

# Carotid intima-media thickness values are significantly higher in patients with prediabetes compared to normal glucose metabolism

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## Abstract

Carotid intima-media thickness (C-IMT) increases in patients with adult type-2 diabetes mellitus (DM) and is used for early detection of macrovascular complications. We aimed to investigate the change of C-IMT in prediabetes and type-2 DM patients compared to subjects with normal glucose metabolism (NGM).

A total of 180 individuals (60 subjects with NGM, 60 patients with prediabetes and 60 patients with type-2 DM) were included in this study. Routine laboratory and micro-macrovascular involvement were investigated. Urine albumin-creatinine ratio (ACR) was measured for urinary albuminuria detection. In addition to routine laboratory examination, right-left common and internal C-IMT (CC-IMT and IC-IMT) were measured.

Systolic and diastolic blood pressure values were found to be higher in prediabetes and type-2 DM groups than NGM group. The prevalence of nephropathy and presence of CAD were higher in type-2 DM groups than prediabetes. Glucose, glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, blood urea nitrogen, creatinine, high sensitive C reactive protein (hs-CRP) levels and urinary ACR were significantly higher in patients within prediabetes and type-2 DM groups than NGM group. Glucose, HbA1c and hs-CRP levels were found to be higher in type-2 DM groups than prediabetes. Estimated glomerular filtration rate and high-density lipoprotein (HDL) cholesterol level was found to be lower in patients within prediabetes and type-2 DM groups than NGM group. Right-left-mean CC-IMT and IC-IMT values were found to be higher in prediabetes and type-2 DM groups than NGM group. Left IC-IMT, left CC-IMT, and mean IC-IMT values were found to be higher in type-2 DM patients compared to prediabetes. LDL and HDL cholesterols, HbA1c, and hs-CRP levels were independently associated with IC-IMT and CC-IMT.

C-IMT values were significantly higher in impaired glucose metabolism compared to NGM. C-IMT measurement may be used as part of routine screening of macrovascular complication in patients with prediabetes and newly diagnosed type-2 DM.

**Abbreviations:** ACR = albumin-creatinine ratio, A-IMT = aortic intima media thickness, BUN = blood urea nitrogen, CAD = coronary artery disease, CC-IMT = common C-IMT, C-IMT = carotid intima media thickness, C-US = carotid ultrasonography, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, HDL = high-density lipoprotein, hs-CRP = high sensitive C reactive protein, HT = hypertension, IC-IMT = internal C-IMT, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, LDL = low-density lipoprotein, NGM = normal glucose metabolism.

**Keywords:** diabetes mellitus, intima-media thickness, macrovascular complications, prediabetes

## 1. Introduction

Type-2 diabetes mellitus (DM) is a chronic, progressive disease and causes microvascular and macrovascular complications in many organs including the eyes, kidneys, heart, and peripheral vessels and

nerves in the long term. These organ involvements are the most common causes of increased mortality and morbidity due to DM. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are 2 known disorders of glucose metabolism known as prediabetes and are associated with microvascular and macrovascular complications.<sup>[1-7]</sup> In epidemiological studies, the prevalence of prediabetes is 14% in the age group  $\geq 45$  years old,<sup>[8,9]</sup> and it is reported that the risk of developing lifetime DM in these individuals is between 48% and 74%.<sup>[8,9]</sup> For this reason, early diagnosis and treatment of both clinical conditions may prevent or delay the development of micro- and macrovascular complications.

The artery wall contains 3 layers as tunica intima, tunica media and tunica adventitia. The atherosclerotic process occurs in the first 2 walls, resulting in a structural change in the early period as an increase in carotid intima-media thickness (C-IMT). IMT on the posterior wall is clearly distinguishable with carotid ultrasonography (C-US). C-IMT increases in patients with type-2 DM.<sup>[10,11]</sup> IMT is used in early detection of macrovascular complications in these patients. Regardless of age, gender and ethnicities, guidelines for increased C-IMT are considered to be  $>0.9$  mm in patients with DM.<sup>[12,13]</sup>

Studies about the C-IMT evaluation obtained from internal and common C-IMT (IC-IMT and CC-IMT) in prediabetes is limited

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and not clear in the literature.<sup>[14–19]</sup> For this reason, the importance of C-IMT in adult patients with prediabetes is unknown; this is not a routine examination. We suggested that C-IMT determined by C-US might indicate early changes at the cellular level before onset of increase in IMT in patients with prediabetes.

Therefore, in this study, we aimed to investigate the change of different location of C-IMT in patients with prediabetes and newly diagnosed type-2 DM compared to subjects with normal glucose metabolism (NGM).

