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A window of opportunity against diabetes: frequency of microvascular and macrovascular complications in prediabetes

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ABSTRACT

Objectives: To determine the chronic complications of diabetes mellitus (DM) in patients with prediabetes, and to compare prediabetics with normoglycemic group participants in terms of the presence of the complications of DM.

Methods: An observational study was conducted between December 2018 to April 2019. The patients aged 18-65 years were recruited from an internal medicine outpatient clinic of a tertiary care hospital. A total of 106 prediabetic patients and 54 normoglycemic subjects were included to the study. OGTT-0th, OGTT-2nd and HbA1c levels, lipid parameters, blood pressure, the homeostasis model assessment of insulin resistan (HOMA-IR), body mass index (BMI) were estimated. Nephropathy (urine protein/urine creatinine ratio, serum creatinine [sCre], Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation-- creatinine clearance), retinopathy by dilated fundus examination and neuropathy (10-g monofilament testing and electroneuromyography [ENMG]) were assessed.

Results: Age, gender, BMI, HOMA-IR, smoking status, lipid parameters, systolic blood pressure were similar in both groups. The values of oral glucose tolerance test (OGTT)-0th, OGTT-2nd and glycated hemoglobin (HbA1c) were higher in prediabetics. Although not statistically significant, proteinuria was slightly more occurred in the prediabetics than the controls. sCre was significantly higher, and CKD-EPI equation was significantly lower in prediabetics than in controls (p = 0.012, p = 0.001, respectively). We did not detected diabetic retinopathy in any participants. Neuropathy was slightly more occured in prediabetics, but it was not significantly different (p = 0.309). There were no correlation between sCre, CKD-EPI, proteinuria and age, BMI, HOMA-IR, OGTT-0th, OGTT-2nd, and HbA1c.

Conclusions: Managing the prediabetes by early diagnosis is very meaningful in terms of prevention from DM and its complications. So, prediabetes may be a window of opportunity for diabetes associated morbidity.

Keywords: Complications, nephropathy, neuropathy, prediabetes, retinopathy

Prediabetes (PD) is explained as an intermediate condition with plasma glucose levels ranging between normoglycemia and diabetes mellitus (DM) [1]. PD is classified as isolated impaired fasting glucose

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(IFG) (a fasting plasma glucose value of 100 to 125 mg/dL) or impaired glucose tolerance (IGT) (a 2-hour plasma glucose value of 140 to 199 mg/dL) in the 75-gram oral glucose tolerance test (OGTT). Glycated hemoglobin (HbA1c) level of 5.7% to 6.4% is also considered to be PD [1, 2].

The complications of PD and DM, which has rapidly increasing prevalence in many countries such as USA [2] and Turkey [3], are a major public health problem. These complications contain microvasculary (retinopathy, nephropathy and neuropathy) and macrovasculary complications (cardiovascular events, cerebrovascular disease and peripheral artery disease). As a result of complications of DM; hemodialysis, cardiac interventions, eye exams, various interventional procedures and surgical operations are being performed, that leads to an increase in economic costs, hospitalizations and mortality [4, 5]. In addition, quality of life and labor conditions are also severely affected [6]. Although these complications are relatively less in PD than DM, they can be seen even in the prediabetic stage of hyperglycemia [7, 8]. It is shown in many studies that PD was associated with cardiovascular events and mortality, but there are only a few studies that determining microvasculary complications in prediabetic patients compared to the normal population [9-11].

In our study, we aimed to determine the chronic complications of DM in prediabetic patients, and to compare prediabetics with normoglycemic control group participants in terms of the presence of the diabetic complications.

METHODS

Participants

A cross-sectional study was conducted between December 2018 - April 2019. Fasting plasma glucose (FPG) and HbA1c levels were determined for all participants who admitted to recruit voluntary healthy subjects in the tertiary hospital's internal medicine outpatient clinic for routine health control. Glucose values of OGTT-0th and OGTT-2nd were conducted for all participants without diagnosed diabetes. Then, people whom had blood glucose levels in prediabetic range, or normal range were included to the study, consecutively. PD was defined as 0-hour plasma glucose value (OGTT-0th) of 100-125 mg/dL (IFG) and/or 2-hour plasma glucose value (OGTT-2nd) of 140 mg/dL to 199 mg/dL (IGT) (1). HbA1c value of 5.7% to 6.4% was also considered to be PD [1].

