Assessment of Subclinical Atherosclerosis with Aortic Velocity Propagation in Patients with Type 2 Diabetes and Chronic Kidney Disease

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ABSTRACT

Introduction: Diabetes mellitus (DM) and chronic kidney disease (CKD) accelerate the process of atherosclerosis. To improve clinical outcomes, non-invasive imaging modalities have been proposed to measure and monitor atherosclerosis. Recently, colour M-mode-derived propagation velocity of the descending thoracic aorta [aortic velocity propagation (AVP)] has been shown to be associated with coronary and carotid atherosclerosis.

Patients and Methods: The study population included 90 patients with type 2 diabetes who had CKD (Group 1) and 40 age- and sex-matched patients with type 2 diabetes who had a normal renal function (Group 2). Carotid intima-media thickness (CIMT) and AVP were measured. Patients with known coronary heart disease or end-stage renal disease were excluded.

Results: Compared with Group 1, patients in Group 2 had significantly lower AVP (Group 1= 29.85 ± 3.95 cm/s and Group 2= 41.05 ± 3.34 cm/s, p< 0.001) and higher CIMT (Group 1= 1.06 ± 0.11 mm and Group 2= 0.78 ± 0.10 mm, p< 0.001). There were significant correlations between AVP and CIMT (r= -0.669, p< 0.001).

Conclusion: Patients with diabetes who have CKD exhibit more subclinical atherosclerosis, which is determined by more prominent AVP and CMIT, than patients with diabetes who have a normal renal function. These simple methods might improve patient selection for the prevention of primary atherosclerotic progression.

Key Words: Aortic velocity propagation; carotid intima-media thickness; type 2 diabetes; chronic kidney disease; atherosclerosis

Kronik Böbrek Hastalığı Olan Tip 2 Diyabetli Hastalarda Aortik Yayılım Hızı ile Subklinik Aterosklerozun Değerlendirilmesi

ÖZET

Giriş: Diabetes mellitus (DM) ve kronik böbrek hastalığı (KBH) aterosklerozu hızlandırmaktadır. Klinik sonuçları iyileştirmek için, aterosklerozu değerlendiren ve izleyen invaziv olmayan görüntüleme yöntemleri geliştirilmektedir. Son zamanlarda, inen torasik aortun renkli M-mod yayılım hızının [aortik yayılım hızı (AYH)] koroner ve karotisaterosklerozu ile ilişkili olduğu gösterilmiştir.

Hastalar ve Yöntem: Çalışma popülasyonu KBH olan tip 2 diyabetli 90 hasta (grup 1) ve yaş ve cinsiyet benzer, normal böbrek fonksiyonlarına sahip tip 2 diyabetli 40 hastadan (grup 2) oluşmaktaydı. Karotis intima-media kalınlığı (KİMK) ve AYH ölçüldü. Bilinen koroner kalp hastalığı veya son dönem böbrek yetmezliği olan hastalar çalışmaya dahil edilmedi.

Bulgular: Grup 2 ile karşılaştırıldığında, grup 1 hastalar daha düşük AYH düzeylerine (grup 1= 29.85 ± 3.95 cm/sn ve grup 2= 41.05 ± 3.34 cm/s, p< 0.001) ve daha yüksek KİMK düzeylerine (grup 1= 1.06 ± 0.11 mm ve grup 2= 0.78 ± 0.10 mm, p< 0.001) sahipti. AYH ve KİMK arasında anlamlı korelasyon mevcuttu (r= -0.669, p< 0.001).

Sonuç: KBH olan diyabetli hastalar, normal böbrek fonksiyonlu diyabetli hastalara göre daha belirgin AYH ve KIMK değerleri ile belirlenen daha fazla subklinik ateroskleroza sahiptir. Bu basit metodlar, aterosklerozun progresyonunun primer önlenmesi için hasta seçimini geliştirebilir.

