Cardiovascular Risk Factors in Patients With Prediabetes and its Relationship With Metabolic Syndrome

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ABSTRACT

Introduction: Prediabetes, defined as high plasma glucose which is neither normoglycemic nor diabetic, is noteworthy in that it causes complications. We aimed to reveal cardiovascular risk factors and related parameters via comparing prediabetics with age, sex and body mass index-matched control group in this study.

Patients and Methods: The patients, aged 18-65 years, were recruited from a tertiary care hospital. A total of 74 patients with prediabetes were included into the study to be compared with the control group of 34 normoglycemic subjects. Laboratory parameters, health indicators, insulin resistance, SCORE and Framingham risk score of participants were measured for cardiovascular risk factors.

Results: Total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides, insulin resistance, smoking status, blood pressure, SCORE, Framingham risk score, waist circumference, cardiovascular conditions (coronary artery disease, stroke, heart failure, hyperlipidemia, hypertension) were statistically similar between the two groups. Oral glucose tolerance tests (0^{th}, 2^{nd}), HbA1c and CRP were higher in the prediabetic group. Patients with prediabetes had more common participants with metabolic syndrome. When some outcomes affecting the presence of metabolic syndrome in participants with prediabetics were evaluated by regression analyses, obesity and HDL were found to be related factors. There was no correlation between C-reactive protein and any parameter.

Conclusion: We report that cardiovascular risk factors, which are often overrated in number-driven targets and evidence-based approach of the treatment of diabetes, may present in the prediabetic stage before the onset of diabetes. In addition, the parameters related to these factors and the relationship of prediabetes with metabolic syndrome were revealed.

Key Words: C-Reactive protein; risk factors; metabolic syndrome; prediabetes

Prediyabet Olan Hastalarda Kardiyovasküler Risk Faktörleri ve Metabolik Sendrom ile İlişkisi

ÖZET

Giriş: Normoglisemik olmayan, ama diyabetik de olmayan yüksek plazma glukozu olarak tanımlanan prediyabet; komplikasyonlara yol açması nedeniyle dikkat çekicidir. Bu çalışmada; yaş, cinsiyet ve vücut kitle indeksi yönünden eşleştirilmiş prediyabet ve kontrol gruplarında, kardiyovasküler risk faktörleriyle ilişkili parametreleri karşılaştırmayı amaçladık.

Hastalar ve Yöntem: Üçüncü basamak bir hastaneden 18-65 yaşları arasındaki hastalar alındı. Prediyabetik olan 74 hasta ile normoglisemik 34 katılımcının olduğu kontrol grubu çalışmaya dahil edildi. Laboratuvar parametreleri, sağlık göstergeleri, insülin direnci, SCORE ve Framingham risk skorları kardiyovasküler risk faktörleri açısından ölçüldü.

Bulgular: Total kolesterol, düşük yoğunluklu lipoprotein-kolesterol, yüksek yoğunluklu lipoprotein-kolesterol, trigliseritler, insülin direnci, sigara içme durumu, kan basıncı, SCORE, Framingham risk skoru, bel çevresi, kardiyovasküler durumlar (koroner arter hastalığı, inme, kalp yetmezliği hiperlipidemi, hipertansiyon) iki grup arasında istatistiksel olarak benzerdi. Prediyabetik grupta oral glukoz tolerans testleri (0.,2.), HbA1c ve CRP daha yüksekti. Prediyabetli hastaların metabolik sendrom daha yaygın idi. Prediyabetli katılımcılarda metabolik sendrom varlığını etkileyen bazı sonuçlar regresyon analizleri ile değerlendirildiğinde, obezite ve HDL ilişkili faktörler olarak bulunmuştur. C-reaktif protein ile herhangi bir parametre arasında korelasyon yoktu.

Sonuç: Diyabet tedavisinin sayı güdümlü hedeflerinde ve kanıta dayalı yaklaşımda sıklıkla dile getirilen kardiyovasküler risk faktörlerinin diyabetin başlamasından önceki prediyabetik aşamada ortaya çıkabileceğini bildirdik. Ayrıca, bu faktörlerle ilişkili parametreler ve prediyabetin metabolik sendrom ile ilişkisi ortaya konulmuştur.

