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Ankle Brachial Index (ABI) measurement associated with High Sensitivity-C-Reactive Protein, Insulin Resistance and Pulse Pressure Levels in Type 2 Diabetes Mellitus Patients

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Article Info

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Abstract

Atherosclerosis is common occurrence in type 2 diabetes mellitus (T2DM) patients. Peripheral arterial disease (PAD) is a major arteries disease caused by atherosclerosis as a vascular complication of T2DM. It can be detected by using ankle brachial index (ABI) measurement. A total of 187 subjects were recruited in present study and underwent ABI measurement. Thirty one of T2DM patients were abnormal low ABI≤0.9 (as Gr-1) and 156 non-T2DM subjects were normal ABI>0.90 (as Gr-2). Comparison of clinical characteristics of these two groups, Gr-1 were significantly increased in pulse pressure (PP), dyslipidemia, insulin, insulin resistance (IR) and high sensitivity-C-reactive protein (hs-CRP) ($p<0.05$) than Gr-2. Multiple forward stepwise linear regression analyses of the significant variables showed that in these decreased ABI, independent predictors of decreased ABI were hs-CRP (β =-0.488, R^2 = 0.238, $p<0.001$), PP (β = -0.320, R^2 = 0.336, $p<0.001$), triglyceride/high density lipoprotein-cholesterol (TG/HDL-C) ratio (β =-0.279, R^2 = 0.397, $p<0.001$), IR (β =-0.143, R^2 = 0.415, $p<0.001$), and Age (β = -0.115, R^2= 0.428, $p<0.001$). In conclusion, abnormal ABI≤0.9 or PAD is associated with increased PP, inflammation, IR, dyslipidemia and age. ABI measurement is a useful tool to estimate PAD and cardiovascular diseases risk marker in asymptomatic patients.

Keywords: Ankle brachial index; Peripheral arterial disease; Atherosclerosis; Highsensitivity C-reactive protein; Pulse pressure; Insulin resistance.

Introduction

Atherosclerosis progression is the process affected by the alteration of vascular endothelial cell beds with clinically demonstrated life threatening consequences including coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease (PAD) [1]. Peripheral arterial disease is one of the common evidence of atherosclerosis. The prevalence of PAD was increased with age, hypertension, diabetes and smoking [2-5]. People with PAD often have lower extremity circulation problems and they are at higher risk for both cardiovascular disease (CVD) and cerebrovascular disease event [2]. Peripheral arterial disease is commonly assessed by using ankle brachial systolic blood pressure index (ABI) measurement [6, 7]. The ABI result is the ratio of Doppler- or sphygmomanometry-determined lower extremity blood pressure to brachial artery blood pressure. Reproducibility of the ABI measurement is good with

the mean error of 8-9% within or between measurements [8]. Peripheral arterial disease severity is assessed according to the levels of ABI: (i) 0.91-1.30: normal, (ii) 0.70-0.90: mild occlusion, (iii) 0.40-0.69: moderate occlusion, (iv) <0.40: severe occlusion and (v) >1.30: poorly compressible vessels. The American Diabetes Association recommends measuring ABI in all adults older than 50 years and history of smoking, hypertension or diabetes or in any patient having PAD and other CV risk factors [9].

C-reactive protein (CRP) is an inflammation marker recommended for risk assessment for primary prevention of cardiovascular disease [10, 11]. Increased CRP level is associated with increased risk of cardiovascular disease [12] and increased vascular stiffness can be caused by atherosclerosis and aging.

