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CONTENTS

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ORIGINAL ARTICLE

PREDICTING PROGRESSION TYPE 2 DIABETES MELLITUS: A 3-YEAR FOLLOW-UP STUDY EXAMINING RISK FACTORS FOR TYPE 2 DIABETES IN PATIENTS WITH PREDIABETES

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ABSTRACT

Aim: To study the risk factors in patients with prediabetes that can lead to the progression of impaired glucose tolerance in the form of type 2 diabetes mellitus.

Materials and methods: The selection of patients for this study was carried out on an outpatient basis at the Department of Therapy and Family Medicine, Uzhhorod National University. Patients with prediabetes were identified based on the American Diabetes Association criteria. Informed consent was obtained from all patients before the start of the study. Patients were randomly assigned to one of two groups: Group 1 (n=37) that received typical treatment according to the recommendations of the American Diabetes Association and the control Group 2 (n=42). At the 3rd year of the study, we determined the body mass index, glucose levels and glycated hemoglobin levels of the patients, also their medical documentation was analyzed and patients were interviewed about concomitant diseases.

Results: Analyzing the 3-year follow-up of patients with prediabetes, cases of type 2 diabetes mellitus were detected in both groups, but there is no statistically significant difference when comparing the indicators between the groups ($p>0.05$).

Conclusions: In our study, we analyzed the risk factors in patients with prediabetes that can lead to type 2 diabetes. During a 3-year follow-up, we identified cases of type 2 diabetes mellitus.

KEY WORDS: type 2 diabetes mellitus, type 2 diabetes, prediabetes, risk factors, treatment, diagnostics

INTRODUCTION

There are conditions that precede non-infectious diseases, such as prediabetes (PD) can precede type 2 diabetes mellitus (T2DM), subclinical hypothyroidism (SH) can precede hypothyroidism, nonalcoholic steatohepatitis can precede non-alcoholic fatty liver disease and/or cirrhosis, etc. [1-3]. All these conditions are usually curable, after comprehensive, adequate and timely treatment. But not all doctors and patients often pay attention to this. Meanwhile, while statistical information on T2DM is available, the number of patients with PD is still a matter of debate [4].

PD is a condition where blood glucose levels (BGL) are higher than normal but not high enough to be classified as diagnosis T2DM [5]. People with PD are at a higher risk (HR) of developing T2DM. T2DM is a chronic metabolic disease that affects millions of people worldwide [6]. It is characterized by high BGL due to impaired insulin secretion and/or action [7]. Today, it is already known that PD is closely associated with SH and cardiovascular events and other complications. Therefore, it is important to identify individuals with PD and intervene early to prevent the onset of T2DM. Early identification of individuals with PD can enable early intervention and prevent progression to T2DM [8].

There are several risk factors (RF) that can be used to predict PD. The American Diabetes Association (ADA) developed diagnostic criteria for T2DM and PD [5]. In addition to these criteria, several other RF have been identified in literature [9]. A systematic review identified the following RF as predictors of PD: age, body mass index (BMI), waist circumference, fasting glucose levels (FGL), glycemic hemoglobin (HbA1c) levels, family history (FH) of DM, physical activity, smoking, and alcohol consumption [10].

Several RF have been identified for the development of PD and T2DM, and include:

1. Age: The risk of PD and DM2 increases with age. Individuals over 45 years of age are at a higher risk (HR) than younger individuals [11].
2. FH: Individuals with a FH of DM2 are at a HR of developing PD and T2DM [12].
3. Increased body weight: Overweight and obesity are significant RF for PD and T2DM. The risk increases with BMI. Overweight or obese with a BMI over 25 kg/m^2 have a HR [11].
4. Lack of physical activity is a RF for PD and T2DM [13].
5. Women who have had gestational diabetes (GD) are at a HR of developing PD and T2DM later in life. History of GD or giving birth to a baby weighing >4 kilograms [14].

6. Ethnicity: Some ethnic groups, such as Black, Hispanic, and American Indian, are at a HR of developing PD and T2DM [15].
7. High blood pressure is a RF for PD and T2DM. High blood pressure defined as ≥140/90 mmHg or if patient is on antihypertensive medication [16].
8. Dyslipidemia: Abnormal lipid levels, including high levels of triglycerides and low level of High-density lipoprotein (HDL) cholesterol, are associated with an HR of PD and T2DM. Abnormal lipid levels is defined as HDL cholesterol <35 mg/dL or triglycerides >250 mg/dL [17, 18].
9. Polycystic ovary syndrome (PCOS): Women with PCOS are at a HR of developing PD and T2DM [19].
10. Sleep disorders, such as obstructive sleep apnea, are associated with a HR of PD and T2DM [20].

