | 2 (1.6%)                  | 4 (3.3%)            | 6 (4.9%)| 15 (12.2%)   |
| Mean/SD | 139/4.57           | 147/16.29              | 138/50/10.6             | 125.28/41.5               | 140.29/12.9         | 171.95/71.6| 129.59/31.9 |

PPPG [mg/dL]

|       |                     |                        |                         |                           |                     |               |               |
| < 180 | 159 (53.0%)         | 10 (6.3%)              | 12 (7.5%)               | 0.06                      | 11 (6.9%)           | 2 (1.3%)| 5 (3.1%)     |
|       | 0.17                | 0.06                   | 0.22                    | 0.47                      | 2 (1.3%)            | 0.19   | 38 (23.9%)   |
| > 180 | 141 (47.0%)         | 15 (10.6%)             | 20 (14.2%)              | 2 (1.4%)                  | 7 (5.0%)            | 5 (3.5%)| 17 (12.1%)   |
| Mean/SD | 215/8.84           | 206/48.3               | 186/5.9                 | 175/50.2                  | 204/27.9            | 242/89.7| 190/65.8    |

HbA1C [%]

|       |                     |                        |                         |                           |                     |               |               |
| < 7   | 121 (40.3%)         | 8 (6.6%)               | 7 (5.8%)                | 0.06                      | 12 (9.9%)           | 2 (1.7%)| 2 (1.7%)     |
|       | 0.64                | 0.06                   | 0.03*                   | 0.07                      | 2 (1.7%)            | 0.24   | 24 (8.4%)    |
| 7.1–8 | 55 (18.3%)          | 4 (7.3%)               | 8 (14.5%)               | 2 (3.6%)                  | 2 (3.6%)            | 1 (1.8%)| 2 (3.6%)     |
| 8.1–9 | 77 (25.6%)          | 9 (11.7%)              | 13 (16.9%)              | 0 (0.0%)                  | 1 (1.3%)            | 4 (5.2%)| 11 (14.3%)   |
| > 9   | 47 (15.6%)          | 4 (8.5%)               | 0 (0.0%)                | 3 (6.4%)                  | 0 (0.0%)            | 7 (14.9%)| 9 (19.1%)    |
| Mean/SD | 8.3/1.9            | 8.4/1.5                | 7.0/0.4                 | 7.2/1.7                   | 8.0/0.8             | 9.9/1.6| 7.9/2.0     |

Total 300 25 (8.3%) 32 (10.7%) 2 (0.7%) 18 (6.0%) 7 (2.3%) 22 (7.3%) 61 (20.3%)

*statistically significant; BMI — body mass index; DISH — diffuse idiopathic skeletal hyperostosis; FPG — fasting plasma glucose; HbA1c — glycated hemoglobin; PPPG — post prandial plasma glucose; SD — standard deviation
Table 2. Association of the musculoskeletal manifestations with different variables

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Adhesive capsulitis</th>
<th>Carpal tunnel syndrome</th>
<th>Dupuytren's contracture</th>
<th>Diabetic cheiroarthropathy</th>
<th>Flexor tenosynovitis</th>
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</tr>
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<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
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<td>Sex</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>130(43.3%)</td>
<td>11 (8.5%)</td>
<td>23 (17.7%)</td>
<td>0.001*</td>
<td>2 (1.5%)</td>
<td>0.10</td>
<td>7 (5.4%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Joint pain</td>
<td>82 (27.3%)</td>
<td>7 (8.5%)</td>
<td>17 (20.7%)</td>
<td>0.001*</td>
<td>0 (0.0%)</td>
<td>0.38</td>
<td>1 (1.2%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>22 (7.3%)</td>
<td>0 (0.0%)</td>
<td>1 (4.5%)</td>
<td>0.33</td>
<td>0 (0.0%)</td>
<td>0.69</td>
<td>0 (0.0%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Restriction of movements at the joints</td>
<td>55 (18.3%)</td>
<td>5 (9.1%)</td>
<td>10 (18.2%)</td>
<td>0.04</td>
<td>0 (0.0%)</td>
<td>0.50</td>
<td>1 (1.8%)</td>
<td>0.14</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>100 (33.3%)</td>
<td>10 (10.0%)</td>
<td>12 (12.0%)</td>
<td>0.59</td>
<td>1 (1.0%)</td>
<td>0.61</td>
<td>6 (6.0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>65 (21.6%)</td>
<td>8 (12.3%)</td>
<td>8 (12.3%)</td>
<td>0.62</td>
<td>1 (1.5%)</td>
<td>0.32</td>
<td>2 (3.1%)</td>
<td>0.26</td>
</tr>
<tr>
<td>OHA</td>
<td>294 (98.0%)</td>
<td>25 (8.5%)</td>
<td>31 (10.5%)</td>
<td>0.63</td>
<td>1 (0.3%)</td>
<td>0.001*</td>
<td>18 (6.1%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Insulin use</td>
<td>41 (13.7%)</td>
<td>3 (7.3%)</td>
<td>4 (9.8%)</td>
<td>0.83</td>
<td>1 (2.4%)</td>
<td>0.13</td>
<td>3 (7.3%)</td>
<td>0.70</td>
</tr>
<tr>
<td>WH ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>151 (50.3%)</td>
<td>17 (11.3%)</td>
<td>22 (14.6%)</td>
<td>0.02</td>
<td>1 (0.7%)</td>
<td>0.99</td>
<td>8 (5.3%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Mean/SD</td>
<td>0.95</td>
<td>0.1/0.04</td>
<td>0.9/0.06</td>
<td>0.9/0.05</td>
<td>0.9/0.06</td>
<td>0.9/0.04</td>
<td>0.9/0.06</td>
<td>0.9/0.06</td>
</tr>
<tr>
<td>Total</td>
<td>300</td>
<td>25 (8.3%)</td>
<td>32 (10.7%)</td>
<td>2 (0.7%)</td>
<td>18 (6.0%)</td>
<td>7 (2.3%)</td>
<td>22 (7.3%)</td>
<td>61 (20.3%)</td>
</tr>
</tbody>
</table>