Age related increases in blood pressure (BP) usually show the systolic blood pressure (Syst) elevation while maintaining or having a slight decrease in a diastolic BP. This induces in the widening of pulse pressure (difference of systolic and diastolic blood pressure) [13]. However, BP can be divided into two components: (i) steady (mean arterial pressure; MAP) and (ii) pulsatile (pulse arterial pressure, PP) [14]. Previous research has linked elevated PP (estimate of arterial stiffness) with a higher risk of cardiovascular morbidity and mortality [15, 16]. Arterial hypertension (steeper age-related widening of PP) also promotes vascular stiffness [17]. High peripheral resistance is the hallmark of arterial hypertension, but always exerts hemodynamic changes that could counteract the effect of the increase in MAP on PP. In this regard, peripheral resistance maintains a reciprocal relationship with stroke volume and PP [18]. In the present study, we aim to demonstrate that PAD (ABI<0.9) is associated with increased PP, inflammation, IR, dyslipidemia and age. ABI measurement can use as the tested tool to estimate subclinical atherosclerosis and CVD risk in patients with PAD.

Methods

Study Population

Two hundred and five of female participants from the Cardiovascular Diseases in Diabetes Patients Project during October 2012-December 2013 were used in the present study. Volunteers were excluded, if they had an ongoing febrile illness, history of a connective tissue disorders, non-atherosclerotic arterial disease, history of lower extremity bypass or percutaneous angioplasty in the preceding year and those with an ABI >1.3 caused by poorly compressible arteries in the lower extremities. Eighteen participants didn't participate in ABI measurement section was excluded from the study. The number of eligible participants was 187 in the present study. Thirty one subjects with T2DM were identified as PAD with abnormal low ABI ≤0.9(Gr-1) and 156 subjects without T2DM were identified as without PAD with normal ABI ≥0.9(Gr-2). The research protocol was approved by the Ethics Committee of the Naresuan University. All participants gave informed consent before their provided blood samples and underwent assessment for ABI measurement.

Anthropometric, Blood Pressure and ABI Measurements

Questionnaires were used to record clinical characteristics including diagnosis of hypertension, diabetes, a history of MI or stroke, smoking, alcohol use, and medications of each participant at the study visit. Anthropometric measurements of the study included height; weight and waist circumference (WC).The body mass index (BMI) was calculated from height and weight as kg/m^2. Blood pressure (BP) was measured by using Omron HEM-7080 (Omron Health care, Tokyo, Japan). Pulse pressure (PP) was determined by subtracting the diastolic from the systolic blood pressure (Syst), and mean arterial pressure (MAP) was calculated by using the formula: [(systolic blood pressure) + (2 x diastolic blood pressure)]/3 [19].

Ankle brachial index measurement is made in the supine position after 5 min of rest by using Sphygmanometer and Sphygmograph (Vasera, VS-1500N ver. 04; Fukuda Denshi, Japan). A pneumatic-cuff is placed around the ankle and the pressure is measured at both the dorsalis pedis and posterior tibial arteries using a hand held continuous wave Doppler probe (5-10 MHz). We used the same technique measurement in both arms for brachial artery pressure. The higher of the two ankle pressures is divided by the brachial artery pressure. In subjects with normal lower limb arterial circulation, the systolic pressure at the ankle is usually 10-15 mmHg higher than the arm measurement, it caused from pulse wave velocity [20], resulting in an ABI >1.10. Following the recommendation of the International medical societies for the ABI calculation, the highest pressure in the leg is divided by the highest pressure in the arm [9, 21-22]. Reproducibility of the ABI measurement seemed to be good. In the ABI study, the mean error of 8-9% within or between observers is smaller than with established screening measures [8]. The lower of the resting ABI values for the right and left arms and legs was used in the analyses involving the ABI. PAD was defined as an ABI ≤ 0.9 in both arms and legs.

Blood Sample Collection and Biochemical Determination

Fasting venous blood was collected from all participants. Plasma glucose (Glu), blood urea nitrogen (BUN), total cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) were measured by enzymatic method (Roche diagnostic, Switzerland). Serum creatinine (CT) level was determined based on the Jaffe reaction. LDL-C level was calculated with Friedewald's formula in specimens with TG level<400 mg/dl.