Anahtar Kelimeler: C-Reaktif protein; risk faktörleri; metabolik sendrom; prediyabet

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INTRODUCTION

Prediabetes (PD), defined as high plasma glucose which is neither normoglycemic nor diabetic, is noteworthy in that it causes complications[1]. The risk of developing type 2 diabetes mellitus (T2DM) is raised six fold in prediabetics, and PD has significant pathophysiological effects on not only insulin resistance (IR) but also cardiovascular disease (CVD)[2]. PD is known to be an increased risk factor for CVD. Whereas it is known that increased blood glucose level is the major risk factor for this, studies that reveal other factors are limited[3,4].

CVD, one of the leading causes of high morbidity and mortality in the world, is the focal point of all complications, as it accounts for up to 80% of deaths in patients with T2DM[5]. Clinical risk factors that affect cardiovascular events are mentioned in the literature as follows: age, hyperglycemia, hyperlipidemia, hypertension, chronic kidney disease, IR, obesity, waist circumference, metabolic syndrome (MetS), smoking, and etc[3].

In this study, prediabetic subjects were compared with age, sex and body mass index (BMI)-matched control group, and cardiovascular risk factors were evaluated. Factors related to the presence of MetS were revealed in prediabetics, who had more common participants with MetS. Correlation results of the C-reactive protein (CRP) level, which was shown to be higher in prediabetics, were also presented.

PATIENTS and METHODS

Design

A controlled, cross-sectional study was conducted from March to September 2019 in a tertiary city hospital.

Participants

Patients admitted for routine health check-up were included into the study and then classified as normal or prediabetic according to American Diabetes Association. PD was defined as OGTT-0^{th} 100-125 mg/dL and/or OGTT-2^{nd} 140-199 and/or HbA1c 5.7-6.4%[1].

Exclusion criteria were as follows: renal disorders (nephrotic syndrome, lupus, vasculitis, recent urinary tract infection, urinary calculus, renal failure), endocrinological disorders (diabetes mellitus, thyroid dysfunctions, Cushing disease, acromegaly), hematologic conditions (myeloproliferations or cytopenia), malignancies, treatment with corticosteroids.

Measurement of Laboratory Parameters

A fasting venous blood sample was collected after an overnight fast of at least 8-hour for biochemical investigations and samples were processed in the hospital laboratory on the same day. OGTT-0^{th}, OGTT-2^{nd}, fasting plasma insulin, total cholesterol, low-density lipoprotein-cholesterol (LDL-c), high-density lipoprotein-cholesterol (HDL-c), triglycerides, other biochemical tests, hemogram and C-reactive protein (CRP) were estimated using a Roche Cobas 8000 immunoassay analyzer (Roche Diagnostics, USA). Glycated hemoglobin (HbA1c) was 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.

Health Indicators

Waist circumference, evaluated approximately 2 cm below the navel, height, weight, and BMI were measured at the time of diagnosis. BMI was categorized as normal (< 30 kg/m^2) and obese (30 kg/m^2 and above)[6]. In order to exclude the effect of obesity, the control group consisted of subjects with similar BMI to the prediabetic group. Accompanied by waist circumference and laboratory findings, MetS were diagnosed defined on International Diabetes Federation diagnostic criteria[7].

Blood pressure was measured by the same nurse using an automatic blood pressure monitor. Hypertension was defined as either use of antihypertensive treatment or increased systolic blood pressure (≥ 140) and diastolic blood pressure (≥ 90)[8].

Hyperlipidemia was defined as either use of anti-lipidemic treatment or worsening of lipid profile according to ESC/EAS Guidelines for the Management of Dyslipidaemias[9].

It is stipulated to have a definitive diagnosis with at least one of the imaging methods (magnetic resonance imaging, echocardiography, computed tomography, angiography) for coronary artery disease, stroke and heart failure.

Insulin Resistance

Fasting blood samples were obtained for plasma insulin and plasma glucose determinations in order to calculate the homeostasis model assessment of insulin resistance (HOMA-IR). It was determined by the formula:

HOMA-IR = Fasting plasma insulin (mU/L) x Fasting plasma glucose (mmol/L)/22.5. If the result is ≥ 2.5, it indicates the presence of IR. The higher the score, the greater IR is measured[10].

SCORE

To calculate the predicted 10-year risk of CVD, we used the SCORE, which requires age, sex, total cholesterol level, smoking and systolic blood pressure[11]. The SCORE was expressed as percentage (%).

Framingham Risk Score (FRS)

To calculate the predicted 10-year risk of CVD, we used the FRS which requires age, sex, total cholesterol and HDL-c, smoking status, systolic blood pressure, treatment for hypertension and diabetes status. The FRS was expressed aspercentage (%)[12].