*statistically significant; BMI — body mass index; DISH — diffuse idiopathic skeletal hyperostosis; FPG — fasting plasma glucose; Hba1c — glycated hemoglobin; OHA — oral hypoglycemic agents; PPPG — post prandial plasma glucose; SD — standard deviation; W/H — waist-hip
tive disorders, as the population studied by Kumar and Das was from a relatively poorer state of India than ours.

This study revealed the carpal tunnel syndrome in 10.7% and flexor tenosynovitis in 2.3% people with T2D, which is lower than the figures reported by other researchers [26–28]. The incidence of carpal tunnel syndrome in patients with diabetes has also been related to the occupation, sex, and anthropometric factors such as wrist shape [27]. The higher manual work and less use of gadgets for routine work in our population may be the reason for this difference.

The prevalence of diffuse idiopathic skeletal hyperostosis was 7.3% and diabetic cheiroarthropathy was 6%. A higher incidence of diabetic cheiroarthropathy was reported by many authors [17–19]. Diabetic cheiroarthropathy, also known as the stiff hand syndrome, is one of the long-term complications of diabetes [29]. The lower prevalence in this study may be due to the lesser number of participants who had long-standing diabetes of more than 11 years. Many authors reported a higher prevalence of DISH than that found in this study [30, 31]. This difference may be due to the inclusion of the study sample with other causative factors, such as obesity, deranged lipid profile and postmenopausal women in these studies.

The association of musculoskeletal complications in patients with T2D with advanced age, longer duration of disease and higher BMI observed in our study was also reported by other authors [17,19, 32]. However, they have not studied the correlation with the specific musculoskeletal manifestation and the variables in details, unlike this study.

Limitation
The present study has few limitations including small sample size and a single-center model. Also, the design of this study was hospital-based, targeted to the patients attending the outpatient clinic, which might not reflect the accurate occurrence of musculoskeletal manifestations in this region. The study is also subject to recall bias, because it relied on self-reported data. It was a cross-sectional study; therefore, a causal link cannot be established between the dependent and independent variables. In spite of its limitations, this study has a significance for public health, because it represents an important step towards establishing the relationship between T2D and the development of musculoskeletal manifestations.

Conclusions
Musculoskeletal manifestations are common in T2D and often remain unidentified. The authors observed their prevalence of 50.7% in this study and the most frequent (20.3%) condition was osteoarthritis of the knee, followed by carpal tunnel syndrome (10.7%) and adhesive capsulitis of the shoulder (8.3%). The present study shows a statistically significant correlation with variables such as age, duration of diabetes, presence of hypertension, BMI, waist/hip ratio and HbA1c levels. A thorough physical examination of the musculoskeletal system should be an integral part of the diabetic patient workup. This would help in the early detection, the prevention and timely management of chronic disabilities due to these disorders. Future studies with larger sample sizes are required to substantiate this observation, especially in the developing countries like India.

Article information
Data availability statement
The data of the study will be available on request.

Ethics statement
The project was approved by the institutional ethical committee.

