European Review for Medical and Pharmacological Sciences 2023; 27: 7557-7568

Vascular complications and associated comorbidities in newly diagnosed pre-diabetes: is it the tip of the iceberg?

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Abstract. – OBJECTIVE: The aim of this study was to investigate the prevalence of microvascular and macrovascular diabetic complications and the associated comorbidities in newly diagnosed pre-diabetic individuals.

PATIENTS AND METHODS: This cross-sectional study includes 100 newly diagnosed pre-diabetic individuals. Fasting plasma glucose, HbA1c, and oral glucose tolerance (OGTT) were tested according to the American Diabetes Association's diagnostic criteria for pre-diabetes, besides anthropometric measurements, lipid profiles, and demographic and biochemical parameters. Comorbidities like hypertension, obesity, dyslipidemia etc., were evaluated. All participants were screened for microvascular (retinopathy, nephropathy, neuropathy) and macrovascular [coronary artery disease (CAD) and cerebrovascular event-peripheral artery disease] complications.

RESULTS: Microvascular complications were found in 12% of the participants (neuropathy: 4%, nephropathy: 8%) and 19% had macrovascular complications. Of the participants, 21% of the cases presented hypertension, 21% dyslipidemia and 48% obesity. A high probability of developing non-alcoholic fatty liver disease-related fibrosis [estimated using non-alcoholic fatty liver disease fibrosis score (NFS)] was found in 68% of cases. History of dyslipidemia (OR: 5.00, 95% CI: 1.10-22.56; *p*=0.037) was an independent risk factor for the development of vascular complications.

CONCLUSIONS: Diabetic vascular complications were found in approximately one-third of pre-diabetic cases. Dyslipidaemia was found to be an important risk factor for the development of vascular complications in these individuals.

Key Words:
Prediabetes, Diabetic complications, Microvascular, Macrovascular, Comorbidities, Risk factors.

Introduction

Pre-diabetes (PD) is an intermediate stage of diabetes mellitus (DM) in which an individual's normal and high plasma glucose levels do not meet the diagnostic criteria for diabetes mellitus[1]. Currently, PD demarcates individuals with impaired fasting plasma glucose and glucose tolerance. Based on the 2021 data published by the International Diabetes Federation[2] regarding the individual components of PD, the worldwide prevalence rates for impaired glucose tolerance and impaired fasting glucose are reported as 10.6% (541 million individuals) and 6.2% (319 million individuals), respectively; a drastic increase in these numbers is predicted by 2045. Notably, the majority of PD individuals are from low- and middle-income nations (69.2%), and approximately half of these individuals are less than 50 years of age[1,2].

Previous studies[3,4] have shown that PD increases the risk of developing DM by 4.66-12.13 times, and HbA1c levels of 6.0%-6.5% contribute to a 50% increase in the risk of diabetes. Furthermore, there is evidence suggesting that PD increases the risk of any cause of mortality, cardiovascular disease, chronic kidney disease, certain cancers, and dementia[5]. Although there are continual advancements in the treatment of diabetes mellitus every day, the condition remains an important cause

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of mortality and morbidity, with diabetic macro and microvascular complications being the most significant causes. There is a strong relationship between the duration (in years) of diabetes and its complications; however, micro and macrovascular complications may develop during the pre-diabetic stage as well[6]. Palladino et al[7] reported that about half of the patients diagnosed with type 2 DM already had some macro or microvascular complications at the time of diagnosis.

There is ample literature demonstrating that, besides being a precursor to diabetes, PD itself constitutes an important cause of mortality and morbidity. Accordingly, decreasing its prevalence may help prevent diabetic complications and any-cause mortality, and delay the progression to diabetes. For this purpose, a comprehensive assessment of the relationship between PD and diabetic complications is needed. Therefore, the present study aimed to determine the prevalence of diabetic micro and macrovascular complications in pre-diabetic individuals, as well as the risk factors that influence diabetic complications in these patients.

Patients and Methods

Study Design and Population

This cross-sectional study was conducted at a tertiary diabetes care center between August 2021 and April 2022. We included subjects aged >18 years of age, who had normal vitamin B12 and folic acid levels, and were diagnosed with pre-diabetes in the diabetes clinic. Using power analysis, a minimum sample size of 72 was determined using the following values: 5% α error, test power (1-β)=0.8, and effect size=0.57 with a two-sided alternative hypothesis (H1). Pregnant or breastfeeding females, patients who had neurological or renal diseases of non-diabetic origin, rheumatological diseases, were receiving chemotherapy or radiotherapy, had a history of organ transplantation, acute infections, chronic liver disease, chronic alcohol consumption or were infected with hepatitis A, B, C or HIV were excluded from the study. The study was approved by Malatya Clinical Research Ethics Committee (04.08.2021/165). Written informed consent was obtained from all participants.

Data Collection

Detailed anamnesis and systemic examination for all participants were undertaken by an endocrinologist working at the diabetes clinic; participants' sociodemographic data, medical history, and physical examination findings were recorded in data collection forms. The following biochemical tests were performed on blood samples collected after 12 hours of fasting: plasma glucose, HbA1c, insulin, oral glucose tolerance test (OGTT), blood urea nitrogen (BUN), creatinine, uric acid, Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, triglycerides (TG), high-density lipoproteins-cholesterol (HDLc), vitamin D, vitamin B12, folic acid, C-reactive protein (CRP), and complete blood count. HbA1c was measured by the high-performance liquid-chromatography method (Adams A1c Ha-8160-BIODPC SN:10912002 Manufacturer: Arkray Factory Inc. 1480 Koji, Konan-Cho, Koka-Shi Shiga, Japan European Representative Arkray Europe, Prof. J.H. Bavincklaan 51183 At Amstelveen, The Netherlands made In Japan)[8]. Low-density lipoprotein cholesterol (LDLc) was estimated using the Friedewald formula: LDL-c=(Total cholesterol, CHL)−(HDLc)−(TG/5)[9]. Insulin, C-peptide was measured by chemiluminescence immunoassay (ADVIA Centaur® XPT, SN: IRL09441548, Made in: Ireland, Siemens Healthcare Diagnostics Inc. 511 Benedict Avenue Tarrytown, NY 10591-5097 USA, EC REP: Siemens Healthcare Diagnostics Ltd. Sir William Siemens Sq Frimley, Camberley, UK GU16 8QD). Vitamin B12 and folic acid were measured using a chemiluminescence immunoassay (Beckman Coulter Dxl800, lnc. 4300 N. Harbor Blvd. Fullerton, CA. 92835 USA, Revision date November 2008 and Beckman Coulter Treiand Inc. Mervue Business Park, Mervue, Galway. Ireland 353 91 774068) and CRP by the nephelometric method (Type BN II System, SN: 202826, Siemens Healthcare Diagnostics Products GmbH, 35041 Marburg, Germany). Vitamin D levels were measured with the liquid-chromatography tandem-mass-spectrometry (LC-MS/MS) method (Thermo Fisher Scientific, TSQ Series Mass Spectrometer System TQU04576 Quantum Access MAX, 355 River Oaks Parkway San Jose, CA, USA). Automated urine sediment analysis was performed by complete urinalysis flow cell digital imaging and automated urine chemistry analysis by dual-wavelength reflectance photometry (BT URICELL 1280-1600 URINALYSIS)[10]. Arterial blood pressure (ABP) was measured by the endocrinologist using an automated oscillometric measuring device on both arms after at least five minutes of