## 2. Methods

In our study, it was reported that at least 50 patients per group were required to predict 5% error and 80% power for C-IMT difference. This cross-sectional study included 180 individuals with 3 different glucose metabolic states that were not different in terms of age and gender. The study was conducted between November 2018 and May 2019 in the diabetes polyclinic of the Internal Medicine Department of Adana City Training and Research Hospital. Subjects included in the study were grouped as: Group I: healthy controls or subjects with NGM (36 females, 24 males and  $56.1 \pm 5.7$  years); Group II: patients with newly diagnosed prediabetes (39 females, 21 males and  $57.7 \pm 6.1$  year) and Group III: patients with newly diagnosed type-2 DM (35 females, 25 males and  $56.0 \pm 10.9$  years). 2016 American Diabetes Association (ADA) guidelines were used to group patients.<sup>[20]</sup> Patients who had previously been referred to the DM polyclinic according to their laboratory results with unknown glucose metabolism status and undiagnosed with prediabetes or DM were divided into 3 groups according to the glucose metabolism status;

- (1) Patients are accepted with type-2 DM: glycated hemoglobin (HbA1c) levels  $\geq 6.5\%$ , fasting plasma glucose  $\geq 126$  mg/dL and 2nd hour plasma glucose with 75 gr Oral glucose tolerance test (OGTT)  $\geq 200$  mg/dL,
- (2) Subjects are accepted as prediabetes with: HbA1c 5.7% to 6.5%, fasting plasma glucose  $\geq 100$  mg/dL and  $< 126$  mg/dL (IFG) and 2nd hour plasma glucose with 75 gr OGTT  $\geq 140$  mg/dL and  $< 200$  mg/dL (IGT),
- (3) Subjects are accepted as NGM with: HbA1c  $< 5.7\%$ , fasting plasma glucose  $< 100$  mg/dL and 2nd hour plasma glucose with 75 gr OGTT  $< 140$  mg/dL).

Patients with known carotid atheroma or plaque (C-IMT  $> 1.5$  mm) were excluded from the study. Patients with priorly known type-1 and type-2 DM, known severe renal disease (the estimated glomerular filtration rate [eGFR]  $< 30$  mL/min/1.73 m<sup>2</sup>), severe heart valve disease, alcohol addiction, abdominal aortic aneurysm and dissection, inflammatory diseases, active thyroid disease, chronic liver disease, cancer and/or pregnancy were removed from study. The study was conducted according to the recommendations of the Declaration of Helsinki about biomedical research involving human subjects and the institutional ethics committee approved the protocol (decision/protocol number of your ethics committee approval was 2019/88-30). All forms of voluntary consent for all patients were explained in detail and patients were included in the study after receiving written approval.

After all the patients were included in the study, detailed anamnesis and physical examination were performed. Subsequently, baseline demographic characteristics of all groups were questioned for age, gender, hypertension (HT), presence of hyperlipidemia, smoking, coronary artery disease (CAD), and stroke history. Pulse rate, systolic blood pressure (SBP) and

diastolic blood pressure (DBP) were recorded. Body mass index was calculated by measuring weight and height.

Blood samples were taken from an antecubital vein after patients rested for 20 minutes in the supine position. Blood samples were collected in tubes containing ethylenediaminetetraacetic acid. The samples were spun at 3000 rpm for 10 minutes at 0°C. Fasting blood glucose, blood urea nitrogen (BUN), creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride levels at the time of admissions are measured with the standard automated laboratory method (Abbott Aeroset, Minnesota) using appropriate commercial kits (Abbott). HbA1c measurement was made with an automated chemistry analyzer (Abbott Aeroset) using appropriate commercial kits (Abbott). Serum aspartate aminotransferase, alanine aminotransferase, high sensitive C reactive protein (hs-CRP) were measured with an automated chemistry analyzer (Abbott Aeroset) using appropriate commercial kits (Abbott). Morning urine was used to determine the standard albuminuria. Albuminuria was determined by calculating the urine albumin-creatinine ratio (ACR) in lab results. The eGFR was calculated by the Modification of diet in Renal Disease Study Group formula as follows:  $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age}) - 0.203$  (0.742 for female patients).

Guideline recommendations were used to identify microvascular and macrovascular complications related to type-2 DM.<sup>[20]</sup> Macrovascular complications were accepted as cardiovascular diseases CAD and stroke. Microvascular complications were accepted as nephropathy, retinopathy, and neuropathy. The kidney disease: improving global outcomes criterion was used to determine the patient's nephropathy or the stage for diabetic kidney disease.<sup>[21]</sup> Neuropathy was confirmed by detailed history and evaluation of temperature and vibration sensation.<sup>[22]</sup> Retinopathy was detected through a comprehensive eye examination.<sup>[23]</sup>

Left and right common-internal carotid arteries were examined with a high-resolution ultrasound Doppler system (Philips EPIQ 7), equipped with an 8 to 12 MHz high-resolution linear transducer (Philips Health Care, Bothell, WA). Ultrasound scanner setting was made to be useful for all B-mode C-US examination (gain [55–65 dB]; penetration depth [2.5–4 cm]; dynamics range [50–60]; and zoom range [0.8–2.0]). All arteries were studied in both longitudinal and transversal sections. All arteries were scanned longitudinally to visualize the IMT in the posterior or far wall of artery. All measurements were made on frozen images. Two frozen images that have the highest quality for the operator opinions were selected for analysis in each study. The IMT is defined as the distance from the front edge of the first echogenic line to the anterior margin of the second line. The first line represents the intima-lumen interface and the second line represents the collagen-containing top layer of the adventitia. Vascular IMT was measured using ultrasonic calipers in case by 2 independent and blinded observers. All IMT values were calculated as the mean of 6 measurements. Subjects were examined in the supine position. Patients head turned 45° from the site being scanned for carotid artery. Carotid IMT measured from the far wall of the right and left carotid artery within 10 mm proximal (for CC-IMT) and after (for IC-IMT) to bifurcation on 2-dimensional ultrasound images. Values higher than 0.90 mm was accepted as increased C-IMT.<sup>[12,13,24]</sup>