Author contributions
All authors are responsible for the study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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Dayanand Medical College and Hospital, Ludhiana, Punjab, India. No external funding was secured for this study.

Acknowledgements
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Conflicts of interest
The authors declare that there is no conflict of interest.

REFERENCES


Prevalence and Severity of Chronic Obstructive Pulmonary Disease in People with Type 2 Diabetes: A Cross-Sectional Study

ABSTRACT

Objective: The aim of the study was to determine and evaluate the prevalence of chronic obstructive pulmonary disease (COPD) in patients with type 2 diabetes and the impact of diabetes on lung function and the severity of the COPD.

Materials and methods: This was a retrospective observational study conducted in a private clinic setup among 1200 patients and was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE). Chronic Obstructive Lung Disease (GOLD) criteria, 2023 were used to diagnose COPD and for diabetes mellitus (DM) were executed according to the American Diabetes Association (ADA) and International Diabetes Federation (IDF) consensus statement.

Results: The prevalence of type 2 diabetes (T2D) was 27% among 1200 COPD patients. Among 335 patients with diabetes 37% had newly detected T2D. Prevalence in mild, moderate, severe, and very severe COPD among patients having documented T2D was 14.6%, 18.8%, 37%, and 29.5%, respectively. Furthermore, among diabetes patients 7.5% were having HbA1c < 7%, 63.9% were having HbA1c 7–10% and 28.6% were having HbA1c > 10%. As compared to people without diabetes (56.64 ± 3.55), in patients with diabetes (46.22 ± 4.19) there was a severe decline in lung function (mean FEV1) and it was statistically significant (p = 0.001). Comorbidities, as shown by multivariate Cox proportional hazards analysis, including hypertension (HR, 1.902; 95% CI, 1.261–2.403), dyslipidemia (HR, 1.391; 95% CI, 1.172–1.698), cerebrovascular disease (HR, 1.532; 95% CI, 1.132–2.008), coronary artery disease (HR, 1.427; 95% CI, 1.079–1.830), kidney disease (HR, 1.006, 95% CI, 0.833–1.397) and liver disease (HR, 1.083, 95% CI, 0.821–1.427) were independent clinical factors associated with T2D.

Conclusions: Chronic obstructive pulmonary disease is one of the comorbidities found in patients with T2D. A significant number of cases of new-onset diabetes are observed among patients with pre-existing COPD. Therefore, the outcome of this research advocates that targeted surveillance and management of diabetes are important in clinical care of the COPD population. (Clin Diabetol 2023; 12; 5: 308–314)

Keywords: COPD, type 2 diabetes, comorbidities, prevalence, screening

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality across the globe and is characterized by progressive airflow obstruction and airflow limitation [1, 2]. Worldwide, COPD is considered the leading form of lung disease and is substantially increasing the economic and social burden, as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report [3, 4]. From a global perspective, COPD is responsible for approximately 3 million deaths annually [5]. It has been projected that with the substantial increase in the prevalence of obesity, smoking, and ageing, COPD and related conditions will account for more than 5.4 million annual deaths in 2060 [6].

COPD is also associated with comorbidities such as diabetes, high blood pressure, etc., and their impact on health increases [7, 8]. At all stages of COPD, this comorbidity can occur and increase the risk of hospitalization and mortality [9, 10]. Therefore, the cost of treating the disease is growing exponentially [11]. There are few global studies that link diabetes to COPD and their impact on prognosis [12].

Diabetes mellitus (DM) is a clinical condition caused by a lack of insulin secretion or action. It is regarded as one of the most significant emerging health threats in the 21st century. In addition to the classical complications of the disease, COPD is more frequent and even more severe in patients with diabetes mellitus, which can increase morbidity and mortality. The increase in frequency of COPD in patients with diabetes may be because of hyperglycemic environment which favors chronic systemic inflammation and therefore affect their lung function and, in turn, their prognosis [13–17].

Due to the large growth in the incidence of both DM and COPD in India, as well as the rise in obesity, smoking, and environmental pollution, treating doctors face a significant problem. The purpose of this study is to determine the prevalence of COPD in individuals with type 2 diabetes (T2D), as well as the effects of diabetes on lung function and the severity of COPD.

Materials and methods

Study design

This is a retrospective observational study carried out in a private clinic in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [18, 19]. About 1200 patients who participated in a COPD consultation were assessed and interviewed. In the course of the consultation and prior to the interview, each participant provided written informed consent. To diagnose COPD among participants, the questionnaire was adapted from the GOLD criteria (2023), according to which the spirometric criterion postbronchodilator value (FEV1)/forced vital capacity (FVC) 0.70 was taken [20]. People diagnosed with COPD were screened for DM according to the American Diabetes Association (ADA) [21] and International Diabetes Federation (IDF) consensus statement [22].