Anahtar Kelimeler: Aortik yayılım hızı; karotis intima-media kalınlığı; tip 2 diabetes mellitus; kronik böbrek hastalığı; ateroskleroz

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Submitted: 01.03.2016
Accepted: 14.03.2016

INTRODUCTION

In patients with diabetes, heart diseases, especially coronary heart disease (CHD), is a major cause of morbidity and mortality[1]. These patients have a higher prevalence of coronary heart disease, show more severe coronary ischaemia and are more likely to have a myocardial infarction (MI) and silent myocardial ischaemia compared to individuals without diabetes. Type 2 diabetes was found to be a CHD equivalent in the National Cholesterol Education Program; therefore, it has been elevated to the highest risk category[2,3]. In some patients with diabetes, the perception of ischemic pain is reduced, and this may lead to atypical angina symptoms, silent ischaemia or silent infarction. In diabetes, silent ischaemia is considered to occur, at least in part, because of autonomic denervation of the heart[4].

In western countries, diabetic nephropathy is the most common cause of chronic kidney disease (CKD). Both the National Kidney Foundation and American College of Cardiology/American Heart Association recommend that CKD be considered a CHD risk equivalent because CKD is associated with an adverse cardiovascular prognosis[5]. In CKD patients, there are many traditional and non-traditional risk factors for the development of cardiovascular disease. Also, the prevalence of traditional cardiovascular risk factors, such as hypertension, smoking, diabetes, dyslipidaemia and old age, are increased in these patients[6].

Atherosclerosis is often asymptomatic until it reaches a high level. Thus, the detection of early atherosclerosis using imaging can predict the risk of future cardiovascular events. Measurement of carotid intima-media thickness (CIMT) is one of the most widely used and best validated atherosclerosis imaging techniques. CIMT increase is correlated with cardiovascular risk factors and the severity of coronary atherosclerosis, and it can predict cardiovascular events in population groups. Recent studies have demonstrated that the colour M-mode-derived propagation velocity of the descending thoracic aorta [aortic velocity propagation (AVP)] was associated with coronary and carotid atherosclerosis[7].

In this study, we investigated the degree of subclinical atherosclerosis and association of CIMT and AVP in patients with type 2 who had CKD and those with type 2 diabetes who had a normal renal function and no known atherosclerosis.

PATIENTS and METHODS

This study population included 90 patients with type 2 diabetes who had CKD (Group 1) and 40 age- and sex-matched patients with type 2 diabetes who had a normal renal function (Group 2). Patients with a diagnosis of CVD, aortic aneurysm, severe valvular heart disease, left ventricular ejection fraction < 40%, arrhythmia, inadequate echocardiographic image quality and end stage renal disease (ESRD) were excluded. All patients underwent the treadmill exercise test for CVD, and patients who had abnormal results were excluded from the study. The study complied with the declaration of Helsinki and was approved by the local research ethics committee. All the subjects provided written informed consent.

Biochemical Tests

Blood glucose, HbA1c, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured after 12-14 h of overnight fasting. Urea and creatinine values of all patients were measured and the glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Study (MDRD) equation. Independent of the aetiology, the presence of kidney damage or decreased kidney function for ≥ 3 months is defined as CKD. CKD patients were staged according to GFR levels: Stage 1, GFR > 90 mL/min per 1.73 m^2, Stage 2, GFR= 60 to 89 mL/min per 1.73 m^2, Stage 3a, GFR= 45-59 mL/min per 1.73 m^2, Stage 3b, GFR= 30-44 mL/min per 1.73 m^2, Stage 4, GFR = 15-29 mL/min per 1.73 m^2 and Stage 5, GFR < 15 mL/min per 1.73 m^2 or treatment by dialysis. Stage 5 or ESRD patients were excluded from this study[8].

Transthoracic Echocardiographic Examination

Two experienced echocardiographers who were blinded to the clinical data and ongoing therapy performed the echocardiographic examinations. The patients were at rest and in the left lateral decubitus position. A commercially available echocardiographic device (Vivid 3, General Electric, Chicago, IL, USA) with a 3.0 MHz transducer was used. The procedure was performed according to established standards. Although the patients were in a supine position, colour M-mode Doppler recordings were obtained with the cursor parallel to the main flow direction in the descending aorta from a suprasternal window. The colour Doppler Nyquist limit was adapted to 30-50 cm/s and switching to the M-mode with a recorder sweep rate of 200 mm/s; an M-mode spatiotemporal velocity map in the shape of flame was displayed (Figure 1A,B). In cases where the slope of the flame was unclear, baseline shifting was used to change the aliasing velocity until a clear delineation of the isovelocity slope was seen. Then, the distance between points corresponding to the beginning and end of the propagation slope was divided by the duration between corresponding time points to determine AVP. Thus, AVP gives an idea about the velocity at which the flow is propagating down the artery. At least three measurements were obtained and their mean was recorded as the AVP value.