A total of 160 participants (106 prediabetic and 54 control group participant), 18-65 years old, were enrolled to the study. Exclusion criteria were as follows: renal failure, proteinuria, recent urinary tract infection (UTI), corticosteroids use, and endocrinological disorders (diabetes mellitus, thyroid function disorders, cushing disease, acromegaly). Also, the patients did not have any announcement or educational programs including diet restriction or regular exercise.

Health Indicators

Height and weight were measured and body mass index (BMI) calculated as weight in kilograms divided by height in meters squared. BMI was categorized as normal (BMI < 30 kg/m^2), and obese (BMI: 30 kg/m^2 and above) [12].

Measurement of Laboratory Parameters

A fasting venous blood sample was collected after an overnight fast of at least 12-h for biochemical investigations and samples were processed at the hospital laboratory on the same day. Fasting plasma insulin (FPI) and glucose, serum blood urea nitrogen (BUN), serum creatinine (sCre), plasma and urine protein were estimated using a Roche Cobas 8000 immunoassay analyzer (Roche Diagnostics, USA). Plasma glucose values at 0th and 2nd hours were conducted by OGTT, and HbA1c levels were measured for all participants. HbA1c were estimated using an Adams A1c HA-8180V automatic analyzer (Arkray Diagnostics, USA). All assays were performed with specific kits and calibrators supplied by the manufacturers. While evaluating the status of complications, laboratory analyzes of the participants were also made on the same day.

Insulin Resistance (IR)

Twelve-hour fasting blood samples were obtained for FPI and FPG determinations in order to calculate the homeostasis model assessment of insulin resistance (HOMA-IR). It was defined by the formula [13]: HOMA-IR = FPI (mU/L) × FPG (mmol/L)/22.5. If the result is ≥ 2.5, it indicates the presence of insulin resistance. The higher the score, the greater the insulin

resistance is measured.

Nephropathy Assessment

A random spot urine sample was collected as part of each routine clinical assessment. Proteinuria is measured by "urine protein/urine creatinine ratio (PCR)". Creatinine clearance was evaluated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [14].

Ophthalmic Assessment

All patients with hyperglycemia received a comprehensive ophthalmic assessment consisting of autorefractometer measurement, visual acuity assessment with Snellen, slit-lamp biomicroscopy, stereoscopic fundus examination measurements. Mydriatic eye drops to dilate the pupils are administered before retinal examinations. A combination of 0.5% tropicamide and 2.5% phenylephrine was used to dilate the pupil. Patients with microaneurysms, retinal hemorrhage, macular edema, hard exudates, soft exudates, intraretinal microvascular abnormalities, neovascularization, vitreous hemorrhage who have one or more of findings were classified as diabetic retinopathy after dilated fundus examination by an ophthalmologist (ES) who was blinded to the paticipants' clinical data. The screening protocol was performed in accordance with the guideline recommendation [15].

Neuropathy Assessment

Symptoms and signs of neuropathy were assessed in all patients by a neurologist (MFG) who were blinded to the participants' clinical data. All patients were performed 10-g monofilament testing to identify feet at risk for neuropathy. Assessment for distal symmetric polyneuropathy were included a careful history and assessment of either temperature or pinprick sensation (small-fiber function). The screening protocol was performed in accordance with the guideline recommendation [15]. Patients who had suspicion of neuropathy referred to neurology department for electroneuromyography (ENMG). In all patients, neurophysiological studies were done using standard procedures by a neurologist (MFG) by using Nihon Kohden Neuropack MEB-9200 (4-channel amplifier). Measurements were performed at temperatures of 33-34 °C. The criteria suggested by the American Academy of Neurology and the American Academy of Physical Medicine and Rehabilitation were used in order to entrapment neuropathy and polyneuropathy [16]. Participants who had clinically neuropathy, and verified with electrodianostical test, determinated as neuropathy.

Macrovasulary Complications

Information about the diseases of the patients was obtained by anamnesis. Cardiovascular disease (CVD) was asked to the participants. It was accepted that there was no cardiovascular disease complication in patients with normal electrocardiogram and coronary angiography findings.