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 (IBM Corp., Armonk, NY, USA). Whereas parametric variables

were presented as means (standard deviations), non-parametric variables were presented as medians (interquartile ranges). Kolmogorov-Smirnov test and histograms analyses were used to determine if continuous variables were normally distributed or not. Two independent groups of parametric variables were compared using Student t test and non-parametric variables were used Mann Whitney U test. Categorical data were analyzed by Chi-square or Fisher's exact test. Binary logistic regression was used to estimate odds ratios (ORs) and 95% confidence interval. Relationship between non-parametric variables were analyzed by Spearman correlation tests. P value of < 0.05 was considered to indicate statistically significant differences.

RESULTS

A total of 74 subjects with prediabetes and age, sex, BMI-matched 34 control group participants were enrolled to the study.

Lipid profile (total cholesterol, LDL-c, HDL-c, triglycerides), HOMA-IR, the presence of IR, smoking status, alcohol use, systolic blood pressure, diastolic blood pressure, SCORE, FRS, waist circumference, cardiovascular conditions (coronary artery disease, stroke, heart failure, hyperlipidemia, hypertension) were statistically similar between the two groups. The comparison of thr prediabetic and control groups' data was summarized in Table 1.

Glycemic index (OGTT-0th, OGTT-2nd, HbA1c) and CRP were higher in the prediabetic group. Patients with PD had more common participants with MetS.

When some outcomes affecting the presence of MetS in participants with PD were evaluated by univariate and multiple regression analyses, obesity and HDL-c were found to be effective factors on this condition (Table 2). There was no correlation between CRP and any parameter (Table 3).

DISCUSSION

To the best of our knowledge, the present study is one of the few studies to explain whether PD is associated with risk factors of CVD. As expected from these results, the blood glucose panel (OGTT-0th, OGTT-2nd, HbA1c) was higher in the prediabetic group than in the normoglycemic control group. According to the findings obtained from other data, the presence of MetS was more common in prediabetics than normoglycemics. The source of the increased frequency of CVD in prediabetics previously shown in the literature may be related to the MetS. The frequency of increased cardiovascular events in MetS is already known[3]. In our study, which evaluated in age, sex and BMI-matched groups, the increase in the blood glucose panel and the presence of MetS can be shown as the factor of increased cardiovascular risk in patients with PD.

Even without T2DM, the natural course of hyperglycemia leads to IR, and IR increases in PD. Moreover, progression from PD to T2DM is due to the accompanying worsening of weight gain[13]. In our study, IR was found to be similar in prediabetics compared to the control group; this may be due to the design of the study as BMI-matched for more specific outcomes. According to our study, we showed that even if people are prediabetic, IR may not develop unless they gain weight. This is one of the indicators that weight control is the cornerstone of the fight against T2DM.

When meta-analysis and reviews and many prospective cohort studies are evaluated, they have been found to evaluate data for the association between coronary artery disease and congestive heart failure in prediabetics. In these studies, dyslipidemia and hypertension have been found quite prevalent among prediabetics[13,14]. Furthermore, it has been reported that PD is associated with obesity, MetS, hypertension, hypertriglyceridemia and decreased HDL-c levels[13]. Moreover, prediabetics have an increased risk of stroke[15]. Coronary artery disease, heart failure, dyslipidemia, stroke, hypertension were more common in the prediabetics in our study, but they were not statistically significant (Table 1). Comparison with obesity-matched control group may explain why this difference was not shown statistically. Triglyceride levels were also similar in the prediabetics compared to the control group in the present study; however, the presence of MetS was more common in individuals with PD, and the multivariate analysis suggested that these findings could be due to obesity and HDL-c levels (Table 2).

Inflammation plays a critical role in plaque formation and plaque rupture. For this reason, it is suggested that CRP, which is an acute phase reactant, can be used as a risk factor. There is also evidence that CRP has direct proinflammatory effects by triggering the synthesis of local adhesion molecules, reducing endothelial nitric oxide activity, altering LDL-c uptake by macrophages and stimulating intravascular thrombosis[16,17]. CRP levels increase with hypertension, obesity, smoking, MetS, T2DM, low HDL-c and high triglyceride levels[16-20]. The number of studies on the relationship between PD and CRP is quite limited. Although the CRP level has been shown to increase in prediabetics, there are comparatively scarce data. It is demonstrated that elevated serum CRP levels are associated with PD[21]. It has also been shown that elevated CRP levels independently predict the development of PD markers in subjects with normoglycemics, associated with elevated HbA1c levels[22] In another study, it has been revealed that elevated CRP is associated with high BMI and HbA1c, and low HDL-c in Korean children and adolescents[23]. In our study, CRP was higher in the prediabetic group in line with the literature. However, there was no correlation between CRP and any parameter (Table 3).