### 2.1. Statistical analysis

All statistical analyzes were performed with SPSS 22.0 (Chicago, IL) statistical software package. The variables were divided into 2

groups as categorical and continuous variables. The normal distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. The kappa coefficient was used to examine the interobserver variability of the C-IMT measurements. The continuous variables in the group were expressed as mean  $\pm$  standard deviation. Categorical variables are given in numbers and percentages. Continuous variables that showed normal distribution was compared using the analysis of variance, whereas the Kruskal–Wallis test was used for non-normally distributed samples. The statistical details between the groups are indicated on the tables. Chi-square ( $\chi^2$ ) test was used to compare categorical variables. For multiple comparisons of groups' proportions, we used the Bonferroni corrected  $z$  test. The kappa coefficient was used to examine the interobserver variability of all US measurement<sup>2</sup>. The univariate correlation analysis of the parameters associated with CC-IMT and IC-IMT was performed using the Pearson and Spearman correlation method. Statistically significant parameters were included in the linear regression analysis and the parameters most closely related to CC-IMT and IC-IMT were determined. ROC curve analysis was performed to determine the patients with increased C-IMT. Parameters with area under the curve  $>0.650$  were determined. From these parameters, limit value determination was done to determine the best sensitivity and specificity in the determination of presence of increased C-IMT. Statistical significance level was accepted as  $P < .05$ .

### 3. Results

The study data were compared by dividing the patients in 3 groups as NGM, prediabetes and type-2 DM groups according to glucose metabolism status. Cohen kappa values that evaluate intraobserver variability were over 90% for C-IMT measurements.

When clinical and demographic findings were compared among the study groups, all demographic findings were similar among the groups. SBP and DBP values were found to be higher in prediabetes and type-2 DM groups than NGM group (Table 1). The prevalence of nephropathy and presence of CAD were higher type-2 DM groups than prediabetes. Glucose, HbA1c, total cholesterol, LDL cholesterol, triglyceride, BUN, creatinine, hs-CRP levels, and urinary ACR were significantly higher in patients within prediabetes and type-2 DM groups than NGM group. Glucose, HbA1c, and hs-CRP levels were found to be higher in type-2 DM groups than prediabetes. Only, eGFR and HDL cholesterol level were found to be lower in patients with in prediabetes and type-2 DM groups than NGM group (Table 1).

When vascular ultrasound findings were compared between study groups, right-left-mean CC-IMT and IC-IMT values were found to be higher in prediabetes and type-2 DM groups than NGM group (Table 2, Figs. 2 and 3). Left IC-IMT, left CC-IMT, and mean IC-IMT values were found to be higher in type-2 DM patients compared to prediabetes (Table 2, Figs. 1 and 2). The

**Table 1**

**Baseline characteristics of the study groups according to glucose metabolism status.**

Variable	Normal glucose metabolism n=60	Patients with prediabetes n=60	Patients with type 2 DM n=60	P
Age, yr	56.1 $\pm$ 5.7	57.7 $\pm$ 6.1	56.0 $\pm$ 10.9	.420
Sex (male)	24	21	25	.336
Presence of hypertension, n (%)	–	16 (27%)	22 (37%)	.327
Presence of current smoker, n (%)	–	11 (18%)	12 (20%)	.500
Presence of hyperlipidemia, n (%)	–	14 (23%)	23 (38%)	.113
Presence of CAD, n (%)	–	4 (7%)	15 (25%)	.011
Nephropathy, n (%)	–	13 (22%)	31 (52%)	.001
Retinopathy, n (%)	–	4 (7%)	10 (17%)	.153
Neuropathy, n (%)	–	4 (7%)	9 (15%)	.239
Systolic blood pressure, mm Hg	123 $\pm$ 6.2 <sup>†,‡</sup>	131 $\pm$ 11	129 $\pm$ 13	.001
Diastolic blood pressure, mm Hg	81 $\pm$ 5.6 <sup>†,‡</sup>	86 $\pm$ 8.8	87 $\pm$ 8.4	.008
Heart rate, beats/min	76 $\pm$ 14	79 $\pm$ 11	81 $\pm$ 11	.304
Body mass index, kg/m <sup>2</sup>	27.5 $\pm$ 2.2	28.1 $\pm$ 2.5	28.5 $\pm$ 2.3	.063
Plasma glucose, mg/dL	88.9 $\pm$ 5.6 <sup>†,‡</sup>	112 $\pm$ 7.1 <sup>*</sup>	191 $\pm$ 94	<.001
HbA1c (%)	5.42 $\pm$ 0.21 <sup>†,‡</sup>	6.24 $\pm$ 0.73 <sup>*</sup>	8.91 $\pm$ 2.28	<.001
Total cholesterol, mg/dL	130 $\pm$ 18 <sup>†,‡</sup>	162 $\pm$ 39	165 $\pm$ 47	<.001
LDL cholesterol, mg/dL	96 $\pm$ 18 <sup>†,‡</sup>	132 $\pm$ 32	144 $\pm$ 39	<.001
HDL cholesterol, mg/dL	58 $\pm$ 6.9 <sup>†,‡</sup>	48 $\pm$ 15	44 $\pm$ 14	<.001
Triglycerides, mg/dL	88 $\pm$ 30 <sup>†,‡</sup>	169 $\pm$ 45	210 $\pm$ 145	<.001
Aspartate aminotransferase, IU/L	19.2 $\pm$ 2.6	20.7 $\pm$ 5.5	22.7 $\pm$ 5.9	.066
Alanine aminotransferase, IU/L	14.7 $\pm$ 2.4 <sup>†,‡</sup>	18.1 $\pm$ 7.0	22.4 $\pm$ 9.4	<.001
Blood urea nitrogen, mg/dL	22.9 $\pm$ 4.2 <sup>†</sup>	23.5 $\pm$ 6.2	32.8 $\pm$ 9.8	<.001
Creatinine, mg/dL	0.49 $\pm$ 0.07 <sup>†,‡</sup>	0.72 $\pm$ 0.17	0.70 $\pm$ 0.18	<.001
eGFR, mL/min/1.73 m <sup>2</sup>	109 $\pm$ 16 <sup>†,‡</sup>	96 $\pm$ 19	97 $\pm$ 14	<.001
High sensitive C reactive protein, mg/dL	0.19 $\pm$ 0.10 <sup>†,‡</sup>	0.40 $\pm$ 0.17 <sup>*</sup>	0.88 $\pm$ 0.86	<.001
Urinary albumin creatinine ratio, mg/g	12.5 $\pm$ 8.3 <sup>†,‡</sup>	49.6 $\pm$ 137	62.8 $\pm$ 119	.019