quiet rest in the sitting position and ensuring no smoking or caffeine intake in the last 30 minutes; the measurement was repeated after five minutes. Weight and height measurements were also taken by the nurse using a height and weight scale (Jadever-Türkter NLD-W 300 kg). Additionally, all patients were given 82.5 g glucose monohydrate dissolved in 300 ml water over 10 minutes as per the standard OGTT protocol; plasma glucose analysis was performed 2 hours after the administration.

Definitions

A diagnosis of pre-diabetes was defined by the presence of at least one of the following criteria: a) fasting plasma glucose (FPG)=100-125 mg/dl (impaired fasting glucose, IFG); b) OGTT 2-hr PG=140-199 mg/dl (impaired glucose tolerance, IGT); c) HbA1c levels=5.7%-6.4%[11].

Insulin resistance of the participants was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) formula: fasting plasma glucose (mmol/L) × Fasting plasma insulin (mIU/L)/22.5; a cut-off value of ≥2.5 was considered to ascertain insulin resistance[12]. For evaluating vascular complications, a positive history of coronary artery disease (CAD) and cerebrovascular disease was noted. In addition, the electrocardiography (ECG) results of all participants were examined for vascular complications according to the Minnesota Code Classification[13].

Retinopathy was examined by a senior ophthalmologist using dilated fundus examination and retinal imaging by optic coherence tomography (OCT), which is widely used in ophthalmology practice. For evaluating nephropathy, spot urine samples obtained before blood sampling were examined for the protein-creatinine ratio. Nephropathy was divided into three groups: mild (<150), moderate (150-500), and severe (>500) in mg/g. Abnormal parameters were tested again after six weeks. In addition, an estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula; eGFR percentiles were calculated, and values above the 95th percentile were defined as glomerular hyperfiltration (GH). An eGFR of <60 mL/min/1.73 m^2 was used to ascertain chronic kidney disease (CKD)[14].

Neuropathy was evaluated using electroneurography (ENG), neurological examination, and the Michigan Neuropathy Screening Instrument (MNSI). An MNSI score of 4 out of 15 on the items regarding symptoms (numbness, tingling, burning, pain) and ≥2.5 on the physical findings' items (physical appearance of the skin of the feet, presence of ulcerations, deep tendon reflexes, and reduced duration of vibration) indicated neuropathy[15]. The following neurological examination findings were documented – hypoesthesia, reduced tendon reflexes, reduced vibration, and motor deficit. Patients with an abnormal ENG accompanied by the aforementioned MNSI scores in the presence of characteristic symptoms and examination findings were confirmed as having polyneuropathy (PNP). Patients with normal ENG but having neuropathic symptoms without any examination findings other than hypoesthesia were evaluated as having potential small fiber neuropathy[15].

Patients with a body mass index (BMI) of 25-30 kg/m^2 were diagnosed as overweight, and those with BMI ≥30 kg/m^2 were diagnosed as obese. For some comparisons, we categorized BMI ≥27 kg/m^2 as metabolically obese[16].

Dyslipidemia (DL) was classified as follows: TG ≥150 mg/dL, LDLc ≥100 mg/dL, and HDLc <60 mg/dL. Arterial blood pressure (ABP) was classified as follows: normal (<120/80 mmHg), elevated blood pressure (120-139/80-89 mmHg); hypertension (≥140/90 mmHg). For some comparisons, we categorized blood pressure (BP) ≥130/85 mmHg as high normal BP[17].

Non-alcoholic fatty liver disease (NAFLD) was classified using NAFLD fibrosis scores (NFS): low probability (<1.455), intermediate probability (≤-1.455 and ≤0.676), or high probability (>0.676) of significant fibrosis estimated by an automatic calculator. The NFS is a simple scoring system based on the patient's age, hyperglycemia, BMI, platelet count, albumin, and the AST/ALT ratio, which are markers of advanced liver fibrosis[18].

Statistical Analysis

Descriptive statistics for the quantitative data were presented as mean±standard deviation, and categorical variables were presented as frequency (n) and percentage (%). The Shapiro-Wilk test was used to assess how closely quantitative variables adhered to the normal distribution. Multivariable logistic regression was performed to compare the risk of having diabetic complications. The adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were determined. Statistical significance was accepted as $p \leq 0.05$. All calculations were performed using SPSS

(Statistical Package for Social Sciences version 23; SPSS IBM Corp., Armonk, NY, USA).

Results

The baseline characteristics of study participants are shown in Table I. We recruited a total of 100 individuals with PD in the study, of whom 52% (n=52) were males. Regarding the American Diabetes Association's (ADA) criteria, 35% of the participants had IFG, 10% had isolated IGT, and 55% had combined glucose intolerance (CGI). We also evaluated comorbidities; 21% had HT (≥140/90 mmHg), 53% had high normal BP (≥130/85 mmHg), 21% had dyslipidemia (any of the parameters), 48% were obese (BMI≥30 kg/m^2), and 77% were metabolically obese (BMI≥7 kg/m^2). Microvascular complications and macrovascular complications were in 12 and 19% of the study population, respectively (Table I).