CIMT Measurements

A cardiologist who was blinded to the clinical data and ongoing therapy evaluated bilateral common carotid arteries of the patients using a 7 MHz transducer attached to an available machine (Vivid 3, General Electric). The CIMTs on both sides

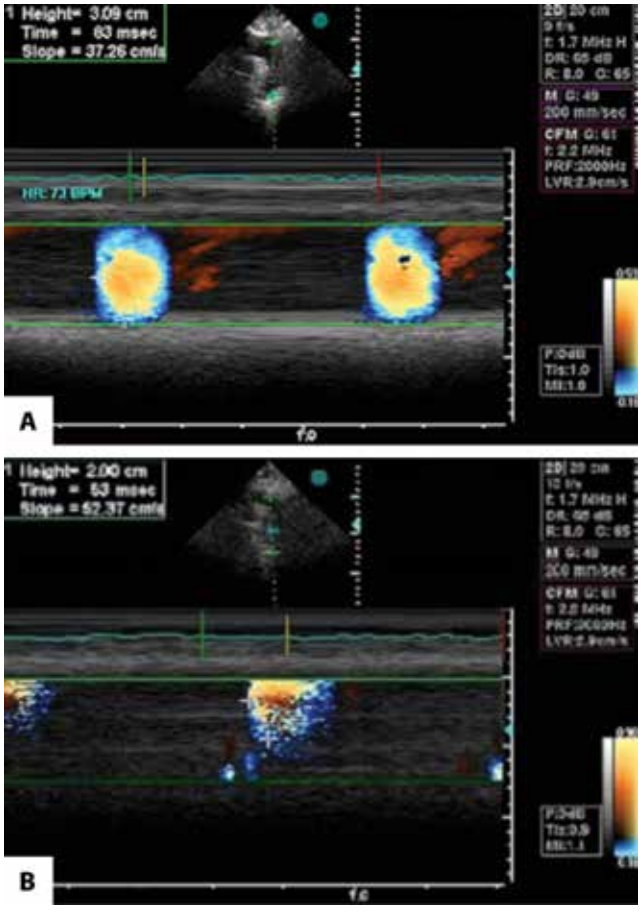

Figure 1. (A,B) Measurement of aortic velocity propagation in Group 1 and Group 2 patients.

were measured in the common carotid artery approximately 1 cm proximal to the bifurcation at the far wall during end diastole. The CIMT was quantified at plaque-free sections of the carotid arteries as the distance between the lumen-intima and media-adventitia interfaces. On each side, three measurements were made and the average CIMT values were used for the analysis. The study procedure involved scanning the near and far walls of both common carotid arteries, the carotid bifurcation and the internal carotid artery for the presence of plaques. According to the American Society of Echocardiography, plaques were defined as the presence of focal wall thickening resulting in a thickness that is at least 50% greater than that of the surrounding vessel wall or as a focal region with a CIMT greater than 1.5 mm that protrudes into the lumen that is distinct from the adjacent boundary[9].

Statistics

Quantitative variables are expressed as mean ± standard deviation and qualitative variables as numbers and percentages. Differences between independent groups were assessed by the Student's t-test for normally distributed quantitative variables, Mann-Whitney's U test for variables without a normal distribution and Chi-square test for qualitative variables. Pearson's correlation analysis was used to assess the correlations between variables. The normality test of data was analysed with the Shapiro-Wilk test. Independent risk factors for AVP and CIMT were analysed with linear regression analysis. All tests were performed with SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL). All results were considered statistically significant at the level of $p< 0.05$.

