Association of female sex and heart rate with increased arterial stiffness in patients with type 2 diabetes mellitus

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Abstract

Objective: This study aimed to evaluate the factors associated with increased arterial stiffness (IAS) measured by pulse wave velocity (PWV) and its clinical implications in patients with type 2 diabetes mellitus (DM).

Methods: This was an observational, cross-sectional study. The ankle–brachial PWV was used to measure arterial stiffness, and 310 patients (mean age, 49±9 years; 180 men) with type 2 DM were divided into two groups according to the results of PWV: Group 1 (IAS; n=214) and Group 2 (normal arterial stiffness; n=96).

Results: Patients in Group 1 were predominantly females (48% vs. 28%, p=0.001) and showed higher blood pressure and faster heart rate (HR). The glomerular filtration rate was lower and the urine microalbumin level was higher in patients with IAS. In multiple regression analysis, female sex and faster HR were independently associated with IAS. In subgroup analysis among female patients, prior stroke was more common in patients with IAS, and faster HR and increased postprandial 2-h C-peptide level were independently associated with IAS.

Conclusion: Female sex and faster HR were independently associated with IAS in patients with type 2 DM. In a subgroup analysis among female patients, prior stroke was more common in patients with IAS, and faster HR and elevated postprandial 2-h C-peptide level were found to be independently associated with IAS. *(Anatol J Cardiol 2017; 18: 347-52)*

Keywords: diabetes mellitus, pulse wave velocity, heart rate

Introduction

Diabetes mellitus (DM) is a group of chronic diseases characterized by hyperglycemia, and its direct and indirect effects on the human vascular tree are major sources of morbidity and mortality in both type 1 and 2 diabetes (1). In particular, since type 2 DM significantly increases the risk of developing cardiovascular diseases (CVD), it is important to predict the probabilities of CVD in patients with type 2 DM; CVD is the primary cause of death and disability (1). It is well-known that increased arterial stiffness (IAS) is an early marker of systemic atherosclerosis and that it also demonstrates an independent predictive value for cardiovascular events in patients with hypertension (2, 3), DM (4), and end-stage renal disease (5) and in elderly subjects (6) and the general population (7). Among several methods to estimate arterial stiffness, pulse wave velocity (PWV) is generally accepted as the most simple, noninvasive, and validated indicator of arterial stiffness (8). PWV indicates the velocity of the blood pressure wave form as it travels a known distance between two anatomic sites within the arterial system. It is determined by the arterial elastic modulus and other parameters (arterial wall thickness and diameter). PWV values positively correlate with arterial distensibility and stiffness (9). The prognostic impact of arterial stiffness measured using PWV in high-risk patients with type 2 DM and its association with cardiovascular risk factors in patients with type 1 DM has already been confirmed (10, 11). In contrast to the well-known prognostic impact of arterial stiffness in patients with DM, factors associated with IAS in patients with type 2 DM are still unclear.

Therefore, this study aimed to evaluate the factors associated with IAS in patients with type 2 DM and its clinical implications in South Korea.

Methods

We conducted an observational, retrospective study. In this study, we enrolled 310 patients with type 2 DM in the Kangnam Sacred Heart Hospital between April 2012 and April 2014 [mean

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Accepted Date:03.08.2017 **Available Online Date:** 04.11.2017

DOI:10.14744/AnatolJCardiol.2017.7773

age: 49±9 years; 180 (58%) males]. Patients with overt heart disease (decompensated heart failure, significant valve dysfunction, pericardial diseases, or pulmonary hypertension) and other significant systemic diseases, those aged ≥65 years, and those with type 1 or gestational DM were excluded from the study. All participants underwent PWV measurements, and the demographic, anthropometric, and metabolic data of the participants were collected. A total of 310 patients were classified into two groups: Group 1 (IAS, n=214) and Group 2 (normal arterial stiffness, n=96), according to the results of PWV (12).

PWV was measured using a VP-2000 automated device (Colin Co., Komaki, Japan). The right and left brachial–ankle PWV were simultaneously measured. The patients were placed in a supine position about 15 min prior to the test. The pressure waveforms of the brachial and tibial arteries were obtained from the occlusion and monitoring cuffs wrapped around the upper arm and lower leg. All measurements were performed in a quiet, temperature-controlled room (22°C±1°C), with the patients fasting overnight. The baseline brachial systolic and diastolic blood pressure (BP), heart rate (HR), and PWV were simultaneously measured.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The need for informed consent from all individual participants was waived because this study was an observational, cross-sectional study.