Study population/study participants

Subjects were excluded if they (1) were aged < 20 years at the time of COPD diagnosis, (2) had a diagnosis of asthma over the study period, (3) were diagnosed as having type 1 DM during the study period, (4) had a prescription of COPD-related medications for < 1 month, (5) pregnant or lactating women and (6) refused to sign written informed consent.

Statistical analysis

For all variables using percentage and frequencies descriptive statistics was performed. With the Bonferroni correction, one-way ANOVA, t-Student, Chi-Square test the differences between groups were calculated and level of significance was set at p < 0.05. For data analysis, the IBM software, Statistical Package for Social Sciences (SPSS), version 19.0 for Windows (SPSS Inc., Chicago, IL, USA) was used.
Results

A total of 1200 patients were assessed in this study, of whom 335 were reported with T2D and 865 were people who did not suffer from diabetes. The average age of the participants was 56.4 ± 11.6 years; the average age in patients with diabetes was 58.8 ± 12.4 years and the average age in people who did not suffer from diabetes was 57.58 ± 10.79 years. The average body mass index (BMI) of the participants was 23.4 ± 3.7 kg/m^2; the average age in patients with diabetes was 23.6 ± 4.2 kg/m^2 and the average age in non-diabetes patients was 22.8 ± 3.6 kg/m^2. The groups differed significantly in smoking habits, with 9.5 ± 4.6 pack-years in diabetic patients versus 12.8 ± 3.4 pack-years in the non-diabetic group (p = 0.001). This study showed that, as compared to people who did not suffer from diabetes (56.6 ± 3.5), in people with diabetes (46.2 ± 4.1) there was a severe decline in lung function (mean FEV1) and it was statistically significant (p = 0.001) (Tab. 1).

The prevalence of diabetes among COPD patients as evaluated in the study was 27%. Total duration of diabetes among pre-diagnosed diabetes patients was 8.0 ± 3.5 years. Among the patients with diabetes, 34% were newly diagnosed. Furthermore, among diabetes patients, 7.5% had HbA1c < 7%, 63.9% had HbA1c 7–10% and 28.6% had HbA1c > 10%. In patients who presented with severe COPD, 37% were newly diagnosed with T2D, and 29.5% had an established T2D history.

Comorbidities, as shown by multivariate Cox proportional hazards analysis, including hypertension (HR, 1.902; 95% CI, 1.261–2.403), dyslipidemia (HR, 1.391; 95% CI, 1.172–1.198), cerebrovascular disease (HR, 1.532; 95% CI, 1.132–2.008), coronary artery disease (HR, 1.427; 95% CI, 1.079–1.830), kidney disease (HR, 1.006, 95% CI, 0.833–1.397) and liver disease (HR, 1.083, 95% CI, 0.821–1.427) were independent clinical factors associated with T2D (Tab. 2).

Discussion

The study assessed the combination of diabetes and COPD in Indian patients. In India, COPD is one of the major health burden due to increasing obesity, smoking and biomes fuel exposure and, as compared to USA and Europe, the mortality due to COPD in India is fourfold higher [23]. Due to the cumulative presence of oxidative stress, weight gain, chronic inflammation, insulin resistant and dysfunction of fat metabolism, COPD is considered as one of the major risk factor for developing new onset of diabetes. The mechanism by which diabetes has adverse effects on the prognosis of COPD is likely to be multifactorial and is not fully understood. Likewise, direct exposure to hyperglycemia