Screening for PD can help identify individuals who are at HR of developing T2DM. ADA recommends to detect PD in persons who are overweight or have been diagnosed with obesity and have one or several additional RF for T2DM [5]. The screening test recommended by the ADA is the HbA1c test, which measures the average BGL over the past 2-3 months. An HbA1c level of 5.7% to 6.4% indicates PD, and an HbA1c level of 6.5% or higher indicates T2DM [5].

Other screening tests that can be used to identify PD include fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT). The ADA recommends an FPG test for screening in individuals who are not pregnant and do not have symptoms of hyperglycemia. An FPG level of 5.6 mmol/L to 6.9 mmol/L indicates PD, and an FPG level of 7.0 mmol/L or higher indicates T2DM [5]. The OGTT is a more sensitive test that involves drinking a glucose solution and measuring BGL at specified intervals. An OGTT result of 7.8 mmol/L to 11.0 mmol/L indicates PD, and an OGTT result of 11.1 mmol/L or higher indicates T2DM [5].

Several randomized controlled trials (RCT) have been conducted to evaluate the effectiveness of interventions for preventing the onset of T2DM in individuals with PD. In a systematic review and meta-analysis of 35 RCTs published between 2019 and 2021, it was proved that lifestyle modifications (LF) that include changes in diet and use of dosed physical exercises considerably reduced the risk of developing T2DM in patients with PD [21].

Another meta-analysis of 27 RCTs published between 2019 and 2020 found that metformin treatment considerably decreased the risk of developing T2DM among persons with PD [22].

In a double-blind RCT published in 2019, demonstrated that a combination of metformin and acarbose was more effective at decreasing HbA1c levels in individuals with PD than either drug alone [23]. Another double-blind RCT published in 2020 found that the use of a continuous glucose monitoring system improved glycemic control (GC) in individuals with PD compared to usual care [24].

In a RCT published in 2020, researchers found that a low-carbohydrate diet was more effective at enhancement of GC and reduced insulin resistance (IR) in persons with PD in comparison to a low-fat diet [25]. Another RCT published in 2021 found that a high-fiber diet was effective at improving GC and decreased IR in persons with PD [26].

AIM

The aim was to study the risk factors in patients with PD that can lead to the progression of impaired glucose tolerance in the form of T2DM.

MATERIALS AND METHODS

The selection of patients for this study was carried out on an outpatient basis at the Department of Therapy and Family Medicine, Uzhhorod National University. Patients with PD were identified based on the ADA criteria, which includes a FPG level of 5.6-6.9-7 mmol/l or two hours after a meal: 7.8-11 mmol/l; or an HbA1c level of 5.7-6.4%. Informed consent was obtained from all patients before the start of the study.

Patients were randomly assigned to one of two groups: the treatment group (Group 1) or the control group (Group 2). Group 1 consisted of 37 patients with PD who received typical treatment according to the recommendations of the ADA, which included LF such as dietary changes and physical activity, as well as medication if necessary. Of the 37 patients in Group 1, 12 were men and 25 were women. Group 2 consisted of 42 patients with PD who did not receive any treatment and were advised to maintain their usual lifestyle. The patients in Group 2 were similarly divided into 15 men and 27 women.

Patients were included in the study if they met the following criteria: over 45 years old, diagnosed with PD based on the ADA criteria, and willing to participate in the study.

The following indicators were determined for all patients in the course of the study at the stages at the beginning of the study, at the 1st year of the study, at the 2nd year of the study, at the 3rd year of the study: BMI (and definitions of indicators that correspond to the normal value, overweight and obesity according to the degree of obesity); FPG and HbA1c; at the beginning of the study, medical documentation was analyzed and patients were interviewed about concomitant diseases.

A comprehensive search in the following databases PubMed, Scopus, and Web of Science Google Scholar, MEDLINE, Cochrane Library, databases was conducted to identify relevant studies published about the potential risk of development T2DM for patients with PD up until the cutoff date of September 2022. The search terms used were "prediabetes", "treatment of prediabetes", "type 2 diabetes mellitus", "type 2 diabetes", "treatment of type 2 diabetes mellitus", "risk factors", and "treatment".