Highly Sensitive C - reactive protein (hs-CRP) Assay

Highly sensitive-CRP concentrations were determined by using latex particle enhanced immune turbid metric assay on the Hitachi 912 auto-analyzer (Roche Diagnostic, Switzerland) that has been standardized against the World Health Organization reference. The normal range of hs-CRP was<3.0 mg/l (<0.03 g/l).

Insulin Assay

Fasting insulin levels were measured based on micro-particle enzyme immunoassay (MEIA) technology using Abbott reagents with Axsym system (Abbott laboratories, Illinois, USA).

All participants underwent evaluation of insulin resistance index (IR) by using the Homeostasis model assessment (HOMA)-formula [23]. HOMA of insulin resistance (IR) was defined using the following formula: fasting glucose (mmol/l) x fasting insulin (μU/ml)/22.5 [23].

Statistical Analysis

All data were expressed as median and inter quartile range, and compared the differences between groups by using the Mann–Whitney *U*-test. Spearman rank correlation was used to assess the correlation of all clinical markers in the study participants. Clinical variables that correlated with PAD (ABI) in the present study were tested as independent variables by using multivariate forward stepwise linear regression analysis. Tests were two tailed, and a p-value<0.05 was considered significant. All analyses were performed using the SPSS statistical package, version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

General characteristics of both groups were demonstrated in Table 1. In the comparison of clinical characteristics of both groups, Gr-1 demonstrated more difficult physical activity, significantly greater PP, TC, TG, hs-CRP, insulin, IR,TG/HDL-C ratio and lower HDL-C levels than Gr-2. Bivariate correlations, ABI was significantly correlated with Syst (r=-0.384, p<0.001), PP (r=-0.437, p<0.001), MPP (r=-0.238, p<0.001), TC (r=-0.326, p<0.001), hs-CRP (r=-0.388, p<0.001), insulin (r= -0.269, p<0.001), IR (r=-0.287, p<0.001) and TG/HDL-C ratio (r=-0.299, p<0.001). The correlation of the other clinical variables was shown in Table 2. We used multiple forward stepwise linear regression analysis to examine effects of variables in the association of these variables with ABI. Statistics were listed in Table 3. Hs-CRP, PP, TG/HDL-C ratio, IR and age showed the association with ABI, which remained highly significant after adjusting for any clinical or laboratory confounding variables [hs-CRP (β = -0.488, R^2 = 0.238, p<0.001), PP (β = -0.320, R^2 = 0.336, p<0.001), TG/HDL-C ratio (β = -0.279, R^2 = 0.397, p<0.001), IR (β = -0.143, R^2 = 0.415, p<0.001) and Age (β = -0.115, R^2 = 0.428, p<0.001)].

Table 1. Comparison of the general characteristics of Gr-1; asymptomatic PAD with T2DM patients andGr-2; without PAD and non-T2DM subjects

Biomarkers	Gr-1 (n=31)	Gr-2 (n=156)	p-value
Age (yrs)	65.0* (60.5-73.5)*	69.0 (63.0-75.0)	0.255
WC (cm)	85.0 (75.5-90.0)	87.0 (80.8-93.0)	0.218
BMI (kg/m^2)	23.0 (21.2-28.2)	24.0 (22.1-26.9)	0.791
Syst BP (mmHg)	129.0 (121.5-150.0)	124.5 (117.0-136.3)	0.072
Diast BP (mmHg)	70.0 (65.5-82.0)	74.0 (70.8-82.0)	0.427
PP (mmHg)	61.0 (54.5-65.0)	51.0 (44.0-59.0)	0.002
MAP (mmHg)	98.0 (82.0-107.0)	93.0 (88.0-100.0)	0.550
Glu (mmol/l)	5.67 (5.25-7.18)	5.69 (5.34-6.15)	0.819
BUN (mmol/l)	5.35 (4.46-6.60)	4.99 (3.92-6.06)	0.854
CT (μmol/l)	79.56 (70.72-88.40)	79.56 (70.72-97.24)	0.443
TC (mmol/l)	6.01 (5.24-6.75)	5.29 (4.54-5.99)	<0.001
TG (mmol/l)	2.91 (2.41-3.67)	1.78 (1.30-2.36)	<0.001
HDL-C (mmol/l)	1.32 (1.06-1.47)	1.49 (1.30-1.74)	0.002
LDL-C (mmol/l)	3.47 (2.46-4.23)	2.72 (2.28-3.45)	0.104
TG/HDL-C ratio	4.84 (3.86-8.02)	2.78 (1.79-3.72)	<0.001
hs-CRP (mg/L)	6.03 (4.14-7.42)	1.58 (0.89-2.85)	<0.001
Insulin (μU/ml)	17.0 (10.55-37.15)	5.60 (4.20-9.20)	<0.001
HOMA-IR	4.20 (2.77-9.75)	1.52 (0.93-2.51)	<0.001