It is known that prediabetics with MetS progress to T2DM after several years[13]. In preventing the development of diabe-

Table 1. Comparison of clinical data between the prediabetic and control groups

	Prediabetes (n= 74)	Control (n= 34)	p
Sex (F/M), n (%)	55/19 (74.3/25.7)	23/11 (67.7/32.4)	0.495
Age (year), mean (SD)	52.07 (7.29)	50.03 (9.24)	0.262
BMI (kg/m^2), mean (SD)	34.16 (7.07)	32.58 (7.66)	0.314
Obesity (+) and, n (%)	53 (71.6)	20 (58.8)	0.194
OGTT-0, mean (SD)	104.92 (8.60)	32.38 (5.12)	**< 0.001**
OGTT-2, mean (SD)	132.61 (33.77)	108.15 (16.68)	**< 0.001**
HbA1c, median (IQR)	6.0 (0.4)	5.5 (0.2)	**< 0.001**
HOMA-IR, median (IQR)	2.28 (1.89)	2.52 (2.02)	0.763
IR (+) and, n (%)	33 (44.6)	17 (50.0)	0.679
Smoking status (yes/no), n (%)	57/17 (77.1/23.9)	22/12 (64.7/35.3)	0.242
Alcohol use (yes/no), n (%)	72 (97.3)	33 (97.1)	0.999
Systolic blood pressure, median (IQR)	120 (20.0)	120 (12.5)	0.287
Diastolic blood pressure, median (IQR)	80 (10.0)	80 (10.0)	0.086
Total cholesterol, mean (SD)	209.7 (39.4)	203.6 (38.0)	0.440
LDL-c, mean (SD)	130.4 (39.1)	119.5 (5.8)	0.144
HDL-c, median (IQR)	45.5 (14.3)	48.5 (14.7)	0.230
Triglycerides, median (IQR)	144.5 (97.0)	142.0 (96.5)	0.784
CRP, median (IQR)	4.4 (4.3)	2.1 (2.7)	**0.015**
SCORE, median (IQR)	0.0 (1.0)	0.0 (1.0)	0.697
10-year risk (FRS), median (IQR)	7.25 (6.73)	7.30 (6.65)	0.269
Waist circumference, mean (SD)	101.7 (13.7)	96.1 (15.0)	0.072
Metabolic syndrome (+) and, n (%)	44 (59.5)	9 (26.5)	**0.001**
Cardiovascular conditions			
Coronary artery disease	4 (5.4)	1 (2.9)	0.495
Stroke	1 (1.4)	0 (0.0)	0.685
Heart failure	1 (1.4)	0 (0.0)	0.685
Dyslipidemia	5 (6.7)	1 (2.9)	0.383
Hypertension	20 (27.0)	7 (20.6)	0.321
Total number of disease	31 (41.9)	9 (26.5)	0.091

F: Female, M: Male, SD: Standart deviation, BMI: Body mass index, OGTT: Oral glucose tolerance test, IQR: Interquartile range, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance, IR: Insulin resistance, MetS: Metabolic syndrome, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, CRP: C-reactive protein, FRS: Framingham risk score. (P< 0.05 considered statistically significant).

tes, the struggle against MetS in prediabetics should be more important, and in this context, attention and awareness should be increased on the level of HDL-c and the presence of obesity.

FRS is a gender-specific algorithm used to estimate 10-year CVD risk of patients. Risk estimation by FRS is very useful for both patients and physicians to decide whether lifestyle modification or preventive medical treatment is necessary to avoid CVD[24]. A study has reported that 68.6% of impaired glucose tolerance subjects were at low risk, 26.3% at moderate and 5.1% at high risk of developing CVD according to FRS[24]. In a retrospective but not controlled study evaluating 57 patients, median of FRS has been calculated as 5% in prediabetics[25]. To the best of our knowledge, there is no study in the literature (pubmed, google academic) comparing the FRS score of pre-

Table 2. Factors affecting the presence of metabolic syndrome in patients with prediabetes