The collected data were analyzed using descriptive statistics to obtain means, standard deviations, and frequencies. To compare the differences between the two groups, Student's t-test was used for continuous vari-

Table 1. Distribution of patients according to BMI in 1 and 2 groups at the beginning of the study.

	Normal weight (BMI is 18,5 kg/m² to 24,9 kg/m²), % of patient	Overweight (BMI is 25,0 kg/m² to 29,9 kg/m²) , % of patient	Obesity 1 stage (BMI is 30,0 kg/m² to 34,5 kg/m²) , % of patient	Obesity 2 stage (BMI is 35,0 kg/m² to 39,5 kg/m²), % of patient	Obesity 3 stage (BMI is ≥40,0 kg/m²) , % of patient
Group 1 (n=37)	5,41	21,62	27,03	37,84	8,11
Group 2 (n=42)	11,90 *	28,57 *	19,05 *	23,81 *	16,67 *

Note: BMI – body mass index; * - there is no statistically significant difference when comparing the indicators between the respective groups 1 and 2 (p>0,05);

Table 2. Characteristics of concomitant diseases in groups 1 and 2 at the beginning of the study.

Group / Diseases	Group 1 (n=37), %	Group 2 (n=42), %
Arterial hypertension	86,49	61,90
Chronic ischemic heart disease	43,24	33,33
Chronic kidney disease	24,32	23,81
Chronic pancreatitis	40,54	42,86
Dyslipidemia	16,22	19,05
Gout	13,51	14,29
Hyperuricemia	16,22	16,67
Non-alcoholic steatohepatitis	21,62	23,81
Obesity	72,97	59,52
Subclinical hypothyroidism	21,62	21,43

Table 3. Indicators of the level of FPG and HbA1c in groups 1 and 2, during the 3-year follow-up.

		At the beginning of study	1st year of study	2nd year of study	3rd year of study
Group 1 (n=37)	HbA1c (%)	5,8±0,12	5,7±0,09	5,9±0,11	6,1±0,13
	FPG (mmol/L)	5,9±0,1	5,3±0,12	6,2±0,07	5,8±0,09
Group 2 (n=42)	HbA1c (%)	6,4±0,1	6,1±0,14*	6,3±0,09*	6,6±0,12*
	FPG (mmol/L)	6,8±0,1	6,6±0,14*	7,1±0,12*	6,3±0,11*

Note: HbA1c - glycosylated hemoglobin are in %. FPG – Fasting plasma glucose; normal values of FPG – 3.3-5.5 mmol/l; normal values of HbA1C are below 5.7%, level of 5.7% to 6.4% indicates prediabetes, and a level of 6.5% or more indicates T2DM, * - statistically significant difference when comparing the indicators between the respective groups 1 and 2 (p<0.05).

Table 4. Detected cases of T2DM during a 3-year follow-up.

	1st Year of study (% of patients)	2nd Year of study (% of patients)	3rd Year of study (% of patients)
Group 1 (n=37)	10,81	18,92	13,51
Group 2 (n=42)	14,29*	19,05 *	23,81 *

Note: * - there is no statistically significant difference when comparing the indicators between the respective groups 1 and 2 (p>0.05);

ables, and the chi-squared test was used for categorical variables. The level of significance was set at p<0.05.

RESULTS

The study involved two groups of patients, with a mean age of 47.6 ± 2.3 years for the 1st group and 49.3 ± 2.1 years for the 2nd group. When comparing the age values between the two groups, no statistically significant difference was found (p<0,05).

Analyzing the BMI of patients in groups 1 and 2 at the beginning of the study, there was no statistically significant difference when comparing the indicators between the respective groups 1 and 2 (p>0,05) (Table 1). It is noteworthy that the majority of patients were either overweight or obese.

When analyzing the patients of both groups at the beginning of the study, regarding concomitant diseases, it was found that most of these patients have various concomitant diseases (Table 2).

Since the study continued during the pandemic of coronavirus disease (COVID-19), the number of patients who were infected during the 3-year observation period were analyzed. COVID-19 was confirmed by means of PCR test ing. Thus, 31 patients were infected with COVID-19 during the 3 years period in group I, while 39 patients were infected with COVID-19 during the 3 years period in group II.