RESULTS

Age, sex and body mass index values were similar between patients with type 2 diabetes who had CKD (Group 1) and those with type 2 diabetes who had a normal renal function (Group 2). Among patients in Group 1, 2 (2.2%) had stage 4, 56 (62.2%) had stage 3 and 32 (35.5%) had stage 2 renal failure. Hypertension was diagnosed in 46.7% of the patients in Group 1 and in 65% of the patients in Group 2. Fifty percent of the patients in Group 1 and 32.5% of the patients in Group 2 were smokers. Glycemic indexes were similar in Group 1 and Group 2 (significance values for fasting plasma glucose and HbA1c were $p= 0.537$ and $p= 0.5$, respectively). LDL-C and TG were higher in Group 2, and HDL-C was higher in Group 1. Left ventricular diastolic diameter (LVDD), left ventricular systolic diameter (LVSD), left ventricular ejection fraction (LVEF), left atrium (LA) diameter, deceleration time (DT), isovolumetric relaxation time (IVRT) and mitral in flow (E/A) were similar between the two groups (Table 1). However, patients in Group 1 were detected to have significantly lower AVP and higher CIMT than patients in Group 2 ($p< 0.001$) (Figure 2,3). There were significant correlations between AVP and CIMT ($r= -0.669$, $p< 0.001$) (Figure 4). When AVP and CIMT were taken as dependent variables, BMI, smoking, hypertension, TG, HDL-C and LDL-C were not significantly influential over AVP and CIMT ($p> 0.05$). However, GFR was found to be influential over AVP and CIMT, although creatinine levels were found to be influential over CIMT ($p< 0.001$) (Table 2,3).

DISCUSSION

Our study demonstrated that in patients with type 2 diabetes who had CKD, the atherosclerotic process was more than that in patients with type 2 diabetes who had a normal renal function and an association was present between CIMT and a new echocardiographic parameter, AVP.

Heart disease, particularly CHD, is a major cause of morbidity and mortality among patients with DM and CKD. The arterial system in these patients undergo remodeling characterized by dilation, hypertrophy and stiffening of the aorta and major arteries[10].

CIMT may aid cardiovascular risk stratification because it comprises a direct measure of atherosclerosis, is associated with future cardiovascular events and is a safe, inexpensive and widely available technique[11]. The American Heart Association Writing Group 3, National Cholesterol Education Program

Table 1. Comparison of clinical, laboratory and echocardiographic variables between patients with type 2 diabetes who had CKD and those with type 2 diabetes who had a normal renal function

	DM type 2 + CKD	DM type 2 with Normal Renal Function	p-value
Age (years)	57.35 ± 11.66	58.97 ± 11.53	0.465
GFR	28.12 ± 7.50	92.33 ± 32.26	< 0.001
Male (%)	54 (60%)	16 (40%)	0.055
BMI (kg/m^2)	27.43 ± 4.53	28.16 ± 5.88	0.447
Hypertension	42 (46.7%)	26 (65%)	0.006
Smoking	45 (50%)	13 (32.5%)	0.064
Systolic BP (mmHg)	127.51 ± 20.62	133 ± 22.62	0.142
Diastolic BP (mmHg)	77.27 ± 12.87	81.05 ± 16.08	0.157
Fasting plasma glucose (mg/dL)	146.92 ± 50.35	152.82 ± 49.85	0.537
HbA1c	7.6 ± 1.2	8 ± 1.8	0.173
LDL-C (mg/dL)	118.61 ± 43.51	134.08 ± 37.33	0.057
HDL-C (mg/dL)	43.10 ± 13.00	39.07 ± 7.02	0.072
Triglyceride (mg/dL)	155.90 ± 106.71	249.21 ± 107.30	< 0.001
CIMT (mm)	1.06 ± 0.11	0.78 ± 0.10	< 0.001
AVP (cm/s)	29.85 ± 3.95	41.05 ± 3.34	< 0.001
LVDD (mm)	4.84 ± 0.51	4.77 ± 0.41	0.496
LVSD (mm)	3.25 ± 0.73	3.06 ± 0.63	0.164
LVEF (%)	59.80 ± 5.28	61.00 ± 3.78	0.198
LA diameter (mm)	3.77 ± 0.55	3.81 ± 0.46	0.690
E	0.58 ± 0.12	0.58 ± 0.13	0.954
A	1.74 ± 7.32	0.71 ± 0.01	0.375
DT (ms)	267 (174-340)	287 (170-316)	0.070
IVRT (ms)	110 (0.89-133)	115 (10.8-128)	0.351