The values were shown as mean  $\pm$  standard deviation or n (%).

ACR=albumin creatinine ratio, CAD=coronary artery disease, eGFR=estimated glomerular filtration rate, HDL=high-density lipoprotein, LDL=low-density lipoprotein, NGM=normal glucose metabolism.

<sup>\*</sup> The significant association between the prediabetes group and type II DM group ( $P < .05$ ).

<sup>†</sup> The significant association between the NGM group and prediabetes group ( $P < .05$ ).

<sup>‡</sup> The significant association between the NGM group and type II DM group ( $P < .05$ ).

**Table 2****Vascular ultrasound finding of the study groups according to glucose metabolism status.**

Variable	Normal glucose metabolism n=60	Patients with prediabetes n=60	Patients with type-2 DM n=60	P
Right internal carotid IMT, mm	0.55 ± 0.07 <sup>†,‡</sup>	0.67 ± 0.10	0.70 ± 0.12	<.001
Left internal carotid IMT, mm	0.57 ± 0.09 <sup>†,‡</sup>	0.67 ± 0.09*	0.75 ± 0.19	<.001
Right common carotid IMT, mm	0.60 ± 0.11 <sup>†,‡</sup>	0.75 ± 0.13	0.76 ± 0.14	<.001
Left common carotid IMT, mm	0.58 ± 0.12 <sup>†,‡</sup>	0.73 ± 0.10*	0.80 ± 0.16	<.001
Mean internal carotid IMT, mm	0.56 ± 0.08 <sup>†,‡</sup>	0.68 ± 0.11*	0.73 ± 0.13	<.001
Mean common carotid IMT, mm	0.60 ± 0.10 <sup>†,‡</sup>	0.75 ± 0.10	0.78 ± 0.14	<.001
Increased common carotid IMT (n, %)	1 (2%) <sup>†,‡</sup>	9 (15%)*	16 (27%)	<.001

The values were shown as mean ± standard deviation or n (%).

IMT = intima-media thickness, NGM = normal glucose metabolism, ROI = region of interest.

\* The significant association between the prediabetes group and type II DM group ( $P < .05$ ).

<sup>†</sup> The significant association between the NGM group and prediabetes group ( $P < .05$ ).

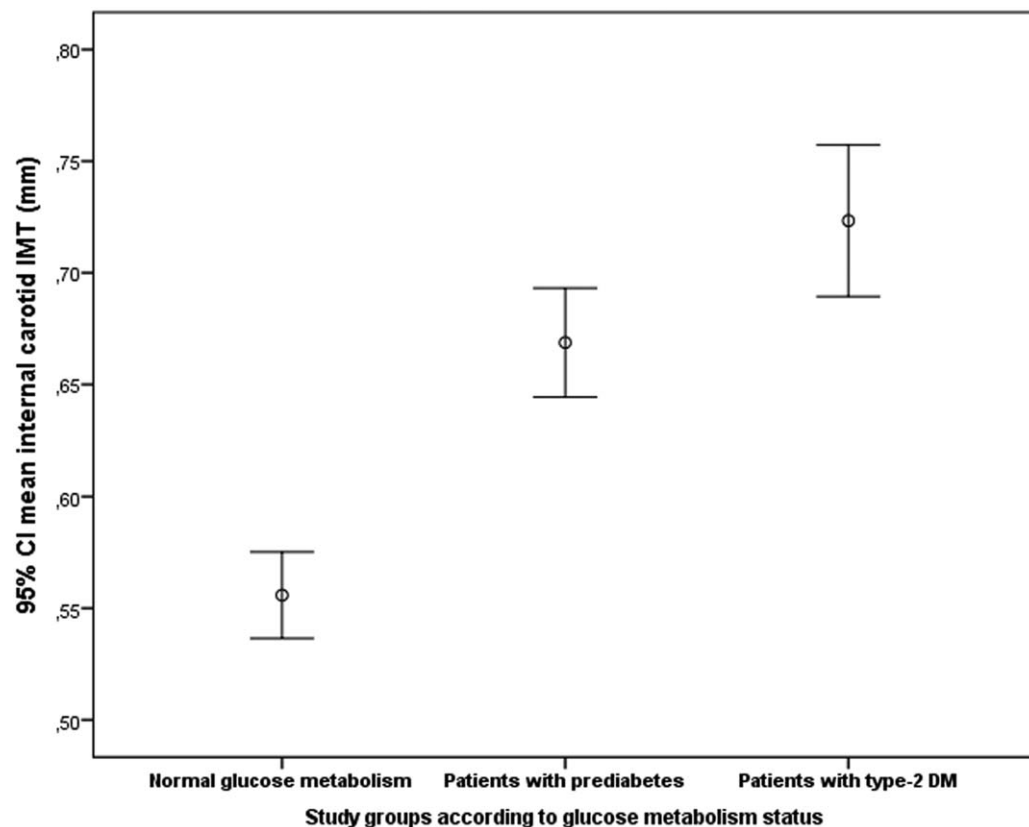
<sup>‡</sup> The significant association between the NGM group and type II DM group ( $P < .05$ ).