Regarding the biochemical parameters, the mean HbA1c was 5.92%±0.18%, the mean fasting blood glucose level was 106.55±8.45 mg/dl, and the mean postprandial glucose was 142.44±29.79 mg/dl. The mean systolic blood

Table I. Demographic and laboratory findings of the study population.

Variables		n	%
Gender	Male	52	52.0
	Female	48	48.0
Age	<40	24	24.0
	≥40	76	76.0
HbA1c (%)	<6	58	58.0
	≥6	42	42.0
Prediabetes type	IFG	35	35.0
	IGT	10	10.0
	CGI	55	55.0
Blood Pressure	Normal (<120/80)	27	27.0
(mm/Hg)	Elevated	52	52.0
	HT (>140/90)	21	21.0
High BP	No	47	47.0
(≥130/85 mmHg)	Yes	53	53.0
HOMA-IR (≥2.5)	No	39	39.0
	Yes	61	61.0
BMI (kg/m^2)	Normal	13	13.0
	Overweight	39	39.0
	Obese	48	48.0
BMI-Metabolically	<27	33	33.0
obese (kg/m^2)	≥27	77	77.0
TG (mg/dL)	<150	57	57.0
	150-400	43	43.0
LDL (mg/dL)	LDL<100	27	27.0
	LDL≥100	73	73.0
HDL (mg/dL)	HDL≥60	22	22.0
	HDL<60	78	78.0
DL (any of	No	79	79.0
parameters)	Yes	21	21.0
Smoking	No	64	64.0
	Yes	36	36.0
History of GDM	No	43	89.6
	Yes	5	10.4
HT	No	76	76.0
	Yes	24	24.0
DL	No	92	92.0
	Yes	8	8.0
	Yes	8	8.0

Variables		n	%
Medications	NO	79	79.0
	ACEI-ARB	13	13.0
	Statin-fenofibrate	8	8.0
Family History-DM	No	39	39.0
	Yes	61	61.0
VIT-D (ng/ml)	≤20	63	63.0
	>20	37	37.0
High ALT	No	89	89.0
	Yes	11	11.0
NFS			
	<-1.455	4	4.0
	Indeterminate	28	28.0
	>0.675	68	68.0
Vascular	No	72	72.0
complications	Yes	28	28.0
Macro-vascular	No	81	81.0
complications	Yes	19	19.0
CAD	No	81	81.0
	Yes	19	19.0
CAD-History	No	91	91.0
	Yes	9	9.0
Ischemia finding	No	91	91.0
on ECG	Yes	9	9.0
CVD&PAD&	No	99	99.0
CAD-History	Yes	1	1.0
Micro-vascular	No	88	88.0
complications	Yes	12	12.0
Diabetic	No	96	96.0
polyneuropathy	Yes	4	4.0
Retinopathy	No	100	100.0
	Yes	0	0.0
Nephropathy	No	92	92.0
	Yes	8	8.0
Glomerular	No	95	95.0
Hyperfiltration	Yes	5	5.0
ENG-CTS	No	88	88.0
	Yes	12	12.0

Blood pressure (BP), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), body mass index (BMI), triglycerides (TG), high-density lipoproteins (HDL), Low-density lipoprotein (LDL), Dyslipidemia (DL), alanine aminotransferase (ALT), non-alcoholic fatty liver disease fibrosis score (NFS), coronary artery disease (CAD), cardiovascular diseases (CVD), electroneurography (ENG), Gestational diabetes (GDM), Hypertension (HT).

pressure of the study sample was 122.39±16.20 mmHg, and the diastolic blood pressure was 79.96±9.76 mmHg. The mean BMI of the sample was 30.66±6.51 kg/m^2.

When evaluating the risk factors affecting HbA1c levels, we found that participants aged ≥40 years had higher HbA1c levels compared to those aged <40 years (odds ratio, OR: 5.00, 95% confidence intervals, CI: 1.56-16.0; p=0.004). Those with CGI had higher HbA1c levels compared to those with IFG and IGT (OR: 3.99, 95% CI: 1.68-9.47; p=0.001). Furthermore, BMI≥27 kg/m^2 was an independent risk factor for high HbA1c levels (OR: 3.33, 95% CI: 1.12-9.87; p=0.025) (Table II).

Likewise, participants aged ≥40 years were at a greater risk for CGI (OR: 3.24, 95% CI: 1.23-8.52; p=0.014). Additionally, the risk of CGI was higher

Table II. Comparison of vascular complications, risk factors, and clinical characteristics according to HbA1c levels.