| Table 1. Patient Demographics (n = 1200) |
|-----------------------------|-----------------------------|-----------------------------|
| Parameters                  | People with diabetes (T2D)  | People without diabetes     | P     |
|                            | (n = 335)                   | (n = 865)                   |       |
| Sex (male/female)           | 253/82                      | 698/167                     | 0.34  |
| Age [years], mean ± SD      | 58.8 ± 12.4                 | 57.5 ± 10.7                 | 0.07  |
| BMI [kg/m^2], mean ± SD     | 25.6 ± 4.2                  | 22.8 ± 3.6                  | 0.07  |
| Smokers [pack-years], mean ± SD | 9.5 ± 4.6                 | 12.8 ± 3.4                  | 0.001 |
| Duration of COPD [years], mean ± SD | 7.0 ± 2.1                | 6.4 ± 1.9                   | 0.005 |
| FEV1 (percentage predicted), mean ± SD | 46.2 ± 4.1             | 56.5 ± 3.5                   | 0.007 |
| HbA1c levels (mean ± SD)    | 8.9 ± 1.8                   | 5.2 ± 1.3                   | < 0.001 |
| Comorbidity                 |                             |                             |       |
| Hypertension                | 218 (65%)                   | 375 (43.4%)                 | < 0.001 |
| Dyslipidemia                | 18 (5.3%)                   | 30 (3.5%)                   | 0.24  |
| Cerebrovascular disease     | 77 (23%)                    | 110 (12.7%)                 | 0.01  |
| Coronary artery disease     | 105 (31%)                   | 175 (20.2%)                 | 0.01  |
| Kidney disease              | 26 (7.8%)                   | 52 (6%)                     | 0.23  |
| Liver disease               | 23 (6.9%)                   | 55 (6.4%)                   | 0.78  |
| COPD severity               |                             |                             |       |
| No ES or hospitalization    | 298 (89%)                   | 785 (90.8%)                 | 0.28  |
| 1 ES                        | 24 (7.2%)                   | 54 (6.2%)                   |       |
| ≥ 2 ES or hospitalization   | 14 (4.2%)                   | 25 (2.9%)                   |       |

BMI — body mass index; COPD — chronic obstructive pulmonary disease; ES — epidural steroid/corticosteroid; FEV1 — forced expiratory volume; HbA1c — glycated hemoglobin; SD — standard deviation; T2D — type 2 diabetes
Table 2. Clinical conditions associated with new-onset T2D among patients with COPD. Multivariate Cox Proportional Hazards Model (n=335)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard ratio (HR)</th>
<th>95% confidence interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.90</td>
<td>1.26–2.41</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.39</td>
<td>1.17–1.19</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>1.53</td>
<td>1.13–2.00</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.42</td>
<td>1.07–1.83</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>1.00</td>
<td>0.83–1.39</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1.08</td>
<td>0.82–1.42</td>
</tr>
</tbody>
</table>

COPD — chronic obstructive pulmonary disease; T2D — type 2 diabetes

in DM patients results in impaired lung function [24, 25]. The impact of hyperglycemia on the respiratory system, as proven in a rat study, is characterized by structural changes in the lung tissue, increased oxidative stress and changed gas exchange [26]. Several studies have shown that inflammatory responses can be caused by hyperglycemia [27], which could lead to restrictive abnormalities in lung tissue and reduced lung function. Therefore, limiting airflow and reducing lung volumes may be considered chronic complications of uncontrolled blood glucose levels in diabetes mellitus. Hyperglycemia can directly promote impaired phagocytic function of polymorphonuclear leukocytes and support bacterial growth in the airways, which has been observed in patients with DM [28, 29]. Thus, the worse outcomes in COPD patients with DM may result from susceptibility to bacterial infection.

The prevalence of T2D in the current study was 27%. The results of this study were consistent with those of other Indian studies carried out in various regions of India. In COPD patients, Mahishale et al. [30] found the prevalence of DM to be 23.63%, whereas Ajit et al. [31] found the similar prevalence at 23.05%. It has been shown in a few previous worldwide studies that 50% of patients hospitalized with acute COPD exacerbations also had abnormal blood glucose levels [32–34]. Newly detected diabetes was found to be 37% in patients with diabetes and 10.3% of the population as a whole. These patients were unfamiliar with their blood glucose levels prior to detection. This result confirms once again that COPD allows the development of a new start of T2D. In new T2D cases, patients with COPD displayed a multivariate relative risk of 1.38 (95% CI: 1.14–1.67), as observed by Rana et al. [35]. Moreover, Feary et al. [36] showed development of new-onset diabetes in COPD patients, with a odds ratio of 2.04 (95% CI: 1.97–2.12).

Based on recent evidence, COPD constitutes an important risk factor the development of T2D [37, 38]. In COPD patients who also had T2D, our study documented that these patients also had other clinical comorbidities such as hypertension, cerebrovascular disease, and coronary artery disease, and these patients were at high risk of developing other metabolic syndrome and cardiovascular disease [39, 40]. This process is exacerbated by increasing risk factors such as physical inactivity, systemic inflammation and smoking [41, 42]. Thus, COPD-affected patients who also have associated comorbidities such as cerebrovascular disease, hypertension and coronary artery disease are subject to the T2D incident. Several studies have also confirmed that COPD itself emerges as one of the main risk factors for the development of T2D [43]. Current guidelines for COPD do not recommend systematic screening for DM in patients with COPD [2]. Results from the current study suggest that when patients present with some warning co-morbidities, a blood glucose survey in patients with COPD should be conducted.