prevalence of increased CC-IMT value was higher in type-2 DM group than prediabetes and NGM groups. Similarly, the prevalence of increased CC-IMT value was higher in prediabetes group than NGM group (Table 2).

The demographic, clinical, laboratory, and ACR parameters associated with IC-IMT and CC-IMT in the univariate analysis are summarized in Table 3. Linear regression analysis was performed with these IMT-related parameters (Table 3). LDL and HDL cholesterol, HbA1c, and hs-CRP levels were independently associated with IC-IMT and CC-IMT (Table 3). The relationship between CC-IMT and HbA1c and

LDL cholesterol levels were shown in Figures 3 and 4, respectively.

ROC analysis was performed to determine the parameters that best predict the development of increased C-IMT from clinical, demographic, laboratory, and urine data that were different in patients with increased C-IMT (Table 4). According to this analysis, the parameters found to be significant in the presence of increased C-IMT are; LDL and HDL cholesterol, HbA1c, and hs-CRP levels (Table 4). The cut-off value and predicted the possibility of presence of increased C-IMT for this parameters were taken in Table 4.



**Figure 1.** Error Bar diagram for mean internal carotid IMT measurements according to glucose metabolism status. IMT = intima-media thickness.

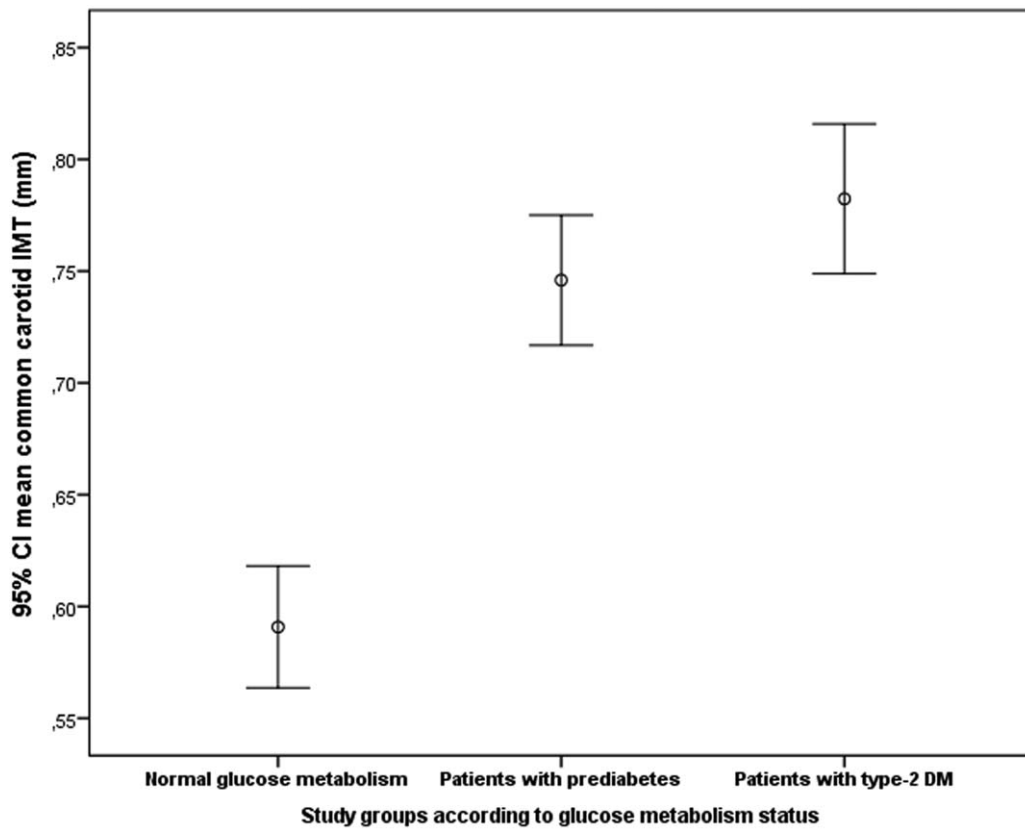


Figure 2. Error Bar diagram for mean common carotid IMT measurements according to glucose metabolism status. IMT=intima-media thickness.