AVP: Aortic flow velocity propagation, BMI: Body mass index, BP: Blood pressure, CIMT: Carotid intima-media thickness, DM: Diabetes mellitus, DT: Deceleration time, GFR: Glomerular filtration rate, HDL-C: High-density lipoprotein cholesterol, IVRT: İsovolumetric relaxation time, IVS: İnterventricular septum, LA: Left atrium, LDL-C: Low-density lipoprotein cholesterol, LVDD: Left ventricular diastolic diameter, LVEF: Left ventricular ejection fraction, LVSD: Left ventricular systolic diameter.

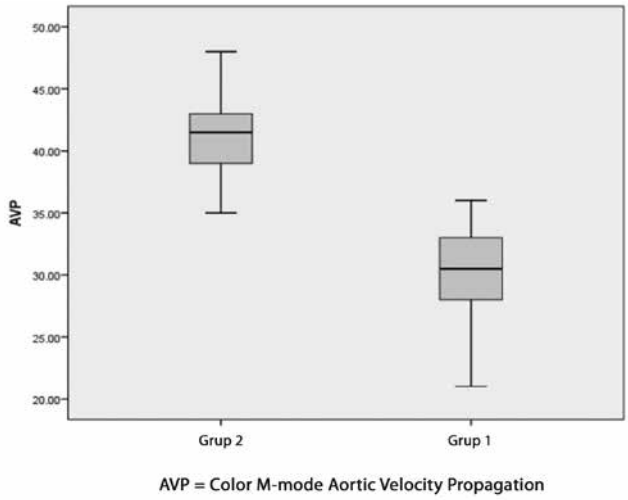

Figure 2. Error bar of colour M-mode aortic velocity propagation in Group 1 and Group 2 patients.

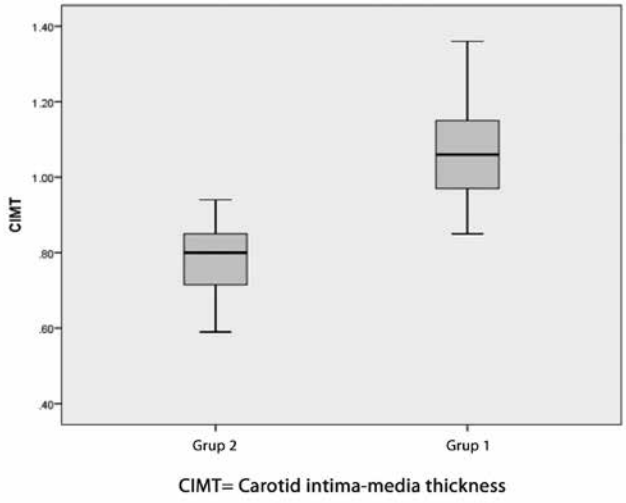

Figure 3. Error bar of carotid intima-media thickness in Group 1 and Group 2 patients.

Adult Treatment Panel III (NCEP-ATP III), American Society of Echocardiography, Screening of Heart Attack Prevention and Education (SHAPE) guideline and European Society of Hypertension recommend measuring CIMT for refining CVD risk assessment in patients with subclinical atherosclerosis[12-15]. Research showed markedly increased CIMT in patients with high CHD risk like diabetes and CKD[16-18]. In our study, CIMT was significantly higher in patients with type 2 diabetes who had CKD when compared to those with type 2 diabetes who had a normal renal function and similar age, body mass index and glycemic regulation values.