Variables		HbA1c<6% n (%)	HbA1c≥6% n (%)	Total n (%)	OR (95% CI)	p-value
Age (year)	<40	20 (83.3)	4 (16.7)	24 (100.0)	Ref	0.004
	≥40	38 (50.0)	38 (50.0)	76 (100.0)	5.00 (1.56-16.0)	
Gender	Male	34 (65.4)	18 (34.6)	52 (100.0)	Ref	0.119
	Female	24 (50.0)	24 (50.0)	48 (100.0)	1.88 (0.84-4.22)	
Vascular	No	41 856.9)	31 (43.1)	72 (100.0)	Ref	0.732
complications	Yes	17 (60.7)	11 (39.3)	28 (100.0)	0.85 (0.35-2.08)	
Macro-vascular	No	46 (56.8)	35 843.2)	81 (100.0)	Ref	0.613
Complications	Yes	12 (63.2)	7 (36.8)	19 (100.0)	0.76 (0.27-2.14)	
Micro-vascular	No	51 (58.0)	37 (42.0)	88 (100.0)	Ref	0.980
Complications	Yes	7 (58.3)	5 (41.7)	12 (100.0)	0.98 (0.29-3.34)	
Neuropathy	No	55 (57.3)	41 (42.7)	96 (100.0)	Ref	0.637
	Yes	3 (75.0)	1 (25.0)	4 (100.0)	0.44 (0.04-4.45)	
Nephropathy	No	3 (75.0)	1 (25.0)	4 (100.0)	Ref	0.717
	Yes	54 (58.7)	38 (41.3)	92 (100.0)	1.42 (0.33-6.03)	
Glomerular	No	57 (60.0)	38 (40.0)	95 (100.0)	Ref	0.158
Hyperfiltration	Yes	1 (20.0)	4 (80.0)	5 (100.0)	6.00 (0.64-55.76)	
ENG-CTS	No	53 (60.2)	35 839.3)	88 (100.0)	Ref	0.222
	Yes	3 (41.7)	7 (58.3)	10 (100.0)	2.12 (0.62-7.21)	
CAD	No	46 (56.8)	35 (43.2)	81 (100.0)	Ref	
	Yes	12 (63.2)	7 (36.2)	19 (100.0)	0.76 (0.27-2.14)	0.613
Smoking	No	36 (56.3)	28 (43.8)	64 (100.0)	Ref	
	Yes	22 (61.1)	14 (38.9)	36 (100.0)	0.81 (0.35-1.88)	0.636
HT-History	No	48 (63.2)	28 (36.8)	76 (100.0)	Ref	
	Yes	10 (41.7)	14 (58.3)	24 (100.0)	2.4 (0.94-6.11)	0.063
DL-History	No	54 (58.7)	38 (41.3)	92 (100.09)	Ref	0.717
	Yes	4 (50.0)	4 (50.0)	8 (100.0)	1.42 (0.33-6.03)	
Pre-diabetes type	IFG&IGT	34 (75.6)	11 (24.4)	45 (100.0)	Ref	0.001
	CGI	24 (43.6)	31 (56.4)	55 (100.0)	3.99 (1.68-9.47)	
BMI (kg/m^2)	<27	18 (78.5)	5 (21.7)	23 (100.0)	Ref	0.025
	≥27	40 (51.9)	37 (48.1)	77 (100.0)	3.33 (1.12-9.87)	
Triglyceride	<150	33 (57.9)	24 (42.1)	57 (100.0)	Ref	0.980
	≥150	25 (58.1)	18 (41.9)	43 (100.0)	0.99 (0.44-2.20)	
LDL	<100	16 (59.3)	11 (40.7)	27 (100.0)	Ref	0.877
	≥100	42 (57.5)	31 (42.5)	73 (100.0)	1.07 (0.43-2.63)	
HDL	<60	12 (54.5)	10 (45.5)	22 (100.0)	Ref	0.710
	≥60	46 (59.0)	32 (41.0)	78 (100.0)	0.83 (0.32-2.16)	
High BP	No	29 (50.0)	18 (42.9)	47 (100.0)	Ref	0.480
(≥130/85 mmHg)	Yes	29 (50.0)	24 (57.1)	53 (100.0)	1.33 (0.60-2.96)	
Vit-D	≤20	24 (64.9)	13 (35.1)	37 (100.0)	Ref	0.286
	>20	34 854.0)	29 (46.0)	63 (100.0)	1.57 (0.68-3.63)	
HOMA-IR	No	25 864.1)	14 (35.9)	39 (100.0)	Ref	0.323
	Yes	33 (54.1)	28 (45.9)	61 (100.0)	1.51 (0.66-3.46)	
NFS	Low&inter	21 (65.6)	11 (34.4)	32 (100.0)	Ref	0.289
	High	37 854.4)	31 (45.6)	68 (100.0)	1.60 (0.66-3.82)	

Blood pressure (BP), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), body mass index (BMI), high-density lipoproteins (HDL), Low-density lipoprotein (LDL), Dyslipidemia (DL), non-alcoholic fatty liver disease fibrosis score (NFS), coronary artery disease (CAD), electroneurography (ENG), Hypertension (HT).

in those with HbA1c≥6% (OR: 3.99, 95% CI: 1.68-9.47; p=0.001), high normal BP≥130/85 mmHg (OR: 2.62, 95% CI:1.16-5.90; p=0.018) and BMI ≥27 kg/m^2 (OR: 4.95, 95% CI: 1.75-14.03; p=0.001) compared to the risk of IFG or IGT alone (Table III).

Furthermore, positive history of DL (OR: 5.00, 95% CI: 1.10-22.56; p=0.037) was independent risk factors for vascular complications. (Table IV).

No statistically significant differences were observed between the independent variables examined in the study and the diabetic microvascular complications of the participants (Table V).

Lastly, the history of DL was an independent risk factor for diabetic macrovascular complications (OR: 5.13, 95% CI: 1.15-22.82; p=0.040). Participants with TG levels ≥150 mg/dl had a higher risk for diabetic macrovascular complications than those with TG levels <150 mg/dl (OR: 0.28, 95% CI: 0.08-0.94; p=0.032) (Table VI).

Table III. Comparison of vascular complications, risk factors and clinical characteristics according to pre-diabetes subtypes.