Table 3

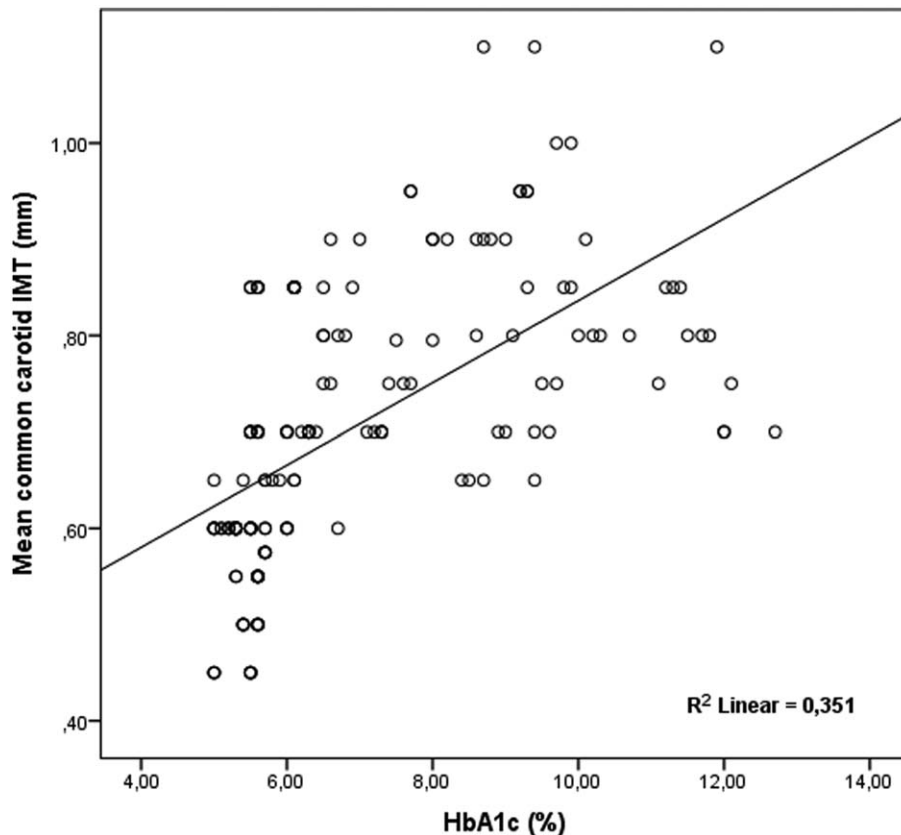
The parameters associated with C-IMT and IC-IMT and analysis for parameters significantly correlated with IMTs.

Internal carotid intima-media thickness				
	Univariate analyze		Multivariate analyze	
	P	r	P	β
Age, yr	.008	0.224	.865	0.009
Creatinine, mg/dL	<.001	0.292	.767	0.064
Plasma glucose, mg/dL	<.001	0.285	.521	0.056
HbA1c (%)	<.001	0.433	<.001	0.488
Creatinine, mg/dL	<.001	0.292	.630	0.102
eGFR, mL/min/1.73 m <sup>2</sup>	<.001	-0.381	.512	-0.054
hs-CRP, mg/dL	<.001	0.324	.023	0.170
Total cholesterol, mg/dL	.014	0.196	.170	0.099
LDL cholesterol, mg/dL	<.001	0.516	<.001	0.602
HDL cholesterol, mg/dL	.001	-0.250	.004	-0.221
Triglycerides, mg/dL	.001	0.252	.419	0.062
Urinary ACR, mg/g	.009	0.233	.548	0.054

Common carotid intima-media thickness				
	Univariate analyze		Multivariate analyze	
	P	r	P	β
Age, yr	.010	0.206	.865	0.009
Creatinine, mg/dL	<.001	0.460	.767	0.064
Plasma glucose, mg/dL	<.001	0.279	.521	0.056
HbA1c (%)	<.001	0.389	<.001	0.474
Creatinine, mg/dL	<.001	0.460	.630	0.102
eGFR, mL/min/1.73 m <sup>2</sup>	<.001	-0.450	.546	-0.087
hs-CRP, mg/dL	<.001	0.373	.001	0.236
Total cholesterol, mg/dL	.017	0.189	.170	0.099
LDL cholesterol, mg/dL	<.001	0.435	<.001	0.532
HDL cholesterol, mg/dL	.002	-0.249	<.001	-0.326
Triglycerides, mg/dL	.002	0.238	.419	0.062
Urinary ACR, mg/g	.009	0.231	.548	0.054

ACR=albumin creatinine ratio, eGFR=estimated glomerular filtration rate, hs-CRP=high sensitive C reactive protein, IMT=intima-media thickness, R<sup>2</sup><sub>Adjusted</sub> = 0.550 and 577 for IC – IMT and CC – IMT, respectively in multivariate analyses.



**Figure 3.** Simple Scatter/Dot diagram of the relationship of HbA1c levels with common carotid IMT. There is significant correlation between common carotid IMT and HbA1c levels. HbA1c=glycated hemoglobin, IMT=intima-media thickness.