	Univariate Analysis			Multivariate Analysis		
Variable	**P**	**OR**	**95% CI**	**P**	**OR**	**95% CI**
Sex	0.217	0.514	0.18-1.48	-	-	-
Age	0.895	1.004	0.94-1.07	-	-	-
BMI	**0.001**	1.170	1.07-1.28	0.841	0.982	0.82-1.18
Obesity	**< 0.001**	0.112	0.04-0.36	**0.034**	0.111	0.01-0.85
OGTT-0	0.323	1.026	0.98-1.08	-	-	-
OGTT-2	0.804	1.002	0.99-1.02	-	-	-
HbA1c	0.968	0.968	0.20-4.59	-	-	-
HOMA-IR	**0.023**	1.559	1.06-2.29	0.962	0.989	0.62-1.58
IR	**0.012**	0.276	0.10-0.76	0.577	0.608	0.11-3.49
Smoking status	0.086	2.643	0.87-8.01	-	-	-
Alcohol use	-	-	-	-	-	-
Systolic blood pressure	**0.004**	1.062	1.02-1.11	0.190	1.049	0.98-1.13
Diastolic blood pressure	**0.008**	1.075	1.02-1.13	0.728	1.018	0.92-1.13
Total cholesterol	0.278	0.993	0.98-1.01	-	-	-
LDL-c	0.141	0.990	0.98-1.00	-	-	-
HDL-c	**0.006**	0.928	0.88-0.98	**0.035**	0.924	0.86-0.99
Triglycerides	**0.009**	1.011	1.00-1.02	0.469	1.004	0.99-1.02
CRP, median (IQR)	0.508	0.980	0.93-1.04			
ESC Score	0.940	1.021	0.59-1.76	-	-	-
10-year risk (FRS), median (IQR)	0.270	1.045	0.97-1.13	-	-	-
Waist circumference	**< 0.001**	**1.086**	1.04-1.14	0.596	1.026	0.93-1.13

OR: Odds ratio, Cl: Confidence interval, BMI: Body mass index, OGTT: Oral glucose tolerance test, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance, IR: Insulin resistance, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, CRP: C-reactive protein, FRS: Framingham risk score. (P< 0.05 considered statistically significant).

Table 3. Correlation analysis of CRP levels in patients with prediabetes

	Rho	**p**		**Rho**	**p**
Age	0.148	0.210	Total cholesterol	-0.060	0.611
BMI	0.225	0.054	LDL-c	-0.090	0.448
OGTT-0	-0.118	0.316	HDL-c	-0.183	0.119
OGTT-2	0.203	0.083	Triglycerides	0.221	0.058
HbA1c	-0.058	0.624	SCORE	0.021	0.858
HOMA-IR	0.214	0.068	10-year risk (FRS), median (IQR)	0.131	0.266
Systolic blood pressure	0.081	0.494	Waist circumference	0.213	0.069
Diastolic blood pressure	0.073	0.535			

BMI: Body mass index, OGTT: Oral glucose tolerance test, HbA1c: Glycated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, FRS: Framingham risk score. (P< 0.05 considered statistically significant).

diabetic and healthy individuals, whereas there are many scoring studies in diabetics showing that the cardiovascular risk is increased[26-28]. In our study, similar results were obtained between the prediabetes group (7.25%) and the healthy control one (7.30%) in terms of FRS score (p= 0.269).

The Dyslipidemia Treatment Guide, published jointly by the European Cardiology Association and the European Atherosclerosis Association in July 2011, was handled within the scope of general cardiovascular prevention and developed approaches to some new cardiovascular scores[11]. In SCORE, which is one of these methods, analyses have been performed in patients with a history of T2DM, chronic kidney disease, peripheral artery disease, familial dyslipidemia, stroke, and severe hypertension, and it has been shown many times in the literature that these patients are in the high risk group[11,29]. According to this scoring system, comparison of prediabetic patients with the control group was made by us for the first time in the literature. In addition to the fact that we did not find any statistically significant difference between the two groups, there was low risk in the prediabetics.

CONCLUSION

We report that cardiovascular risk factors, which are often overrated in number-driven targets and evidence-based approach of the treatment of diabetes, may present in the prediabetic stage before the onset of diabetes. In addition, parameters related to these factors and the relationship of prediabetes with metabolic syndrome were revealed.

Ethics Committee Approval: The approval for this study was obtained from Erciyes University Ethics Committee (Number: 2019/100, Date: 06.02.2019).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - UST; Analysis/Interpretation - UST; Data Collection - UST; Writing - UST; Critical Revision - UST; Final Approval - UST; Statistical Analysis - UST; Overall Responsibility - UST.

Conflict of Interest: The authors have no conflict of interest to declare.

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