Statistical analysis

All continuous data are expressed as mean ± SD, and all categorical data are presented as percentage or absolute numbers. Continuous variables were analyzed using the Student's t-test, and dichotomous variables were analyzed using the chi-square test. Baseline demographic parameters were analyzed using these methods and the results are shown in Table 1. Laboratory findings were continuous variables, which were analyzed by the Student's t-test; the results are shown in Table 2. In addition, multivariate analysis (logistic regression, SPSS for Macintosh, version 10.0.7a, SPSS, Inc., Chicago, IL, USA) and multiple regression analysis were performed. The results are shown in Table 3. Non-normally distributed variables were analyzed using the Mann–Whitney U test. All variables having $p < 0.05$ were considered statistically significant.

Results

The baseline characteristics of the study population are shown in Table 1. In our study, 214 (69%) patients showed IAS (mean values: 16.5±2.8 vs. 13.1±5.9 m/s, p<0.001). Patients with IAS were predominantly females compared with patients with normal arterial stiffness [103 (48%) vs. 27 (28%), p=0.001]. Systolic (130±22 vs. 113±13 mm Hg, p<0.001) and diastolic BP (80±13 vs. 71±10 mm Hg, p<0.001) were higher in patients with IAS than in those with normal arterial stiffness. In addition, HR was slightly faster (78±14 vs. 71±10 bpm, p<0.001) in patients with IAS than in patients with normal arterial stiffness. Otherwise, there was

Table 1. Baseline demographic characteristics of patient population

	IAS (n=214)	Normal (n=96)	*P*
Age, years	50±9	48±10	0.113
Female	103 (48%)	27 (28%)	0.001
BMI, kg/m^2	25.2±4.6	24.9±4.6	0.645
PWV, m/s	16.5±2.8	13.1±5.9	<0.001
SBP, mm Hg	130±22	113±13	<0.001
DBP, mm Hg	80±13	71±10	<0.001
Heart rate, beats/min	78±14	71±10	<0.001
Hypertension	80 (37%)	27 (28%)	0.154
Current smoker	71 (33%)	37 (39%)	0.419
Micro-complications	119 (56%)	50 (52%)	0.622
Macro-complications	34 (16%)	7 (7%)	0.223
CAD	14 (7%)	2 (2%)	0.162
CVA	20 (9%)	5 (5%)	0.264
Duration of DM, years	6.3±6.9	4.9±6.4	0.098
Current medications			
Insulin	84 (39%)	28 (30%)	0.124
OHA	144 (68%)	53 (57%)	0.070
Beta blocker	17 (8%)	7 (8%)	1.000
RAS blocker	53 (26%)	17 (19%)	0.237

Categorical values are expressed as absolute values and percentage (in brackets). Continuous values are expressed as mean ± SD. CAD – coronary artery disease, CVA – cerebrovascular disease, OHA – oral hypoglycemic agents.

Table 2. Baseline laboratory findings of patients with DM according to the results of PWV results

	IAS (n=214)	Normal (n=96)	*P*
GFR, mg/g creatinine	79.5±17.0	82.5±12.9	0.032
TC, mg/dL	175.5±41.1	181.7±46.5	0.303
HDL, mg/dL	47.2±13.1	44.7±10.6	0.103
LDL, mg/dL	102.5±36.3	111.5±37.9	0.078
HbA1c, %	9.2±2.2	9.6±2.8	0.170
Fasting C-peptide	2.2±1.4	2.0±1.4	0.193
PP2 C-peptide	5.8±5.1	5.1±4.4	0.326
*BUN, mg/dL	14.5 (6.4-57.3)	13.9 (6.2-45.9)	0.615
*TG, mg/dL	119.0 (32.0-887.0)	126.5 (32.0-700.0)	0.144
*Cr, mg/dL	0.9 (0.5-3.0)	0.9 (0.3-1.8)	0.906
*Fasting insulin, µU/mL	6.6 (0.1-41.0)	4.1 (0.2-30.8)	0.240
*PP2 insulin, ng/mL	18.3 (0.10-172.2)	14.07 (0.20-172.5)	0.207
*Total vitamin D, ng/mL	11.3 (3.7-124.5)	10.8 (3.6-35.6)	0.381
*Urine MA, mg/dL	2.00 (0.1-187.6)	1.30 (0.1-228.5)	0.118

Data are expressed as mean ± SD. BUN, blood urea nitrogen; Cr, creatinine; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MA, microalbumin; PP2, postprandial 2-h, TC, total cholesterol; TG, triglyceride.
*Analyzed using the Mann–Whitney U test and data are expressed as median (IQR).