Variables		IFG&IGT n (%)	CGI n (%)	Total n (%)	OR (95% CI)	p-value
Age (year)	<40	16 (66.7)	8 (33.7)	24 (100.0)	Ref	0.014
	≥40	29 (38.2)	47 (61.8)	76 (100.0)	3.24 (1.23-8.52)	
Gender	Male	27 (51.9)	25 (48.1)	52 (100.0)	Ref	0.148
	Female	18 (37.5)	30 (52.5)	48 (100.0)	80 (0.81-3.99)	
Vascular complications	No	31 (43.1)	41 (55.9)	72 (100.0)	Ref	0.531
	Yes	14 (50.0)	14 (50.0)	28 (100.0)	0.75 (0.31-1.81)	
Macro-vascular	No	37 (45.7)	44 (54.3)	81 (100.0)	Ref	0.778
Complications	Yes	8 (42.1)	11 (57.9)	19 (100.0)	1.15 (0.42-3.17)	
Micro-vascular	No	38 (43.2)	50 (56.8)	88 (100.0)	Ref	0.322
Complications	Yes	7 (58.3)	5 (41.7)	12 (100.0)	0.54 (0.16-1.84)	
Neuropathy	No	42 (43.2)	54 (56.3)	96 (100.0)	Ref	0.324
	Yes	3 (75.09)	1 (25.0)	4 (100.0)	0.25 (0.02-2.58)	
Nephropathy	No	41 (44.6)	51 (55.4)	92 (100.0)	Ref	0.999
	Yes	4 (50.0)	4 (50.0)	8 (100.0)	0.80 (0.18-3.41)	
Glomerular						
Hyperfiltration	No	44 (46.3)	51 (53.7)	95 (100.0)	Ref	0.375
	Yes	1 (20.0)	4 (80.0)	5 (100.0)	3.45 (0.37-32.0)	
ENG-CTS	No	40 (45.5)	48 (54.5)	88 (100.0)	Ref	0.805
	Yes	5 (41.7)	7 (58.3)	12 (100.0)	1.16 (0.34-3.95)	
CAD	No	38 (46.9)	43 (53.1)	81 (100.0)	Ref	0.427
	Yes	7 (36.8)	12 (63.2)	19 (100.0)	1.51 (0.54-4.24)	
Smoking	No	27 (42.2)	37 (57.8)	63 (100.0)	Ref	0.451
	Yes	18 (50.0)	18 (50.0)	36 (100.0)	0.73 (0.32-1.65)	
HT-History	No	35 (46.1)	41 (53.9)	76 (100.0)	Ref	0.707
	Yes	10 (41.7)	14 (58.3)	24 (100.0)	1.19 (0.47-3.02)	
DL-History	No	41 (44.6)	51 (55.4)	92 (100.0)	Ref	0.999
	Yes	4 (50.0)	4 (50.0)	8 (100.0)	0.80 (0.18-3.41)	
BMI (kg/m^2)	<27	17 (73.9)	6 (26.1)	23 (100.0)	Ref	0.001
	≥27	28 (36.4)	49 (63.6)	77 (100.0)	4.95 (1.75-14.03)	
Triglyceride	<150	29 (50.9)	28 (49.1)	57 (100.0)	Ref	0.174
	≥150	16 (37.2)	27 (62.8)	43 (100.0)	1.78 (0.77-3.91)	
LDL	<100	13 (48.1)	14 (51.9)	27 (100.0)	Ref	0.700
	≥100	32 (43.8)	41 (56.2)	73 (100.0)	1.19 (0.49-2.88)	
HDL	<60	6 (27.3)	16 (72.7)	22 (100.0)	Ref	0.058
	≥60	39 (50.0)	39 (50.0)	78 (100.0)	0.37 (0.13-1.05)	
High BP	No	27 (60.0)	20 (36.4)	47 (100.0)	Ref	0.018
(≥130/85 mmHg)	Yes	18 (40.0)	35 (63.6)	53 (100.0)	2.62 (1.16-5.90)	
Vit-D	≤20	20 (54.1)	17 (45.9)	37 (100.0)	Ref	0.163
	>20	25 (39.7)	38 (60.3)	63 (100.0)	1.78 (0.78-4.06)	
HOMA-IR	No	20 (51.3)	19 (48.7)	39 (100.0)	Ref	0.313
	Yes	25 (41.0)	36 (59.0)	61 (100.0)	1.51 (0.67-3.40)	
NFS	Low&inter	15 (46.9)	17 (53.1)	32 (100.0)	Ref	0.796
	High	30 (44.1)	38 (55.9)	68 (100.0)	1.11 (0.48-2.59)	

Blood pressure (BP), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), body mass index (BMI), high-density lipoproteins (HDL), Low-density lipoprotein (LDL), Dyslipidemia (DL), non-alcoholic fatty liver disease fibrosis score (NFS), coronary artery disease (CAD), electroneurography (ENG), Hypertension (HT).

Table IV. Risk factors associated with vascular complications (VAC).

Variables		VAC NO n (%)	VAC YES n (%)	Total n (%)	OR (95% CI)	*p*-value
Age (year)	<40	20 (83.3)	4 (16.7)	24 (100.0)	Ref	0.156
	≥40	52 (68.4)	24 (31.6)	76 (100.0)	2.30 (0.71-7.49)	
Gender	Male	37 (71.2)	15 (28.8)	52 (100.0)	Ref	0.844
	Female	35 (72.9)	13 (27.1)	48 (100.0)	0.91 (0.38-2.19)	
Glomerular	No	68 (71.6)	27 (28.4)	95 (100.0)	Ref	0.999
Hyperfiltration	Yes	4 (80.0)	1 (20.0)	5 (100.0)	0.63 (0.06-5.89)	
ENG-CTS	No	64 (72.7)	24 (27.3)	88 (100.0)	Ref	0.785
	Yes	8 (66.7)	4 (33.3)	12 (100.0)	1.33 (0.36-4.83)	
CAD	No	71 (87.7)	10 (12.3)	81 (100.0)	Ref	<0.001
	Yes	1 (5.3)	18 (94.7)	19 (100.0)	127.80 (15.34-1,064.39)	
HbA1c	<6	41 (70.7)	17 (29.3)	58 (100.0)	Ref	0.732
	≥6	31 (73.8)	11 (26.2)	42 (100.0)	0.85 (0.35-2.08)	
Smoking	No	45 (70.3)	19 (29.7)	64 (100.0)	Ref	0.616
	Yes	27 (75.0)	9 (25.0)	36 (100.0)	0.78 (0.31-1.99)	
HT-History	No	56 (73.7)	20 (26.3)	76 (100.0)	Ref	0.504
	Yes	16 (66.7)	8 (33.3)	24 (100.0)	1.40 (0.52-3.76)	
DL-History	No	69 (75.0)	23 (25.0)	92 (100.0)	Ref	0.037
	Yes	3 (37.5)	5 (62.5)	8 (100.0)	5.00 (1.10-22.56)	
Pre-diabetes type	IFG&IGT	31 (68.9)	14 (31.1)	45 (100.0)	Ref	0.531
	CGI	41 (71.5)	14 (25.5)	55 (100.0)	0.75 (0.31-1.81)	
BMI (kg/m^2)	<27	15 (65.2)	8 (34.8)	23 (100.0)	Ref	0.409
	≥27	57 (74.0)	20 (26.0)	77 (100.0)	0.65 (0.25-1.78)	
Triglyceride	<150	37 (64.9)	20 (35.1)	57 (100.0)	Ref	0.069
	≥150	35 (81.4)	8 (18.6)	43 (100.0)	0.42 (0.16-1.08)	
LDL	<100	19 (70.4)	8 (29.6)	27 (100.0)	Ref	0.825
	≥100	53 (72.6)	20 (23.4)	73 (100.0)	0.89 (0.33-2.37)	
HDL	<60	16 (72.7)	6 (27.3)	22 (100.0)	Ref	0.931
	≥60	56 (71.8)	22 (28.2)	78 (100.0)	1.04 (0.36-3.02)	
High BP	No	36 (50.0)	11 (39.3)	47 (100.0)	Ref	0.335
(≥130/85 mmHg)	Yes	36 (50.0)	17 (60.7)	53 (100.0)	1.54 (0.63-3.75)	
Vit-D	≤20	46 (73.0)	17 (27.0)	63 (100.0)	Ref	0.768
	>20	26 (70.3)	11 (29.7)	37 (100.0)	0.87 (0.35-2.14)	
HOMA-IR	No	24 (61.5)	15 (38.5)	39 (100.0)	Ref	0.062
	Yes	48 (78.7)	13 (21.3)	61 (100.0)	0.43 (0.17-1.05)	
NFS	Low&inter	19 (59.4)	13 (40.6)	32 (100.0)	Ref	0.054
	High	53 (77.9)	15 (22.1)	68 (100.0)	0.41 (0.16-1.02)	
Family history-DM	No	31 (79.5)	8 (20.5)	39 (100.0)	Ref	0.182
	Yes	41 (67.5)	20 (32.8)	61 (100.0)	1.89 (0.73-4.85)	