* Median and inter quartile

Table 2. correlation of the parameters among the asymptomatic peripheral arterial disease patients

Correlation between parameters		Correlation coefficient		Correlation between parameters		Correlation coefficient	
		r	*p*-value			r	*p*-value
ABI	Syst	-0.384	<0.001	PP	MPP	0.422	<0.001
	PP	-0.437	<0.001		Glu	0.149	0.048
	MPP	-0.238	<0.001		TC	0.275	<0.001
	TC	-0.326	<0.001		HDL-C	0.148	0.049
	hs-CRP	-0.388	<0.001		LDL-C	0.193	0.010
	Insulin	-0.269	<0.001	MPP	Glu	0.255	<0.001
	IR	-0.287	<0.001		TC	0.355	<0.001
	TG/HDL-C	-0.299	<0.001		LDL-C	0.363	<0.001
Age	BMI	-0.318	<0.001		Insulin	0.272	<0.001
	CT	0.318	<0.001		IR	0.302	<0.001
	BUN	0.177	0.018	Glu	HDL-C	-0.164	0.030
WC	Syst	0.161	0.032		BUN	0.190	0.011
	Diast	0.328	<0.001		Insulin	0.261	<0.001
	MPP	0.272	<0.001		IR	0.388	<0.001
	Glu	0.342	<0.001	BUN	CT	0.321	<0.001
	HDL-C	-0.241	<0.001		TC	0.210	0.005
	Insulin	0.262	<0.001		LDL-C	0.235	0.002
	IR	0.300	<0.001		TG	0.261	<0.001
BMI	DiastBP	0.204	0.006		TG/HDL-C	0.236	0.002
	Insulin	0.359	<0.001		TG	0.313	<0.001
	IR	0.361	<0.001		LDL-C	0.872	<0.001
Syst	PP	0.741	<0.001		Insulin	0.281	<0.001
	MPP	0.853	<0.001		IR	0.252	<0.001
	Glu	0.237	<0.001		TG/HDL-C	0.232	0.002
	TC	0.350	<0.001	HDL-C	Insulin	-0.270	<0.001
	LDL-C	0.303	<0.001		IR	-0.279	<0.001
	Insulin	0.183	0.015		TG/HDL-C	-0.684	<0.001
	IR	0.224	0.003	hs-CRP	Syst	0.244	<0.001
Diast	MPP	0.813	<0.001		Diast	0.178	0.018
	Glu	0.222	0.003		MPP	0.274	<0.001
	TC	0.273	<0.001		TC	0.221	0.003
	LDL-C	0.303	<0.001		TG	0.351	<0.001
	IR	0.175	0.020		HDL-C	-0.370	<0.001
CT	Insulin	0.312	<0.001		LDL-C	0.184	0.014
	IR	0.297	<0.001		Insulin	0.409	<0.001
TC	TG/HDL-C	0.932	<0.001		IR	0.428	<0.001
TG	HDL-C	-0.407	<0.001		TG/HDL-C	0.429	<0.001
LDL-C	Insulin	0.277	<0.001				
	IR	0.258	<0.001				