A statistically significant decline in FEV1 was observed in COPD patients with T2D in this study. These results also match few other results. Comparison with people who do not suffer from diabetes, in people with diabetes the third National Health and Nutrition Review Survey [44] observed a decline in lung function. It is the fact that in uncontrolled diabetes, impaired lung function is susceptible to rapid deterioration. Lower values for maximum expiratory flow (PEL), FEV1, FVC and VC were associated with comorbid diabetes in the Fremantle Diabetes Study [38]. El-Habashy et al. [45] demonstrated that, compared with healthy controls, there was a significant decrease in pulmonary function tests in patients with T2D (forced expiratory flow –25–75%, maximal voluntary ventilation, FEV1, FEV1/FVC%, and PEF), and further proved that in poorly controlled DM this decline was exaggerated.

For patients with T2D, cardiovascular disease is a major and significant co-morbidity. We found that the survival of patients with COPD was severely affected by co-morbid heart failure. Furthermore, because of common symptoms of shortness of breath, wheezing, coughing, COPD and heart failure (HF) can be confounded [45]. Thus, the diagnosis and management of HF in COPD required the prudence and attention of physicians. The current study also demonstrated the presence of cerebrovascular disease in patients with COPD and T2D. There was little or no documentation on its impact on COPD on the prognosis for cerebrovascular disease available.
Strengths and limitations
This was probably the first study in Eastern India to compare lung function between people with diabetes and COPD patients who did not suffer from T2D. This is one of the highlights of the study. There were a few limitations of our research. First, we did not evaluate the factors that may influence glucose levels like stress reaction and steroid administration etc., and these factors may cause acute transient hyperglycemia. Important pharmacological therapies for patients with COPD, such as much more frequent use of theophylline and fewer inhaled corticosteroid prescriptions, may affect the generalizability of our study results. Second, another limitation is observational nature of the study. Third, because of under-reporting on clinical records, the actual prevalence of certain co-morbidities may be underestimated. This study can provide a starting point for future research on the interaction of COPD with diabetes.

Conclusions
Chronic obstructive pulmonary disease is one of the comorbidities found in patients with DM. A substantial number of new cases of diabetes is observed among patients with COPD. These newly diagnosed T2D patients had no knowledge of their uncontrolled glucose status. Therefore, the results of the study recommend periodic screening for blood glucose in patients with COPD, because the clinical progression of COPD significantly affects DM. Patients with COPD who have uncontrolled blood glucose levels and who also have poor lung function may experience more severe COPD and exacerbations. We documented that in COPD survival, pre-existing diabetes and incident diabetes had an unfavorable prognostic effect. Therefore, the results of this research indicate that in clinical care of the COPD population, targeted surveillance and management of diabetes are important.

Article information
Data availability statement
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions e.g. their containing information that could compromise the privacy of research participants.

Ethics statement
The paper does not report on primary research. All data analysed were collected as part of routine diagnosis and treatment. The program was not set up as a study or research project but as a treatment program; hence ethics approval was not required.

Author contributions
Mridul Bera: retrieved patient’s data, drafted and reviewed the paper. Rishad Ahmed: retrieved patient’s data, drafted and reviewed the paper. Arjun Baidya: retrieved patient’s data, drafted and reviewed the paper. Amit Gupta: retrieved patient’s data, drafted and reviewed the paper. Mrinal Kanti Guha: retrieved patient’s data, drafted and reviewed the paper. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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Conflict of interest
The authors declare that there is no conflict of interest.

REFERENCES


The Effect of the COVID-19 Crisis on Metabolic Control of Patients with Type 2 Diabetes in Tunisia: A Cross-Section and Retrospective Cohort Study

Introduction

The pandemic of coronavirus disease 2019 (COVID-19) was an international health crisis that imposed restrictive measures in order to limit the spread of the virus. These measures affected everyday life, routine healthcare activities and accessibility to medications. The effects of the COVID-19 crisis on metabolic control in patients with type 2 diabetes (T2D) were different in the literature [1–5]. The objective of this study was to determine the impact of the COVID-19 crisis on metabolic parameters in T2D in Tunis, Tunisia.

Materials and methods

It was a cross-sectional study conducted during the months of December 2021 and January 2022 at the outpatient clinic of the department of Endocrinology in La Rabta University Hospital of Tunis. It included 350 consecutive patients with T2D enrolled at routine clinical visit, aged more than 25 years and followed up at the same department for at least three years. Patients with acute infectious or cardio vascular diseases, malignancy and pregnant women were not included.