Blood pressure (BP), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), body mass index (BMI), high-density lipoproteins (HDL), Low-density lipoprotein (LDL), Dyslipidemia

Discussion

Despite an increase in the diagnosis of PD, there is a dearth of literature evaluating both macrovascular and microvascular complications in this population. In this study, we found a 12% prevalence of general diabetic microvascular complications and 19% for diabetic macrovascular complications in individuals with PD. The existing literature reports a 7.9% prevalence of retinopathy and 12% for nephropathy in pre-diabetic individuals[19]. The pre-diabetic state has been shown[20] to increase the risk for cardiovascular events, especially coronary heart disease and related mortality. Mohan et al[21] determined a 14.9% prevalence of CAD in pre-diabetic individuals. Therefore, it is imperative to look out for diabetic complications as an important cause of mortality and morbidity in pre-diabetic individuals. Accordingly, it can be reasonably recommended that individuals diagnosed with PD should be regularly screened for macrovascular and microvascular diabetic complications.

In the current study, the diabetic retinopathy (DR) screening was performed by fundoscopy and OCT, and we did not find any signs of DR in our study sample. These results may be explained by the fact that the study sample consisted of

Table V. Risk factors associated with micro-vascular complications (MIC).

Variables		MIC NO n (%)	MIC YES n (%)	Total n (%)	OR (95% CI)	*p*-value
Age (year)	<40	22 (91.7)	2 (8.3)	24 (100.0)	Ref	0.725
	≥40	66 (86.8)	10 (13.2)	76 (100.0)	1.66 (0.33-8.19)	
Gender	Male	44 (84.6)	8 (15.4)	52 (100.0)	Ref	0.278
	Female	44 (91.7)	4 (8.3)	48 (100.0)	0.50 (0.14-1.78)	
Glomerular	No	84 (88.4)	11 (11.6)	95 (100.0)	Ref	0.480
Hyperfiltration	Yes	4 (80.0)	1 (20.0)	5 (100.0)	1.90 (0.19-18.6)	
ENG-CTS	No	78 (88.6)	10 (11.4)	88 (100.0)	Ref	0.634
	Yes	10 (83.3)	2 (16.7)	12 (100.0)	1.56 (0.29-8.16)	
CAD	No	72 (88.9)	9 (11.1)	81 (100.0)	Ref	0.694
	Yes	16 (84.2)	3 (15.8)	19 (100.0)	1.50 (0.36-6.17)	
Pre-diabetes type	IFG&IGI	38 (84.4)	7 (15.6)	45 (100.0)	Ref	0.322
	CGI	50 (90.9)	5 (9.1)	55 (100.0)	0.54 (0.16-1.84)	
HbA1c	<6	51 (87.9)	7 (12.1)	58 (100.0)	Ref	0.980
	≥6	37 (88.19)	5 (11.99)	42 (100.0)	0.98 (0.29-3.34)	
Smoking	No	55 (85.9)	9 (14.1)	64 (100.0)	Ref	0.529
	Yes	33 (91.7)	3 (8.3)	36 (100.0)	0.55 (0.14-2.20)	
HT-History	No	67 (88.2)	9 (11.8)	76 (100.0)	Ref	0.999
	Yes	21 (87.5)	3 (12.5)	24 (100.0)	1.06 (0.26-4.29)	
DL-History	No	81 (88.0)	11 (12.0)	92 (100.0)	Ref	0.999
	Yes	7 (87.5)	1 (12.5)	8 (100.0)	1.05 (0.11-9.38)	
BMI (kg/m^2)	<27	19 (82.6)	4 (17.4)	23 (100.0)	Ref	0.464
	≥27	69 (89.6)	8 (10.4)	77 (100.0)	0.55 (0.15-2.02)	
Triglyceride	<150	49 (86.0)	8 (14.0)	57 (100.0)	Ref	0.471
	≥150	39 (90.7)	4 (9.3)	43 (100.0)	0.62 (0.17-2.24)	
LDL	<100	24 (88.9)	3 (11.1)	27 (100.0)	Ref	0.999
	≥100	64 (88.7)	9 (12.3)	73 (100.0)	1.12 (0.28-4.50)	
HDL	<60	20 (90.2)	2 (9.1)	22 (100.0)	Ref	0.999
	≥60	68 (87.2)	10 (12.8)	78 (100.0)	1.47 (0.29-7.26)	
High BP	No	42 (47.7)	5 (41.7)	47 (100.0)	Ref	0.693
(≥130/85 mmHg)	Yes	46 (52.3)	7 (58.3)	53 (100.0)	1.27 (0.37-4.33)	
Vit-D	≤20	58 (92.1)	5 (7.9)	63 (100.0)	Ref	0.120
	>20	30 (81.1)	7 (18.9)	37 (100.0)	0.36 (0.10-1.26)	
HOMA-IR	No	31 (79.5)	8 (20.5)	39 (100.0)	Ref	0.056
	Yes	57 (93.4)	4 (6.6)	61 (100.0)	0.27 (0.07-0.97)	
NFS	Low&inter	27 (84.4)	5 (15.6)	32 (100.0)	Ref	0.514
	High	61 (89.7)	7 (10.3)	68 (100.0)	0.62 (0.18-2.12)	
Family history-DM	No	36 (92.3)	3 (7.7)	39 (100.0)	Ref	0.358
	Yes	52 (85.2)	9 (14.8)	61 (100.0)	2.07 (0.52-8.20)	