#### 4. Discussion

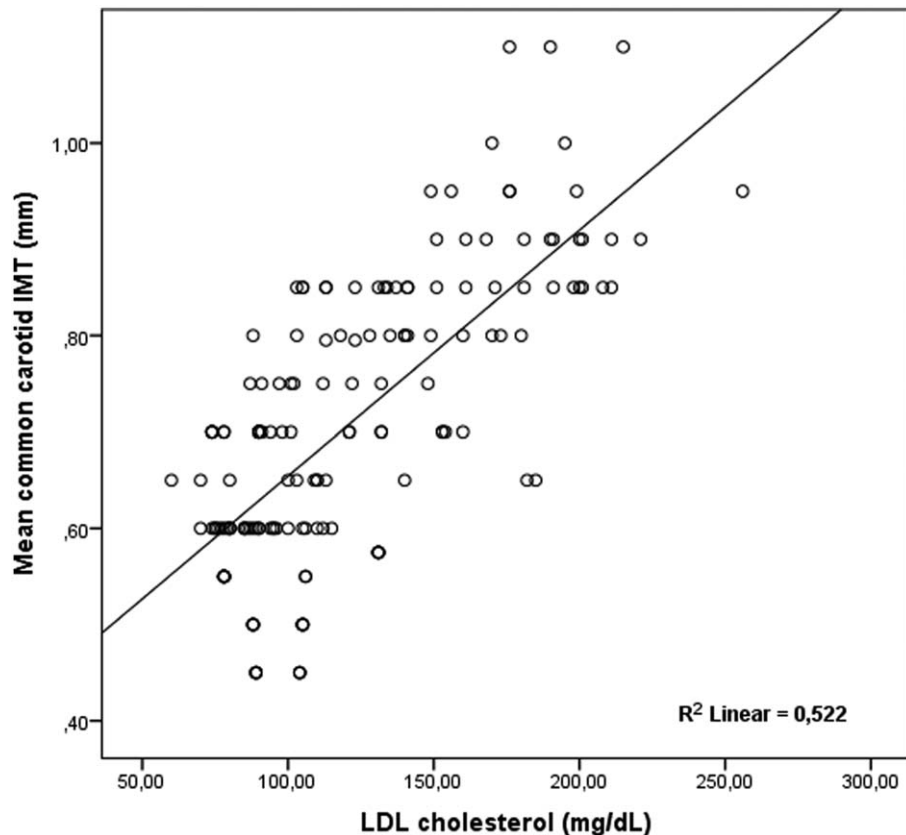
The main finding of this study was that C-IMT was significantly higher in patients with prediabetes than healthy controls with NGM. In addition, we determined that C-IMT values were increased in patients with type-2 DM compared with patients with NGM and prediabetes like previous studies. Another important finding is that both IC-IMT and CC-IMT values are positively correlated with LDL cholesterol, HbA1c, and hs-CRP levels and negatively correlated with HDL cholesterol levels.

C-IMT is an easy to use, simple, inexpensive, noninvasive, and objective evaluation method used in the diagnosis and follow-up of atherosclerotic vascular diseases. DM is a major and known risk factor for the development of atherosclerosis. Increased C-IMT is closely associated with asymptomatic or subclinical atherosclerosis and is recommended as a routine examination in patients with DM.<sup>[10,11]</sup> A significant proportion of patients diagnosed with a newly diagnosed type-2 DM had an increase in IMT in the carotid or other vascular system, suggesting that it may occur in the vascular system before DM develops.

Patients with prediabetes reported to have increased C-IMT.<sup>[14–16]</sup> Therefore, it is important to diagnose patients early in the prediabetes stage and without an increase in C-IMT. However, in a few studies involving patients with DM and prediabetes, there was an increase in C-IMT in patients with type-2 DM compared to the NGM group, while no increase in C-IMT was observed in patients with prediabetes compared to patients with NGM.<sup>[17,18]</sup> The most important reason for this is that the

risk factors that may be associated with C-IMT increase such as obesity, smoking, HT, CAD, dyslipidemia in the control group with NGM may not be excluded. Recently, Gateva et al<sup>[17]</sup> performed a mean C-IMT evaluation in patients with type-2 DM, prediabetes, and obese NGM, and reported no increase in C-IMT in patients with prediabetes compared to patients with obese NGM. In the same study, mean C-IMT was reported to be higher in patients with type-2 DM than in the other 2 groups.<sup>[17]</sup> In another study, patients with prediabetes and NGM but with intermediate cardiovascular risk were included, and therefore patients with prediabetes were not shown to have increased C-IMT compared to patients with NGM group.<sup>[18]</sup> However, in a recent study involving a limited number of patients, it was reported that C-IMT was increased in patients with prediabetes compared to patients with NGM.<sup>[19,25]</sup> In a study by Di Pino et al,<sup>[19]</sup> the study groups were divided into 3 groups as HbA1c  $\geq 6.5\%$ , 5.7% to 6.4%, and  $< 5.7\%$  according to the HbA1c level in ADA guideline, patients with both HbA1c  $\geq 6.5\%$  and 5.7% to 6.4% reported to have higher IMT than the group with HbA1c  $< 5.7\%$ . However, patients with HbA1c  $< 5.7\%$  are not called NGM due to the lack of OGTT, so we cannot say there is no increase in C-IMT in patient with prediabetes compared to NGM.<sup>[19]</sup> Aydin et al<sup>[25]</sup> reported a significant increase in left C-IMT in patients with prediabetes compared with NGM without CAD, while no increase in right C-IMT.