Anatol J Cardiol 2017; 18: 347-52
DOI:10.14744/AnatolJCardiol.2017.7773

Table 3. Factors associated with IAS of patients with DM according to the results of PWV results

	Odds ratio	95% CI	*P*
Univariate			
Female sex	2.371	1.411-3.987	0.001
Systolic blood pressure	1.061	1.039-1.082	<0.001
Diastolic blood pressure	1.090	1.058-1.124	<0.001
Heart rate	1.051	1.027-1.076	<0.001
Glomerular filtration rate	0.988	0.971-1.005	0.150
Urine micro-albumin	1.008	0.997-1.019	0.144
Multiple analysis			
Female sex	2.888	1.516-5.503	0.001
Systolic blood pressure	1.030	1.000-1.062	0.053
Diastolic blood pressure	1.033	0.987-1.082	0.162
Heart rate	1.043	1.013-1.075	0.005
Multiple regression test	Correlation coefficient		P
Female sex	0.211		0.005
Heart rate	0.316		<0.001

Table 4. Female subgroup analysis according to the results of PWV results

	IAS (n=103)	Normal (n=27)	*P*
Age, years	49±9	50±8	0.410
Menopause	62 (68%)	14 (67%)	1.000
PWV, m/s	16.0±2.7	12.2±2.0	<0.001
Systolic BP, mm Hg	126±23	121±14	0.009
Diastolic BP, mm Hg	79±11	72±6	0.008
Heart rate, beats/min	78±13	69±9	0.003
Hypertension	39 (38%)	9 (33%)	0.823
Micro-complications	55 (53%)	11 (41%)	0.283
Macro-complications	21 (20%)	2 (7%)	0.159
Coronary artery disease	7 (7%)	0 (0%)	0.344
Prior stroke	13 (13%)	0 (0%)	0.069
Duration of DM, years	6.6±7.9	6.6±7.01	0.999
Fasting insulin, µU/mL	8.5±6.1	6.3±6.1	0.216
PP2 insulin	26.4±27.4	13.2±10.5	0.079
Fasting C-peptide	2.56±1.44	1.95±1.18	0.130
PP2 C-peptide	6.67±5.22	3.84±2.21	0.001
Vitamin D, total, ng/mL	12.5±5.8	13.1±6.4	0.729
HbA1c, %	9.2±2.4	8.5±2.3	0.208
GFR, mg/dL creatinine	81.0±15.5	82.0±12.5	0.758
Urine MA, mg/dL	10.9±31.4	1.1±1.4	0.006

Categorical values are expressed as absolute values and percentage (in brackets). Continuous values are expressed as mean ± SD. BP, blood pressure; DM – diabetes mellitus; GFR – glomerular filtration rate; MA – microalbumin; PP2 – postprandial 2-h; PWV – pulse wave velocity

no significant difference in the duration of DM or in terms of both micro- [119 (56%) vs. 50 (52%), p=0.622] and macro-vascular complications [34 (16%) vs. 7 (7%), p=0.223] between patients with IAS and those with normal arterial stiffness. The prevalence of current smoking was similar between patients with IAS and those with normal arterial stiffness [71 (33%) vs. 37 (39%), p=0.419].

The baseline laboratory findings of patients with DM according to the results of PWV are shown in Table 2. The glomerular filtration rate (GFR) of patients with IAS was lower (79.5±17.0 vs. 82.5±12.9 mg/g creatinine, p=0.032) than that of patients with normal arterial stiffness. There was no significant difference in the status of glucose control or other parameters between the groups; however, the urine microalbumin level was higher, with borderline statistical significance (14.1±38.7 vs. 7.1±20.7 mg/dL, p=0.065), in patients with IAS than in those with normal arterial stiffness. However, analysis using the Mann–Whitney U test showed no significant difference between groups.