Ethical Issues

The patient's written informed constent to publish the clinical informations and materials was obtained. Ethical approval for the study is received from Erciyes University Ethical Committee. This trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

Statistical Analysis

A power analysis program, G*Power version 3.0.10 software (Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany), The values of CKD-EPI were taken into consideration for the post-hoc power analysis. The effect size of CKD-EPI values was 0.492. The study power was calculated as 0.90 for $\alpha = 0.05$ with a sample size of 54 in the control group and of 106 in the study group. Statistical analyses were performed using the SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Number of cases and percentages were used for categorical variables. Categorical data were analyzed by Chi-square or Fisher's exact test, where appropriate. Shapiro-Wilks test and histograms were used to determine whether continuous variables were normally distributed. Normally distributed variables were presented as means and standard deviations (SD), non-normally distributed variables were presented as medians and interquartile ranges (IQR). Two independent groups of parametric variables were compared using Student t test. For non-parametric variables Mann-Whitney U test was administered. Relationship between non-parametric variables were analyzed by Spearman correlation tests and relationship between parametric variables were analyzed by Pearson correlation tests. A p value of <

0.05 was considered to indicate statistically significant differences.

RESULTS

A total of 106 prediabetic patients and 54 control group participants, 18-65 years aged, were recruited to the study, consecutively. In prediabetic group, 54 (50.9 %) patients had IFG, 15 (14.2%) patients had IGT, 32 (30.2%) patients had both IFG and IGT and 5 (4.7%) patients had only isolated elevated HbA1c.

Age, gender, BMI and the presence of obesity, HOMA-IR and the presence of insulin resistance, systolic blood pressure, presence of hypertension and ACE-i/ARB user, lipid profile were similar in both

Table 1. Comparison of clinical data between prediabetics with the control group

	PD (n = 106)	Control (n = 54)	*p* value
Age (year) (mean ± SD)	49.07 (9.77)	47.00 (11.21)	0.253
Gender (F/M), n (%)	80/26 (75.5/24.5)	38/16 (70.4/29.6)	0.488
Smoking, n (%)			0.075
Never	79 (74.5)	38 (70.4)	
Quit	12 (11.3)	2 (3.7)	
Smoker	15 (14.2)	14 (25.9)	
Obesity (+), n (%)	72 (67.9)	30 (57.7)	0.206
BMI (kg/m^2) (mean±SD)	33.80 (7.50)	32.66 (8.17)	0.400
Hypertension (+), n (%)	22 (21)	8 (15.1)	0.375
ACE-I/ARB user, n (%)	18 (17.3)	4 (7.5)	0.096
Blood Pressure (S/D), median (IQR)	120 (20)/80 (10)	120 (17.5)/70 (10)	0.401/**0.019**
Lipid Profile			
Total cholesterol (mean ± SD)	204.4 (37.69)	200.6 (39.54)	0.353
LDL (mean ± SD)	126.7 (37.76)	120.3 (33.21)	0.234
HDL, median (IQR)	45 (13)	46.5 (12.5)	0.141
Triglyserides, median (IQR)	144 (91)	127 (92.25)	0.252
OGTT-0 (mean ± SD)	105.28 (8.03)	91.59 (5.54)	**< 0.001**
OGTT-2 (mean ± SD)	131.71 (32.36)	108.48 (16.28)	**< 0.001**
HbA1c, median (IQR)	5.90 (0.50)	5.50 (0.30)	**< 0.001**
HOMA-IR, median (IQR)	2.41 (2.20)	2.11 (2.08)	0.318
sCre (mean ± SD)	0.76 (0.11)	0.70 (0.13)	**0.012**
CKD-EPI equation--creatinine clearance (mean ± SD)	96.21 (12.35)	103.28 (11.50)	**0.001**
Proteinuria (mg/24 h), median (IQR)	70.30 (37.86)	64.07 (30.86)	0.298
Neuropathy, n (%)	20 (19.40)	8 (15.70)	0.309
Retinopathy, n (%)	0	0	-
CVD, n (%)	3 (2.83)	0	-

ACE-I = angiotensine converting enzyme inhibitör, ARB = angiotensine receptor blocker, BMI = body mass index, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CVD = cardiovasculary disease, HbA1c = glycated hemoglobin, F/M = female/male, OGTT = oral glucose tolerance test, HOMA-IR = the homeostasis model assessment of insulin resistance, sCre = serum creatinine, S/D = systolic/diastolic, SD = standard deviation. $p < 0.05$ considered statistically significant.

groups. OGTT-0th, OGTT-2nd and HbA1c were significantly higher in the prediabetics than in the normoglycemic participants.