Patients were questioned about age, gender, duration of T2D, ongoing treatment, and COVID-19 infection and vaccination. Number of visits, weight, height, and data on glycemic control (fasting plasma glucose and HbA1c), lipids (total cholesterol, triglycerides, and HDL cholesterol), and serum creatinine during 2019 and 2021 were collected from medical files.

Controlled T2D was defined as HbA1c ≤ 7.0% for patients under 65 years old and ≤ 8.0% for patients over 65 years old or with severe renal insufficiency or coronary artery disease.

The study was approved by the Ethical Committee of University Hospital La Rabta, Tunis. All patients signed an informed consent.

Statistical analysis

Analyses were carried out using the Statistical Package for the Social Sciences version 25 (SPSS Inc., Chicago, IL, USA). Comparisons of continuous and categorical variables were performed using Student and McNemar tests for paired groups, respectively.

Results

Data of 339 patients were analyzed: 134 males (39.5%), mean age = 62.2 ± 9.3 years (28–91), mean duration of T2D = 9.9 ± 6.2 years (2–35), 126 (37.2%) were treated with insulin and 213 (62.8%) with only
oral anti-diabetic agents. Diabetes complications were retinopathy in 94 (27.7%), peripheral neuropathy in 44 (12.9%), and nephropathy in 89 (26.2%). Glomerular filtration rate was below 60 mL/min/1.73m² in 32 (9.4%).

Hypertension was present in 192 patients (56.6%), coronary artery disease in 67 (19.8%), cardiac insufficiency in 23 (6.8%), stroke in 18 (5.3%), and peripheral artery disease in 21 (6.2%). Diabetes foot complications were present in 11 patients (3.2%). One hundred and twenty patients (35.4%) have been infected by COVID-19 and 304 (89.7%) were vaccinated.

There were no significant differences in the number of medical visits and in the mean annual levels of fasting plasma glucose and HbA1c between 2019 and 2021. There were significant improvements in glomerular filtration rate and LDL cholesterol level (Tab. 1).

### Discussion

Metabolic control was not worsened during the COVID-19 crisis in patients with T2D. Studies conducted in different countries showed different impacts of the COVID-19 crisis on glycemic control [1–5]. In the meta-analysis of Silverii et al. (n = 9591, in 2021), no significant variation in HbA1c was detected [1]. However, two meta-analyses showed a significant deterioration in glycemic control with a mean increase in HbA1c of 0.34 % (95% CI: 0.30-0.38) in the study of Ojo et al. [2] (pre-COVID, n = 8478; post-COVID lockdown, n = 8417, in 2022) and 0.14 % (95% CI: 0.13–0.40) in the study of Eberle et al. [3] (n = 1823, in 2021).

The decrease in LDL cholesterol in the present study can be explained by the increased prescription of statins at higher doses. The improvement of glomerular filtration rate can also be secondary to statin intake.

### Article information

**Ethical approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards and with the 1964 Helsinki declaration. Approval was granted by the Ethics Committee of La Rabta University Hospital.

**Data availability**

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

**Author contribution**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Melika Chihouai, Chayma Bel Haj Ali and Anis Grassa. The first draft of the manuscript was written by Melika Chihouai and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Conflict of interest**

The authors declare that there is no conflict of interest.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>2019</th>
<th>2021</th>
<th>p</th>
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<tbody>
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<td>1.9 ± 0.7</td>
<td>0.054</td>
</tr>
<tr>
<td>BMI, mean ± SD [kg/m²]</td>
<td>30.4 ± 6.2</td>
<td>30.5 ± 6.3</td>
<td>0.663</td>
</tr>
<tr>
<td>FPG, mean ± SD [mmol/L]</td>
<td>9.49 ± 3.16</td>
<td>9.82 ± 3.60</td>
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</tr>
<tr>
<td>HbA1c, mean ± SD [%]</td>
<td>8.2 ± 1.7</td>
<td>8.3 ± 1.8</td>
<td>0.327</td>
</tr>
<tr>
<td>GFR, mean ± SD, mL/min/1.73m²</td>
<td>88.6 ± 20.7</td>
<td>90.2 ± 21.9</td>
<td>0.044</td>
</tr>
<tr>
<td>Total Cholesterol, mean ± SD [mmol/L]</td>
<td>4.53 ± 1.08</td>
<td>4.39 ± 1.32</td>
<td>0.058</td>
</tr>
<tr>
<td>Triglycerides, mean ± SD [mmol/L]</td>
<td>1.57 ± 0.88</td>
<td>1.70 ± 1.33</td>
<td>0.118</td>
</tr>
<tr>
<td>HDL cholesterol, mean ± SD [mmol/L]</td>
<td>1.16 ± 0.28</td>
<td>1.16 ± 0.33</td>
<td>0.515</td>
</tr>
<tr>
<td>LDL cholesterol, mean ± SD [mmol/L]</td>
<td>2.66 ± 0.93</td>
<td>2.45 ± 1.08</td>
<td>0.002</td>
</tr>
<tr>
<td>Controlled diabetes* (%)</td>
<td>38.9</td>
<td>38.3</td>
<td>0.912</td>
</tr>
</tbody>
</table>