The factors associated with IAS in patients with DM have been described in Table 3. In the univariate analysis, female sex, higher BP, faster HR, lower GFR, and urine microalbumin level were associated with IAS. In the multivariate analysis, female sex (OR, 2.888; 95% CI, 1.516–5.503; p=0.001) and faster HR (OR, 1.043; 95% CI, 1.013–1.075; p = 0.005) were independently associated with IAS in patients with type 2 DM.

The results of subgroup analysis among female patients are shown in Table 4 and Table 5. Similar to that observed in the whole sample, both systolic and diastolic BP were higher, and HR was faster in female patients with type 2 DM. Prior stroke was more common in patients with IAS, with borderline statistical significance [13 (13%) vs. 0 (0%), p=0.069], compared with patients with normal arterial stiffness. In addition, postprandial 2-h C-peptide (PCP) (6.7±5.2 vs. 3.8±2.2 µU/mL, p=0.001) and urine microalbumin (10.9±31.4 vs. 1.1±1.4 mg/dL, p=0.006) levels were higher in patients with IAS than in patients with normal arterial stiffness. In the multivariate analysis, increased PCP (OR, 1.449; 95% CI, 1.070–1.964; p=0.017) levels and faster HR (OR, 1.096; 95% CI, 1.017–1.180; p=0.016) were independently associated with IAS in female patients with type 2 DM.

Table 5. Factors associated with IAS in female sex

	Odds ratio	95% CI	*P*
Univariate			
Systolic blood pressure	1.032	1.004-1.060	0.026
Diastolic blood pressure	1.078	1.018-1.142	0.010
Heart rate	1.070	1.0232-1.120	0.003
Post-prandial 2 hour C peptide	1.289	1.016-1.635	0.036
Urine micro-albumin	1.158	0.870-1.542	0.315
Urine total protein	1.046	0.935-1.542	0.315
Multivariate			
Systolic blood pressure	1.035	0.996-1.076	0.082
Diastolic blood pressure	0.999	0.907-1.101	0.990
Heart rate	1.096	1.017-1.180	0.016
Post-prandial 2 hour C peptide	1.449	1.070-1.964	0.017

Discussion

We found that approximately 69% of the patients with type 2 DM showed IAS and that IAS is associated with female sex, higher BP, and faster HR. Patients with IAS had lower GFR and higher PCP and urine microalbumin levels than those with normal arterial stiffness. Among these factors, female sex and faster HR were found to be independently associated with IAS in patients with type 2 DM. In the subgroup analysis on female patients, prior stroke occurrence was more common in patients with IAS and faster HR and increased PCP levels were independently associated with IAS.

As observed in our study, there was no significant difference among micro- or macro-vascular complications between the two groups. However, subgroup analysis among female patients showed a tendency of higher prevalence of macrovascular complications in patients with IAS; none of the patients with normal arterial stiffness had experienced stroke. Female sex and faster HR were the only clinical parameters that were independently related to IAS in patients with type 2 DM.

Cherney and Montanari have shown that arterial stiffness is higher in female patients with type 1 DM, which is independent of the effects of clamped hyperglycemia or neurohormonal activation (12). Seker et al. (13) reported that serum 25-hydroxyvitamin D level is associated with both arterial and ventricular stiffness in healthy subjects, and Lieberman et al. (14) reported that vitamin D deficiency is associated with increased PWV in adolescents with or without type 1 DM. Contrast to the findings from these two studies, our study found no significant relation between serum vitamin D level and IAS. This could be attributed to missing data (data regarding serum vitamin D level was available for only 71% of the patients) or incomplete investigation of exogenous supplements of vitamin D. In addition, there was vitamin D deficiency in both groups (<20 ng/mL) in this study. Therefore, it also be indicated if vitamin D supplements would improve IAS or lower cardiovascular events in patients with type 2 DM. In our study, lower GFR and higher urine microalbumin level were found to be associated with IAS. Sjöblom et al.(15) reported that urine microalbumin level, but not reduced GFR, is associated with cardiovascular subclinical organ damage in type 2 DM. Lu et al.(16) reported that reduced GFR is associated with intima-media thickness independently of albuminuria in patients with type 2 DM. However, these two parameters were not independently associated with IAS in multivariate regression analysis, and there was no significant difference in intima-media thickness in patients with IAS and those with normal arterial stiffness (data not shown) in our study.