When measured along the origin of the descending thoracic aorta, AVP may reflect atherosclerosis. Growing evidence suggests that aortic atheroma is a marker of generalised atherosclerosis[19]. In patients who have significant coronary atherosclerosis or subclinical atherosclerosis, a significant association has been shown between AVP and CIMT[20]. Sahin et al. compared patients with ESRD and controls and found decreased AVP and increased pulse wave velocity (PWV) and CIMT in the former group. Also, they found a significant correlation between AVP and CIMT and PWV[21]. Simsek et al. demonstrated that newly diagnosed patients with type 2 diabetes who have not received any treatment have more subclinical atherosclerosis than healthy controls and that this may be evaluated with AVP and CIMT[22]. Gunes et al. found significantly lower AVP in patients with CHD than in patients with normal coronary arteries[7]. Similarly, in our study, the AVP value was lower in patients with type 2 diabetes who

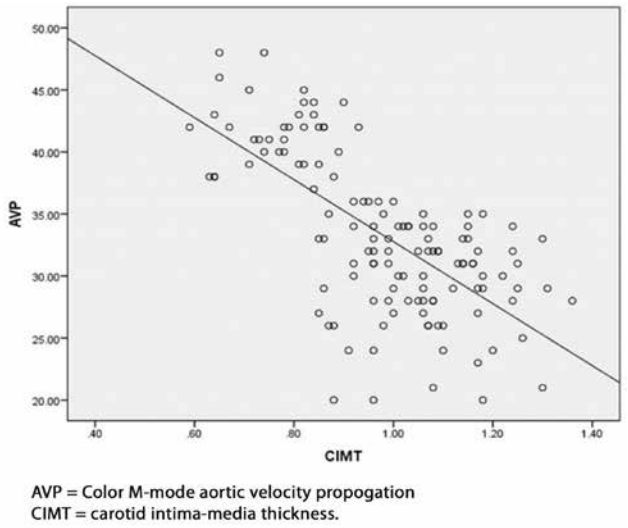

Figure 4. Scatterplot of colour M-mode aortic velocity propagation for carotid intima-media thickness.

Table 2. Linear regression analysis of the relation between AVP and BMI, smoking, hypertension, LDL-C, triglyceride, creatinine and GFR revealed that creatinine and GFR are significantly related with AVP

AVP	Beta	p
BMI (kg/m^2)	–0.008	0.902
Smoking	–0.084	0.167
Hypertension	0.036	0.534
LDL-C (mg/dL)	–0.238	0.051
HDL-C	–0.045	0.488
Triglyceride (mg/dL)	–0.109	0.149
Creatinine	–0.290	0.016
GFR	0.455	< 0.001

AVP: Aortic flow velocity progation, BMI: Body mass index, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, GFR: Glomerular filtration rate.

Table 3. Linear regression analysis of the relation between CIMT and BMI, smoking, hypertension, LDL-C, triglyceride, creatinine and GFR revealed that CIMT is significantly related to GFR only

CIMT	Beta	p
BMI	0.124	0.086
Smoking	–0.022	0.741
Hypertension	–0.099	0.118
LDL-C	0.116	0.375
HDL-C	0.175	0.098
Triglyceride	0.168	0.073
Creatinine	0.183	0.152
GFR	–0.600	< 0.001

CIMT: Carotid intima-media thickness, BMI: Body mass index, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, GFR: Glomerular filtration rate.

had CKD without a known CHD than that in patients with type 2 diabetes who had a normal renal function. A significant correlation was found between CIMT and AVP.

Study Limitations

In this study, we could investigate atherosclerosis with ultrasonographic imaging of carotid arteries in the whole population, we did not have an invasive angiographic search for coronary atherosclerosis. The small size of the study population might have biased the statistical results. To confirm the applicability of the method as a screening method, large population studies are needed.

CONCLUSION

In conclusion screening for atherosclerosis with AVP measurement is a method that can be easily used in clinical practice quickly without any additional costs. It can be used as an alternative, or complementary, to CIMT.

Ethics Committee Approval: Ethics committee approval was received for this study from the institutional review board.

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

FINANCIAL DISCLOSURE

The authors declared that this study has received nofinancial support.

CONFLICT of INTEREST

No conflict of interest was declared by the authors.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MY, TM, AK, İO, YK
Analysis/Interpretation: MY, TM, YK
Data Acquisition: MY, TM, İO, AK, YK
Analysis and/or Interpretation: MY, TM, YK
Final Approval: All of authors

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