Although proteinuria levels were similar (p = 0.298), sCre was significantly higher, and CKD-EPI-creatinine clearance was significantly lower in prediabetic group than in the control group (respectively; p = 0.012, p = 0.001).

Neuropathy was more occurred in PD group, but it was not significantly important (p = 0.309). Twenty (19.4%) prediabetic patients, and 8 (15.7%) control group participants had neuropathy. All neuropathic participants had entrapment neuropathy (median nerve), but in PD group two patients had also polyneuropathy (PNP). One of them had axonal PNP in lower extremities and the other one had sensory-motor mixt type PNP. Nobody had retinopathy in both groups.

In prediabetic group, three patients had CVD. In control group, participants had not any macrovascular complications. The comparison of prediabetic and control groups' data were summarized in Table 1.

Correlation analyses between sCre, CKD-EPI, proteinuria and age, BMI, HOMA-IR, OGTT-0th, OGTT 2nd, HbA1c were performed (Table 2). There were no significant relationship between parameters (r or rho < 0.250), except CKD-EPI and age, that was a negative good correlation (r: -0.511, p < 0.001).

DISCUSSION

In this study, the frequency of microvascular and macrovascular complications in prediabetic patients were determined, and when compared to the control group participants who had the similar age, gender, BMI and IR, similar frequency of microvascular complications were found.

Impaired glucose metabolism has a significant role in atherosclerosis. Previous studies show that increased plasma glucose level is a risk factor for CVD (cardiovascular death, myocardial infarction, stroke and peripheral artery disease) regardless of the presence of diabetes [9, 10, 17]. In our study, we determined three prediabetic patients with CVD. There was no CAD in the normoglycemics. Although our data in terms of macrovascular complications seemed to be incompatible with the literature [1, 3, 15], all of the prediabetic patients whom recruited to the study were newly diagnosed patients because of the study design. It is a new data for the literature that the lower frequency of macrovasculary complications in newly diagnosed prediabetic patients. This outcome also suggests that the earlier the prediabetes is diagnosed, the less complication and the economic burden can be prevented.

Diabetic nephropathy is the leading cause of renal failure and is responsible for morbidity and mortality in diabetes. Proteinuria is a marker of kidney injury, serving as a screening test as well as a means of assessing the degree of nephropathy and risk for cardiovascular events and death in both the diabetic and the non-diabetic population [18, 19]. Lots of studies have shown that the prevalence of microalbuminuria in patients with prediabetes was higher than normoglycemics [20, 21]. It was also reported that prediabetes is a significant risk factor for proteinuria compared to people with completely normal glucose levels in a population-based study conducted with 228778 subjects [22]. Proteinuria is associated with the presence of hypertension, and it is known that proteinuria can be prevented by using angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) [23]. Whereas there were twenty-two patients (21%) with hypertension in prediabetic subjects, in control group eight participants (15.1%) had hypertension in our study, and that difference between groups were not statistically significant. While there were eighteen (17.3%) participants

Table 2. Correlations of kidney function tests and glucose metabolism associated factors

	Age		BMI		HOMA-IR		OGTT-0		OGTT-2		HbA1c	
	r	*p* value	r	*p* value	rho	*p* value	r	*p* value	r	*p* value	rho	*p* value
sCre	-0.005	0.959	-0.237	0.014	-0.085	0.402	-0.016	0.869	-0.125	0.203	-0.064	0.515
CKD-EPI	**-0.511**	**< 0.001**	-0.047	0.632	0.171	0.090	-0.086	0.385	-0.018	0.857	-0.085	0.389
Proteinuria	0.103	0.300	0.171	0.085	0.170	0.094	0.050	0.615	0.066	0.507	-0.128	0.197

BMI = body mass index, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, HbA1c = glycated hemoglobin, HOMA-IR = the homeostasis model assessment of insulin resistance, OGTT = oral glucose tolerance test, sCre = serum creatinine

using ACEi or ARB in prediabetics, there were four (7.5%) participants using ACEi or ARB in control group. Again the difference between groups were not statistically significant. Thus, direct effect of prediabetes on proteinuria could observed. Although it was not statistically significant, proteinuria was a little more occured in the prediabetic patients than in the control subjects in our study. Insulin resistance has the main role in the pathophysiology of PD [24]. IR may also be one of the pathological links between prediabetes and renal dysfunction, as reflected by proteinuria [25, 26]. In our study, similar frequency of IR and similar values of HOMA-IR may be the reason of similar proteinuria levels in the prediabetics and control subjects.