*Controlled T2D was defined as HbA1c ≤ 7% for patients under 65 years old and ≤ 8% for patients over 65 years or with GFR < 30 mL/min/1.73m² or coronary artery disease

BMI — body mass index; FPG — fasting plasma glucose; GFR — glomerular filtration rate; HbA1c — glycated hemoglobin; HDL — high density lipoprotein; LDL — low density lipoprotein; SD — standard deviation
REFERENCES
Association between Random Glucose Level, HbA1c and COVID-19 Mortality: A Single Center, Cross-Sectional Study

Introduction
Although coronavirus disease (COVID-19) caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is no longer new, it is still noted as one of the worst pandemics as it has resulted in millions of confirmed infections and deaths. A prior study has described the increased mortality risk observed among COVID-19 patients with diabetes mellitus (DM), wherein blood glucose level is a critical prognostic factor for COVID-19 mortality in patients with and without DM [1]. On the other hand, conflicting data have been reported on HbA1c levels before admission or at admission in relation to COVID-19-related mortality in patients with DM [2]. This study aims to determine the relationship of random plasma glucose (RPG) and HbA1c levels to COVID-19 mortality in hyperglycemic subjects with and without type 2 diabetes (T2D), as well as in normoglycemic subjects with T2D.

Materials and methods
This retrospective observational study with a cross-sectional method was conducted at a central referral hospital in Makassar, Indonesia from July 2020 until the required sample size was met. This study applied the purposive sampling technique, with the population being hyperglycemic and T2D patients who have been treated for COVID-19 infection and the sample size being 100 subjects who met the inclusion criteria. Application for ethical clearance was submitted to the faculty’s Biomedical Research Ethics Committee and approved prior to the study. For the data analysis process, the chi square test was carried out using SPSS version 25; the statistical test result is considered significant if the p value is less than 0.05.

Results
The results are presented in Table 1.

Discussion
From the correlation of RPG and HbA1c levels to mortality outcomes, the percentage of subjects who died was compared to the percentage of those who survived. In the T2D hyperglycemic variable, 15 subjects died (17.4%), while 71 subjects survived (82.6%). As for the non-T2D hyperglycemic variable, 4 subjects died (57.1%), whereas 3 subjects survived (42.9%). Meanwhile, in the T2D normoglycemic variable, no subject died (0%) and 7 survived (100%). Furthermore, the p-value of = 0.015 (p < 0.05) obtained in the chi-square test signifies a statistically significant relationship between variables. Our results are in line with existing studies, showing that poor blood glucose control...
in T2D or hyperglycemia is associated with mortality in COVID-19 conditions [3, 4]. Based on the findings above, it can be concluded that there is an association of RPG and HbA1c levels to COVID-19 mortality.

### Article information

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**Acknowledgments**
None.

**Conflict of interest**
The authors declare that there is no conflict of interest.

### REFERENCES


### Table 1. Association of Random Plasma Glucose (RPG) and HbA1c to COVID-19 Mortality

<table>
<thead>
<tr>
<th>Quantity and Percentage</th>
<th>Variables</th>
<th>COVID-19 mortality</th>
<th>Total</th>
<th>p-value trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2D hyperglycemic (RPG ≥ 140 mg/dL and HbA1c ≥ 6.5%)</td>
<td>Yes</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>No</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>N</td>
<td>Non-T2D hyperglycemic (RPG ≥ 140mg/dL and HbA1c &lt; 6.5%)</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>%</td>
<td>T2D normoglycemic (RPG &lt; 140mg/dL and HbA1c ≥ 6.5%)</td>
<td>57.1%</td>
<td>42.9%</td>
<td>100%</td>
</tr>
<tr>
<td>N</td>
<td>Total</td>
<td>19</td>
<td>81</td>
<td>100</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td>19,0%</td>
<td>81,0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

HbA1c — glycated hemoglobin; T2D — type 2 diabetes
The chi-square test obtained a p-value of 0.015 (< 0.05), indicating a significant relationship.