Blood pressure (BP), Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), body mass index (BMI), high-density lipoproteins (HDL), Low-density lipoprotein (LDL), Dyslipidemia (DL), non-alcoholic fatty liver disease fibrosis score (NFS), coronary artery disease (CAD), electroneurography (ENG), diabetes mellitus (DM), Hypertension (HT).

newly diagnosed PD individuals. Diabetic retinopathy complications may not develop until very long into the disease course. Similarly, Yadav et al[22] also reported that there were no signs of DR among PD individuals in their study. Furthermore, a previous study[23] described that no significant differences in terms of retinal damage were observed in pre-diabetic individuals as compared to their healthy counterparts in Turkish participants. In contrast, a 6% prevalence of DR was reported[24] in Asian pre-diabetics. Nevertheless, a meta-analysis[25] suggested that the prevalence and risk of DR were elevated in PD individuals, warranting preventive measures against DR in this population. The development of DR in PD may be affected by factors, such as disease duration, ethnicity, gender and comorbidities[22]. Prospective cohort studies that consider confounding factors may elucidate the risk and prevalence of DR in pre-diabetics.

In the current study, proteinuria (≥150 mg/d) and dipstick positivity were found in 8% of the participants, and GH was determined in 5% of the pre-diabetic individuals; however, there were no cases of chronic kidney failure (eGFR<60 ml/min/1.73 m^2). Melson et al26 reported that PD increased the risk of GH and proteinuria. Moreover, Kim et al[27] reported an 11.3% prevalence of CKD in a pre-diabetic sample they followed up

Table VI. Risk factors associated with macro-vascular complications (MAC).

Variables		MAC NO n (%)	MAC YES n (%)	Total n (%)	OR (95% CI)	*p*-value
Age (year)	<40	22 (91.7)	2 (8.3)	24 (100.0)	Ref	0.149
	≥40	66 (86.8)	10 (13.2)	76 (100.0)	3.16 (0.67-14.85)	
Gender	Male	42 (80.8)	10 (19.2)	52 (100.0)	Ref	0.951
	Female	39 (81.3)	9 (18.8)	48 (100.0)	0.96 (0.35-2.63)	
ENG-CTS	No	71 (80.7)	17 (19.3)	88 (100.0)	Ref	0.999
	Yes	10 (83.3)	2 (16.7)	12 (100.0)	0.83 (0.16-4.17)	
Pre-diabetes type	IFG&IGI	37 (82.2)	8 (17.8)	45 (100.0)	Ref	0.778
	CGI	44 (80.0)	11 (20.0)	55 (100.0)	1.15 (0.42-3.17)	
HbA1c	<6	46 (79.3)	12 (20.7)	58 (100.0)	Ref	0.613
	≥6	35 (83.3)	7 (16.79)	42 (100.0)	0.76 (0.27-2.14)	
Smoking	No	51 (79.7)	13 (20.3)	64 (100.0)	Ref	0.656
	Yes	30 (83.3)	6 (16.7)	36 (100.0)	0.78 (0.27-2.28)	
HT-History	No	63 (82.9)	13 (17.1)	76 (100.0)	Ref	0.386
	Yes	18 (75.0)	6 (25.0)	24 (100.0)	1.61 (0.53-4.85)	
DL-History	No	77 (83.7)	15 (16.3)	92 (100.0)	Ref	0.040
	Yes	4 (50.0)	4 (50.0)	8 (100.0)	5.13 (1.15-22.82)	
BMI (kg/m^2)	<27	17 (73.9)	6 (26.1)	23 (100.0)	Ref	0.367
	≥27	64 (83.1)	13(16.9)	77 (100.0)	0.57 (0.19-1.73)	
Triglyceride	<150	42 (73.7)	15 (26.3)	57 (100.0)	Ref	0.032
	≥150	39 (90.7)	4 (9.3)	43 (100.0)	0.28 (0.08-0.94)	
LDL	<100	21 (77.8)	6 (22.2)	27 (100.0)	Ref	0.617
	≥100	60 (82.2)	13 (17.8)	73 (100.0)	0.75 (0.25-2.25)	
HDL	<60	16 (72.7)	6 (27.3)	22 (100.0)	Ref	0.355
	≥60	65 (83.3)	13 (16.7)	78 (100.0)	0.53 (0.17-1.62)	
High BP	No	40 (49.4)	7 (36.8)	47 (100.0)	Ref	0.324
(≥130/85 mmHg)	Yes	41 (50.6)	12 (63.2)	53 (100.0)	1.67 (0.59-4.68)	
Vit-D	≤20	49 (77.8)	14 (22.2)	63 (100.0)	Ref	0.284
	>20	32 (86.5)	5 (13.5)	37 (100.0)	1.82 (0.60-5.57)	
HOMA-IR	No	29 (74.4)	10 (25.6)	39 (100.0)	Ref	0.176
	Yes	52 (85.2)	9 (14.8)	61 (100.0)	0.50 (0.18-1.37)	
NFS	Low&inter	23 (71.9)	9 (28.7)	32 (100.0)	Ref	0.111
	High	58 (85.3)	10 (14.7)	68 (100.0)	0.44 (0.15-1.22)	
Family history-DM	No	33 (84.6)	6 (15.4)	39 (100.0)	Ref	0.461
	Yes	48 (78.7)	13 (21.3)	61 (100.0)	3.76 (0.46-30.5)	

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), body mass index (BMI), high-density lipoproteins (HDL), Low-density lipoprotein (LDL), Dyslipidemia (DL), non-alcoholic fatty liver disease fibrosis score (NFS), diabetes mellitus (DM), Hypertension (HT).

over a period of 8.7 years. Overall, these results emphasize the fact that PD predisposes the patient to proteinuria and GH; therefore, early preventive measures should be followed in these patients.