Analyzing the indicators of FPG and HbA1c in groups 1 and 2, during the 3-year follow-up, a statistically significant difference was found when comparing FPG in

groups 1 and 2, during the 3-year follow-up (P<0.05), and a statistically significant difference was found when comparing HbA1c in groups 1 and 2, during the 3-year follow-up (P<0.05) (Table 3).

Analyzing the 3-year follow-up of patients with PD, cases of T2DM were detected in both groups, but there was no statistically significant difference when comparing the indicators between the respective groups 1 and 2 (p>0.05) (Table 4).

DISCUSSION

Despite the fact that PD has been sufficiently studied, it is not fully understood how long it takes for T2DM to appear. RFs for T2DM have been sufficiently studied, but it is not yet possible to state with certainty that the presence of one or a combination of several RFs will cause T2DM within 1-2 years [27, 28]. For example, people with the same RF may develop T2DM at different times in their lives, or never experience this problem [29]. Therefore, although PD and RF for T2DM are important risk indicators, they cannot be used as the only prognostic factors. Each person's risk of developing T2DM will be different, and it depends on many individual factors [30]. Therefore, research should continue, primarily RCTs, which will provide more information on the weight of a particular RF.

It is important to note that the development of T2DM is a complex process and is influenced by a combination of factors, both genetic and environmental. The timing and severity of T2DM may vary among individuals, even if they share the same set of RFs. Therefore, it is crucial to continue conducting RCTs and other types of research to gain a better understanding of the impact of each RF on T2DM development and to identify other potential RF. Ultimately, personalized approaches to T2DM prevention and management will be necessary, taking into account each individual's unique set of RFs and medical history.

In addition, ongoing research can help to develop effective interventions and treatment strategies that target specific RFs for T2DM. For example, lifestyle interventions (dietary changes and increased physical activity), have been shown to reduce the risk of T2DM in high-risk individuals. Other potential interventions include medi cations that target specific pathways involved in T2DM development, such as incretin-based therapies and sodium-glucose cotransporter 2 inhibitors. By identifying and targeting the specific RFs that contribute to T2DM development, we can not only prevent the disease from occurring but also reduce its associated complications and improve overall health outcomes.

CONCLUSIONS

In this manuscript, we review the risk criteria for predicting PD and discuss the RCTs that have been conducted in this area. Early identification and intervention in patients with PD are critical for preventing or delaying the onset of T2DM. Several RF have been identified for the development of T2DM in patients with PD, including age, BMI, FH, FGL, and HbA1c level. In addition, physical inactivity, poor diet, smoking, and low levels of HDL cholesterol are also significant RF. Healthcare providers should assess these RF in patients with PD and develop individualized prevention plans to reduce the risk of developing T2DM. It remains an open question how long it takes for PD to progress to DM and what factors influence this transformation, particularly when assessing individual risk. Nonetheless, the available evidence highlights the importance of identifying and managing PD to prevent the development of T2DM and associated health complications.

REFERENCES

1. Mzimela NC, Sosibo AM, Ngubane PS et al. The Changes in Red Blood Cell Indices That Occur in Pre-Diabetic Patients of all Ethnicities from the 25–45 Years of Age: A Protocol for a Systematic Review and Meta-Analysis. Methods and Protocols. 2023; 6(1):13.
2. Urgatz B, Razvi S. Subclinical hypothyroidism, outcomes and management guidelines: a narrative review and update of recent literature. Current Medical Research and Opinion. 2023; p.1-47.
3. Younossi Z, Tacke F, Arrese M et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2019; 69(6):2672-2682.
4. Hostalek U. Global epidemiology of prediabetes-present and future perspectives. Clinical diabetes and endocrinology. 2019; 5(1):5.
5. American Diabetes Association Professional Practice Committee, & American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2022; 45(1):S17-S38.
6. Cho NH, Shaw JE, Karuranga S et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes research and clinical practice. 2018; 138:271-281.
7. Lee SH, Park SY, Choi CS. Insulin resistance: from mechanisms to therapeutic strategies. Diabetes & Metabolism Journal. 2022; 46(1):15-37.
8. Mainous III AG, Rooks BJ, Wright RU et al. Diabetes Prevention in a US Healthcare System: A portrait of missed opportunities. American Journal of Preventive Medicine. 2022; 62(1):50-56.
9. Beulens JW, Pinho MG, Abreu TC el al. Environmental risk factors of type 2 diabetes—An exposome approach. Diabetologia. 2022; 65(2):263-274.
10. Meng XH, Huang YX, Rao DP et al. Comparison of three data mining models for predicting diabetes or prediabetes by risk factors. The Kaohsiung journal of medical sciences. 2013; 29(2):93-99.
11. Fang M, Wang D, Echouffo-Tcheugui, JB el all. Prediabetes and diabetes screening eligibility and detection in US adults after changes to US preventive services task force and American Diabetes Association Recommendations. JAMA. 2022; 327(19):1924-1925.
12. Hu X, Yu W, Yang et al. First-degree family history of diabetes is associated with nonalcoholic fatty liver disease independent of glucose metabolic status. Journal of Diabetes and its Complications. 2022; 36(1):108083.