Table 3. Multiple forward stepwise linear regression analyses of the significant variables showed that hs-CRP, PP, IR, TG/HDL-C and Age were independent predictors of PAD with T2DM patients

Variables	β	R^2	Adjusted R^2	*p*-value
hs-CRP	-0.488	0.238	0.234	<0.001
PP	-0.320	0.336	0.329	<0.001
TG/HDL-C	-0.279	0.397	0.387	<0.001
IR	-0.143	0.415	0.402	<0.001
Age	-0.115	0.428	0.412	<0.001

Discussion

The risk of atherosclerotic disease is markedly increased among individuals with diabetes, hypertension and aging. Atherosclerosis is the major cause of the death and disability in these subjects [24], PAD disease is a common evidence of atherosclerosis that share the common risk factors. General characteristic of PAD is usually caused occlusive arterial vessels of the lower extremities, but many are asymptomatic

[25]. The loss of function and long-term disability progression reduced walking speed and distance associated with intermittent claudicating [9, 26], subjects with low ABI<0.9 were a sign of severe atherosclerosis in their arms and legs. Our data supports these PAD patients showing increased PP, TC, TG, TG/HDL-C ratio, hs-CRP, insulin, IR, reduced HDL-C and older age.PAD (low ABI≤0.9)patients were demonstrated higher hs-CRP; an inflammation marker, is a major component and plays the major role in atherosclerosis [10,27]. Increased PP may indicate PAD patients are at high risk in for morbidity and mortality from CVD. Pulse pressure reflects vascular stiffness of the aorta and large arteries and pulse wave velocity that may be cause by atherosclerosis and aging [28]. An increased PP is associated with the development of left ventricular dysfunction and clinical heart failure in the hypertensive and elderly [29]. PAD (low ABI≤0.9) patients were also demonstrated insulin resistance state, decrease insulin function and insulin ability to inhibit lipolysis leads to increase FFAs generation and decrease lipoprotein lipase activity. This generates a chylomicron remnant rich in TG [30], caused elevated hepatic FFAs and VLDL TG-rich particles secretion. These processes also generate HDL particles containing high TG concentrations. This HDL-C high TG containing is hydrolyzed with hepatic lipase to produce TG and smaller HDL that less antiatherogenic activity and easily to remove from the body by the kidney and caused higher TG/HDL-C ratio. Thus, both insulin resistance and dyslipidemia associated with endothelial damage led increased risk of CVD [31] in these PAD (low ABI) patients. Our present study demonstrated the same as Lee et al. [32] reported association of ABI and the development of diabetic retinopathy, similar to PAD, and the study of Subramaniam et al. [33] demonstrated ABI measurement as a marker for CVD assessment in multi-ethnic. Previous studies have been demonstrated PAD patients or abnormal low ABI was associated with enlarge of plaques in aortic arch [34], arterial stiffness (increased PP) and aortic calcification [35].

PAD is often referred to as an under-diagnosed and under-treated public health problem. There are the practice guidelines from the American College of Cardiology/ American Heart Association for the management of PAD patients. They recommend all asymptomatic adult age ≥50 year-olds to measure ABI, especially those with current or history of smoking, diabetes and hypertension, also in adults with lower extremity circulation problems and age ≥70 years old should be assess for early CVD prevention and treatment [2]. ABI measurement is a non-invasive test for atherosclerosis detection. Therefore, routine screening for PAD has been advocated in these adults using ABI measurement. Limitations of the present study were use of cross-sectional data, a relatively small patient sample size and one district. Subjects had only one time ABI measurement.

Conclusion

ABI (or PAD) measurement should be considered as the tool for CVD risk assessment and atherosclerosis risk marker. The ABI measurement is a simple, cheap, noninvasive and reliable as the tested tool and could help the clinicians to diagnose PAD and atherosclerosis risk.

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Conflict of interest

The authors have no conflict of interest to report.

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