We thought that it would be right to compare with healthy controls whether prediabetes increases C-IMT independent of other risk factors. In our study, we performed the right and left



**Figure 4.** Simple Scatter/Dot diagram of the relationship of LDL cholesterol levels with common carotid IMT. There is significant correlation between common carotid IMT and LDL cholesterol levels. IMT=intima-media thickness, LDL=low-density lipoprotein.

CC-IMT and IC-IMT evaluations in detail in patients with NGM, prediabetes including IFG and IGT and newly diagnosed type-2 DM. We showed a significant increase in C-IMT in patients with prediabetes compared to the NGM group. In addition, we found that the incidence of increased C-IMT was significantly higher in patients with type-2 DM compared to patients with prediabetes. The increase in C-IMT value before the development of type-2 DM in the group of patients with prediabetes demonstrated the clinical importance of prediabetes. Therefore, as soon as the clinical condition of prediabetes is diagnosed, patients should be followed closely for the presence of macrovascular disease. C-IMT may be useful in screening for the presence of macrovascular disease.

In studies showing increased C-IMT in patients with prediabetes, increase in C-IMT has been reported to be associated with age, presence of HT, SBP, high fasting glucose, postprandial glucose, dysmetabolic status, and HbA1c level.<sup>[14-19]</sup> HbA1c was the most closely related parameter to C-IMT in patients with prediabetes.<sup>[16,18,19]</sup> In our study, it was found that there was a

close relationship with C-IMT with dysmetabolic status, HbA1c, and hs-CRP levels. Especially in patients with impaired glucose metabolism, it is necessary to struggle these risk factors to prevent the increase of IMT. However, unlike previous studies, there was no significant relationship between SBP and DBP, smoking, and presence of CAD and C-IMT values. The most important reason for this was thought to be that the presence of atheroma or plaque formation in the carotid artery was among the exclusion criteria.

**5. Limitations**

Our study has some important limitations. First of all, the number of patients included in the study was relatively adequate, but our study was single-centered. Multicenter studies involving more patients are needed. In addition, our study was cross-sectional and patients with newly diagnosed DM were taken and we could not have an idea whether DM duration would change study data. As is known, atherosclerosis first starts from the abdominal aorta and therefore abdominal aortic IMT increases

**Table 4**  
ROC curve analysis for predicting presence of increased C-IMT.

Variable	AUROC curve	P	Cut-off	Sensitivity	Specificity
LDL cholesterol, mg/dL	0.737 (0.597-0.878)	<.001	140	79.2%	86.5%
HDL cholesterol, mg/dL	0.625 (0.687-0.897)	.053	40	60.8%	59.4%
HbA1c (%)	0.686 (0.592-0.780)	.004	5.65	70.8%	62.1%
hs-CRP, mg/dL	0.772 (0.688-0.857)	<.001	0.40	82.5%	72.8%

HDL=high-density lipoprotein, hs-CRP=high sensitive C reactive protein, IMT=intima-media thickness, LDL=low-density lipoprotein.

(A-IMT) without an increase in C-IMT. In recent years, publications about the A-IMT have been made and it is thought that A-IMT can be used in macrovascular organ involvement in patients with DM, hyperparathyroidism, and CAD.<sup>[26–29]</sup> However, we did not evaluate A-IMT in our study. There is no study about A-IMT measurement but the C-IMT measurement can be measured automatically and semi-automatically with new software programs, resulting in a lower average value than the manual measurement.<sup>[30,31]</sup> This automatic measurement especially removes operator dependence and is more useful for repetitive measurements. However, our high-resolution device did not have this software program so we could not make this evaluation. In our study, if IMT could be measured automatically and semi-automatically, more objective and meaningful results could be obtained. Previous studies have shown that C-IMT is regressed by medical therapy in patients with DM. Our study is not a follow-up study and therefore no control C-IMT assessments have been performed.<sup>[32]</sup>

In our study, the presence of atheroma or plaque (C-IMT > 1.5 mm) in the carotid artery was included among the exclusion criteria, if this exclusion criterion was not taken and plaque index evaluation was done, it could give information about localized atherosclerosis in prediabetes patients. In a recent study, it was reported that C-IMT normal value was accepted as constant, but it could change with the patient's risk factors and especially age.<sup>[33]</sup> However, with guideline suggestions, this information was not taken into consideration in the present study. Smoking was not among the exclusion criteria in the patients included in our study. Physical activity was also not evaluated. Smoking and reduced physical activity have negative effects on C-IMT.<sup>[33,34]</sup> If these evaluations were made, more meaningful results could be obtained.

## 6. Conclusions

In our study, C-IMT value and increased C-IMT count were significantly higher in patients with newly diagnosed type-2 DM and prediabetes than in NGM group. Therefore, the increase in C-IMT, which is an indicator of subclinical atherosclerosis, can be used to determine the development of early atherosclerosis in patients with type-2 DM and patients with prediabetes. Also, high LDL cholesterol, hs-CRP, HbA1c, and low HDL cholesterol levels are closely associated with C-IMT value in accordance with previous studies. Especially in patients with impaired glucose metabolism, it is necessary to struggle these risk factors to prevent the increase of IMT. For this purpose, it was thought that C-IMT measurement used in the follow-up of patients with DM may be important in patients with prediabetes and may be used in patient follow-up. Our study was conducted in single-centered individuals with the same ethnic identity. Therefore, the information obtained in our study should be supported by multicenter studies with different ethnic backgrounds and more patients.

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## Author contributions

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