Diabetic polyneuropathy (PNP) was only found in 4% of the study population. It is known that PNP may occur in the pre-diabetic population and Ziegler et al[28] reported a prevalence of 11%-25% in the pre-diabetic stage. Diabetic PNP is associated with higher mortality; accordingly, measures to prevent or delay the development of neuropathy in these individuals may reduce diabetes-related mortality and morbidity. Although PNP is commonly observed in both PD and diabetes, the affected individuals do not have enough awareness about neurological complications. Bongaerts et al[29] reported that around 90% of pre-diabetics and 70% of diabetics were not aware of their distal sensorimotor PNP. The current study results corroborate the findings that PNP develops early in the pre-diabetic stage; therefore, we recommend that individuals with PD undergo regular screening to reduce PNP-related morbidity.

We also investigated the prevalence of CAD in individuals with PD to examine the prevalence of macrovascular complications in this population. Diabetes mellitus is known to be a major risk factor for cardiovascular diseases (CVD), and it is known that PD also plays an important role in atherosclerosis and CVD. A previous cohort study[30] reported that 35% of patients, who were admitted for myocardial infarction and did not have a history or diagnosis of diabetes, were diagnosed with IGT. Although the relationship between PD

and CVD has been demonstrated in literature, postprandial glucose levels have been reported[31] to have a stronger relationship with the risk of CVD. Patients with IGT were at a greater risk of CVD than patients with IFG. These results further corroborate the relationship between PD and the prevalence of CAD. Future studies should conduct separate prevalence analyses with respect to IGT, IGF and HbA1c levels in PD for further elucidation.

Regarding the screening for NAFLD, we found that 68% of our participants had a high probability of fibrosis, while 28% had an intermediate probability of developing fibrosis; only 4% of the sample had a low probability of developing NAFLD-related fibrosis. Notably, the ALT levels were normal in 89% of our participants. Cuthberson et al[32] also reported that the risk of NAFLD was higher in pre-diabetics. On the other hand, a previous study[33] reported that only 8.1% of their participants had a high probability of developing NAFLD-related fibrosis based on the NFS results. The greater number of participants with a high probability of fibrosis in the present study may be explained by the fact that our entire study population was composed of pre-diabetic individuals, with the majority being obese. Future studies with larger sample sizes are needed to shed light on the prevalence of NAFLD in pre-diabetics.

It is known[34] that the reduction and prevention of diabetic complications depend on strict glycemic control. The current evidence outlines a link between HbA1c variability, cardiovascular mortality, and diabetic complications[20,31]. In this context, the current study investigated the factors affecting HbA1c levels and found that age≥40 years, BMI>27 kg/m^2, and CGI (IFG+IGT) were risk factors for higher HbA1c. Previous studies[7,35] have identified age, and total cholesterol as risk factors for high HbA1c. The relationship between increasing age and the risk of diabetes has already been delineated; additionally, the existing evidence[6] shows that visceral adiposity is associated with insulin resistance. Therefore, pre-diabetic complications may be mitigated by promoting healthy weight control and reducing visceral adiposity.

We also determined the risk factors for CGI in the present study age≥40 years, high normal BP (≥130/85 mmHg), HbA1c levels>6%, and BMI>27 kg/m^2. In addition, the presence of a DL-history was a risk factor for vascular complications. It can be reasonably assumed that identifying and eliminating the modifiable risk factors in the management of the pre-diabetic stage may reduce vascular complications. Previous literature[36] has shown that age, disease duration, BMI, total cholesterol, HDL, LDL, TG, gender, habitual smoking, hypertension, dyslipidemia, and poor plasma glucose regulation are associated with vascular complications. We also pointed out that modifiable risk factors, such as dyslipidemia, obesity, hypertension, and high HbA1c levels, were associated with vascular complications. Therefore, managing these modifiable risk factors in the prediabetic stage could be the most effective method of reducing diabetes-related complications.

Limitations and Strengths

The current study has some limitations. Since the primary objectives were the determination of the prevalence of vascular complications and associated comorbidities in prediabetic subjects, we did not compose a control group. We included 100 subjects (more than the required number calculated using power analysis), however, more subjects would be better to evaluate the cause-effect relationship between complications, risk factors and laboratory parameters. Another issue, we just calculated NFS but did not further evaluate non-alcoholic steatohepatitis (NASH) with ultrasonography or liver biopsy.

Strengths of the study

To our knowledge, this study is the first study evaluating all vascular complications using ENG and OCT in newly diagnosed prediabetes. All parameters that would affect vascular complications were meticulously excluded. All vascular complications were specifically evaluated by the experts (cardiologist, ophthalmologist, neurologist, and endocrinologist).

Conclusions

Diabetic vascular complications were found in approximately one-third of pre-diabetic cases. The current study suggested that prediabetes may associate with micro and macrovascular diabetic complications and comorbidities like obesity, hypertension, and dyslipidemia. We believe that diabetic vascular complications cannot be reduced without reducing the prevalence of prediabetes and early intervention. Our finding highlights the importance of early diagnosis and evaluation of vascular complications and comorbid diseases in prediabetic subjects.

Conflict of Interest
The authors declare that they have no conflict of interest.

Authors' Contributions
Genç S, Evren B, Aykaç KN, Yavuz AÖ, Bozbay A: Conceptualization, Methodology, Investigation, Data collection, Çankaya C, Yildiz B, Eren H, Tecellioğlu M: Conceptualization, Methodology, Investigation. Yakar B, Önalan E, Şahin IS: Investigation, Methodology, Formal analysis, Writing – original draft, Supervision. Şahin İ: Conceptualization, Methodology, Formal analysis, Supervision, writing – review & editing.

Availability of Data and Materials
All data generated or analyzed during this study are included in this article.

Funding
This article did not receive any grant or other form of financial support.

Ethics Approval
The study was approved by Malatya Inonu University Clinical Research Ethics Committee (04.08.2021/165).

Informed Consent
Written informed consent was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Acknowledgments
The authors are grateful to the Society of Endocrinology and Metabolism of Turkey for providing language assistance.

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