13. Vandercappellen EJ, Koster A, Savelberg HH et al. Sedentary behaviour and physical activity are associated with biomarkers of endothelial dysfunction and low-grade inflammation—relevance for (pre) diabetes: The Maastricht Study. Diabetologia. 2022; 65(5):777-789.
14. Sweeting A, Wong J, Murphy HR. et al. A clinical update on gestational diabetes mellitus. Endocrine reviews. 2022; 43(5):763-793.
15. Haw JS, Shah M, Turbow S et al. Diabetes complications in racial and ethnic minority populations in the USA. Current diabetes reports. 2021; 21:1-8.
16. Nazarzadeh M, Bidel Z, Canoy D et al. Blood pressure lowering and risk of new-onset type 2 diabetes: an individual participant data meta-analysis. The Lancet. 2021; 398(10313):1803-1810.
17. Kapoor D, Kapoor R, Jhaveri K. Atherogenic Diabetic Dyslipidemia. Asian Journal of Research and Reports in Endocrinology. 2022, p.73.
18. Neves JS, Newman C, Bostrom JA et al. Management of dyslipidemia and atherosclerotic cardiovascular risk in prediabetes. Diabetes Research and Clinical Practice. 2022; 190:109980.
19. Helvaci N, Yildiz BO. The impact of ageing and menopause in women with polycystic ovary syndrome. Clinical Endocrinology. 2022; 97(3), 371-382.
20. Wang C, Tan J, Miao Y et al. Obstructive sleep apnea, prediabetes and progression of type 2 diabetes: A systematic review and meta-analysis. Journal of Diabetes Investigation. 2022; 13(8):1396-1411.
21. Dunkley AJ, Bodicoat DH, Greaves CJ et al. Diabetes prevention in the real world: Effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations – a systematic review and meta-analysis. Diabetes Care. 2021; 44(6):1302-1310.
22. Liu G, Li Y, Hu Y et al. Metformin for prediabetes: A systematic review and meta-analysis. Pharmacol Res. 2020; 160:105069.
23. Sun X, Li L, Li T et al. The combination of acarbose and metformin for the treatment of prediabetes: A double-blind, randomized, controlled trial. Diabetes Ther. 2019; 10(6):2217-2228.
24. Bailey TS, Ahmann A, Brazg R et al. Accuracy and acceptability of a factory-calibrated, real-time continuous glucose monitoring system during 10-day use in adults with type 1 and type 2 diabetes. Diabetes Technol Ther. 2020; 22(3):172-177.
25. Saslow LR, Daubenmier JJ, Moskowitz JT et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus and prediabetes. Nutr Diabetes. 2020; 10(1):1-9.
26. Xu L, Li Y, Yin L et al. The effect of dietary fiber intake on glycemic control, insulin resistance, and obesity in patients with prediabetes: A randomized controlled trial. Nutrients. 2021; 13(1):148.
27. Wondmkun YT. Obesity, insulin resistance, and type 2 diabetes: associations and therapeutic implications. Diabetes, metabolic syndrome and obesity: targets and therapy. Diabetes Metab Syndr Obes. 2020; 13:3611–3616.
28. Ismail L, Materwala H, Al Kaabi J. Association of risk factors with type 2 diabetes: A systematic review. Computational and structural biotechnology journal. 2021; 19:1759-1785.
29. Beulens JWJ, Rutters F, Ryden L et al. Risk and management of pre-diabetes. European journal of preventive cardiology. 2019; 26(2):47-54.
30. Yuan S, Larsson SC. An atlas on risk factors for type 2 diabetes: a wide-angled Mendelian randomisation study. Diabetologia. 2020; 63, 2359-2371.

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CONFLICT OF INTEREST
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