Although PD was known to be a risk factor for development of proteinuria, it was shown to have no effect on CKD-EPI in a cross-sectional study with 228.778 Japanese whom aged ≥ 20 years [22]. Several previous population-based studies with 4 to 8 years of follow-up reported that PD did not decrease or increase CKD-EPI [27-29]. More recently, Kawata *et al*. [30] and Melsom *et al*. [31] were obtained unusual results in their studies. CKD-EPI values of prediabetic patients were higher than control group, so they interpreted it as a risk for development of glomerular hyperfiltration related to PD. But in our study, PD has a statistically significant worsening effect on the value of CKD-EPI ($p = 0.001$). To clarify the impact of PD on CKD-EPI, further studies with more patients are needed. In correlation analyses, there were no significant relationship between sCre, CKD-EPI, proteinuria and BMI, HOMA-IR, OGTT-0th, OGTT 2nd, HbA1c. These outcomes may be associated to study protocol. Because all the patients were newly diagnosed. As expected, only age and CKD-EPI had a negative good correlation.

Some authors described narrowing of arterioles lumen, reducing of blood flow in retinal vessels, venulary dilatation and chronic inflammation in PD and early DM without signs of retinopathy [32, 33]. But we did not detected diabetic retinopathy findings in any participants. This result of our study might depend on our evaluation of retinopathy by screening instead of advanced technological methods (laser dopler, adaptive optics, optical coherence tomography, etc.).

Though the epidemiological link between neuropathy and PD is controversial, common thought is that the frequency of neuropathy increases in patients with PD. One case-control study has been shown that a neuropathy incidence is 2% in both prediabetics and normoglycemics, but small fiber neuropathy was not evaluated in that study [34]. In a study, an age-adjusted prevalence of neuropathy of 11.2% in patients with PD and 3.9% in normoglycemic subjects was found [33]. The MONICA/KORA study demonstrated that neuropathy was more common in PD compared to normoglycemics [35]. Although not statistically significant, in our study, neuropathy was slightly more occured in the prediabetic group than the control one. Two third of the patients were obese. As the control group received a similar ratio of obese patients as the prediabetic group, the median nerve entrapment neuropathy in the control group was higher than the incidence in the normal population [36, 37]. Further studies evaluating CTS are needed in more prediabetic patients without obesity.

Limitations

One of the limitations of our study is that we did not measure the excretion of albumin. Although the proteinuria evaluation in the spot urine sample is more accurate than the use of a dipstick test, a timed 24-hour urine collection or/and albumin:creatinine ratio might be more precise in measuring proteinuria and diabetic nephropathy. Although the number of patients included in the study is more than the number of studies in the literature, another limitation is the small number of patients. Because PD is a common condition in the community. And, there is a need for longitudinal studies with a very large population to obtain clear data. Also, the nature of this study is a cross-sectional observational study. Prospective studies are needed for better detection of complications in patients with prediabetes.

CONCLUSION

Managing the PD by early diagnosis is very meaningful in terms of prevention from DM and its complications. Prediabetes may be a window of opportunity for diabetes associated morbidity and mortality. Further analysis on large cohort of patients would be helpful to understand the potential of PD.

Authors' Contribution

Study Conception: UST, MFG; Study Design UST, FT; Supervision: ES, FT; Funding: UST, MFG; Materials: UST, MFG; Data Collection and/or Processing: UST, ES; Statistical Analysis and/or Data Interpretation: UST, FT; Literature Review: UST, FT; Manuscript Preparation: UST and Critical Review: FT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The authors disclosed that they did not receive any grant during conduction or writing of this study.

Ethics Committee Approval

Ethics committee aproval was received from Erciyes University Ethical Committee (Approval Date: Fabruary 6, 2019; Approval Number: 2019/100).

Informed Consent

Written informed consent was obtained from the individuals who participated in this study.

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