In comparison to patients with normal arterial stiffness, the prevalence of IAS was much higher in females than in males [103/130 (79%) vs. 111/180 (62%)] in patients with IAS. Even our data failed to show statistically significant differences in macrovascular complications; however, the incidence of prior stroke was much higher in female patients with IAS, with borderline statistical significance. Macrovascular complications, such as cardiovascular, cerebrovascular, and peripheral vascular disease, disproportionately affect women. DM increases the risk of myocardial infarction, claudication, and stroke to a greater extent in women than in men, and the relative risk of fatal coronary heart disease associated with DM is approximately 50% greater in women than in men (17). Homko et al. (18) attributed this to the fact that women are less likely to simultaneously achieve HbA1c, BP, and LDL cholesterol targets compared with men (18). However, there was no significant difference of these parameters between men and women in our study. Another possible explanation for the increased risks of these cardiovascular events in women with DM may, in part, be the blunting of cardioprotective effects of estrogen in women (19). Laboratory findings showed a significant difference in PCP levels. In terms of C-peptide, both fasting and postprandial C-peptide levels were higher in patients with IAS. Type 2 DM is characterized by impaired β-cell function to maintain normolycemia (20). β-cell function has been reported to be an important predictor of treatment failure in patients with type 2 DM (21). Serum C-peptide level has been established for the assessment of β-cell function, and PCP level is the marker for insulin resistance in patients with type 2 DM before β-cell destruction occurs (22). In addition, Fang et al. (23) reported that insulin resistance evaluated by homeostasis model assessment index correlates with arterial stiffness even before glucose intolerance. The mechanism underlying the induction of IAS by insulin resistance remains unclear. However, the oxidative stress induced by insulin resistance is known to affect vascular stiffness. Recent studies have shown that the introduction of insulin therapy improved β-cell function (24). Despite statistical insignificance, the use of oral hypoglycemic agents was higher in patients with IAS in our study. Therefore, early initiation of insulin therapy before β-cell dysfunction occurs might be a therapeutic target for IAS. Unfortunately, this could not be concluded from our present study since this study did not seek to evaluate the effect of insulin treatment on IAS.

Faster HR was independently associated with IAS in the whole study population and among female patients compared with patients with normal arterial stiffness. Tan et al. (25) showed the dependence of HR on aortic PWV at different arterial pressures in rats and speculated that HR may be a confounding factor that should be considered when performing analysis based on PWV measurements. In our study, both higher BP and faster HR were associated with IAS in patients with type 2 DM, but only faster HR was independently associated with IAS on multivariate regression analysis. A higher resting HR is independently associated with IAS even in normotensive adults, according to the study by Logan et al. (26). Therefore, faster HR might be another important clinical parameter for predicting cardiovascular events or IAS in patients with type 2 DM, regardless of BP or glycemic control. Increased HR is well-known to be associated with several risk factors, such as increased glucose, triglycerides, body mass index, and total cholesterol, for metabolic syn-

Anatol J Cardiol 2017; 18: 347-52
DOI:10.14744/AnatolJCardiol.2017.7773

drome. On the other hand, metabolic syndrome, abdominal obesity, and insulin resistance also activate the sympathetic tone and increase HR (27, 28). Therefore, taken together with previous data and our present findings, increased HR might be another clinical risk factor for predicting IAS in patients with type 2 DM.

In summary, several patients with type 2 DM showed IAS (69%) in our study, and female sex and faster HR were significantly correlated with IAS.

Study limitations

This study has several limitations. First, there were relatively few incidences of macrovascular complications among patients with type 2 DM. Therefore, it was difficult to observe significant relations between IAS and cardiovascular events. Second, our study had a relatively small study population to observe the prevalence of IAS and its clinical implications. Third, some laboratory data, namely vitamin D, C-peptide, and insulin levels were not examined in the whole study population. The final and most important limitation was that we did not measure arterial stiffness by carotid-to-femoral PWV, which was considered to be the gold standard.

Conclusions

Our study showed that female sex and faster HR were independently associated with IAS in patients with type 2 DM. Subgroup analysis among female patients showed that the incidence of prior stroke was higher in patients with IAS and that faster HR and increased PCP levels were independently associated with IAS.

Conflict of interest: There is nothing to declare with this study.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – J.R.C., M.K.K.; Design – M.K.K.; Supervision – J.R.C., M.K.K.; Data collection &/or processing – All authors; Analysis &/or interpretation – M.K.K.; Literature search – All authors; Writing – M.K.K.; Critical review – M.K.K.

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Serdar Akyay, from EFSAD's collections