Comparison of Arterial Stiffness among Type 2 Diabetes with, without Peripheral Neuropathy and Healthy Individuals

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that has effects on arterial function which has been shown to increased arterial stiffness, depressed endothelium dependent vasodilation and impaired microcirculation. However, there is lack of information about the impact of diabetic peripheral neuropathy (DPN) on vascular function. Therefore, the objective of this study was to compare central and peripheral arterial stiffness among diabetic peripheral neuropathy, diabetic and age-match healthy individuals. We studied 20 T2DM patients with DPN (age 60.5±6 years), 21 T2DM patients without DPN (age 57.6±7 years) and 21 healthy controls (age 55.5±8.6 years). All participants underwent blood pressure monitoring and pulse wave velocity (the arterial stiffness parameters) was measured by using vascular screening device. The results showed that in diabetic patients, both brachial and ankle SBP, MAP and PP were significantly higher than healthy control subjects. T2DM with DPN had higher brachial-ankle and carotid-femoral pulse wave velocity than those without DPN and healthy controls. Heart-carotid pulse wave velocity was significantly higher in DPN group when compared with healthy. Multiple linear regression analysis revealed that brachial-ankle PWV ($r=0.429$, $p<0.001$) and fasting blood glucose ($r=0.409$, $p=0.001$) were significant determinants of neuropathy. Our present findings revealed that the presence of diabetic peripheral neuropathy is significantly associated with increased central aortic and peripheral arterial stiffness in type 2 diabetic patient.

Keywords: Type 2 Diabetes Mellitus, Arterial Stiffness, Diabetic Peripheral Neuropathy, Blood pressure

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease with increasing of blood glucose called hyperglycemia. Long-standing hyperglycemia is associated with the changes of organ's functions and structures, including vascular function which has been shown to increase arterial stiffness (Cakar et al., 2015), depressed endothelium dependent vasodilation and impaired microcirculation (Yokoyama, Yokota, Tada, & Kanno, 2007) (Kim et al., 2011), leading to development of serious condition (Cavanagh, Simoneau, & Ulbrecht, 1993). One of the most common complications of diabetes is diabetic peripheral neuropathy (DPN) which has incidence around 47% in diabetic people (Dyck et al., 1993). DPN involves the dysfunction of nervous system and often be described as pain, discomfort, loss or absence of protective sensation muscle weakness and atrophy especially in lower extremities which contributes to foot ulceration, amputation, disability and cardiovascular disease (Boulton et al., 2005). Although many risk factors of cardiovascular disease that associate with DPN such as duration of T2DM, smoking, alcohol consumption, hypertension or obesity have been identified, the extents to emerging risk factor as arterial stiffness was unknown. Understanding the mechanisms of disease pathology will lead to better prevention and treatment strategies. Hence, identifying risk factors for diabetic complication as DPN is important to reduce morbidity, mortality and health care costs. Currently, the information about impact of DPN on arterial stiffness was unclear and required further study.

Due to the fact that this study was preliminary thus we began to start with a convenient sample based on recruitment of specific inclusion characteristics from the diabetic clinics around Nakhon Pathom area near to laboratory setting, Mahidol University. The use of convenient sample saved time and controlled for other variables to eliminate alternative conclusions.

Objective

The aim of this study was to compare central and peripheral arterial stiffness among diabetic peripheral neuropathy, diabetic and age-match healthy individuals.

Conceptual framework

This study involved the evaluation of arterial stiffness and was aimed at comparison of central and peripheral arterial stiffness among diabetic peripheral neuropathy, diabetic and age-match healthy individuals.

The mechanisms underlying impaired vascular function in patients with type 2 diabetes include metabolic derangement such as hyperglycemia, excess liberation of free fatty acids (FFAs) and insulin resistance. It augmented production of pathogenic reactive oxygen species and protein kinase C which

become vascular oxidative stress, decrease nitric oxide synthesis and secretion induced impaired vasodilation effect and repeated low graded inflammation leading to thickened arterial wall and become atherosclerosis (Muniyappa & Quon, 2007).

Research design and methods

The study was a cross-sectional comparison among diabetes with peripheral neuropathy, diabetes and age-matched healthy controls. The selection was purposive sampling method.

Sample size for this study was calculated by the Analysis of Variance model equation, that compares the means of several groups, and used the data from previous study (Yiu et al., 2013). The appropriate sample size was 20 per each group or 60 individuals.

Type 2 diabetic patients; aged 40-70 years were recruited from Nakhon Pathom area. All patients were diagnosed by physician based on the criteria of the American Diabetes Association. Individuals with coronary heart disease, chronic kidney disease, stroke, smoking and neuropathy due to other reasons (e.g. alcoholic neuropathy, carpal tunnel syndrome, liver disease, vasculitis and hypothyroidism) were excluded. Type 2 diabetic patients were divided into 2 groups: those with and without peripheral neuropathy based on criteria in neuropathy screening tests which consist of monofilament, vibration and ankle reflex test. Neuropathy was diagnosed in patients with two or more abnormal neuropathy screening test. Control group was healthy, non-smoking, non-obese and free of overt cardiovascular disease or diabetes as assess by a research health questionnaire. All participants who fulfilled the following inclusion and exclusion criteria participated in the study. The procedures were approved by the Institutional Review Board at Mahidol University.

All procedures were conducted at Faculty of Physical Therapy, Mahidol University. Recruited participants arrived at the laboratory after a 12 hour fast. Metabolic risk factors for cardiovascular disease including glucose, lipids and lipoprotein were determined by taking venapuncture (6 teaspoons). Pulse wave velocity (PWV), arterial blood pressure and augmentation index were measured by an automated vascular testing device (VP-1000 plus, Omron Healthcare; Ukyo-ku, Kyoto, Japan) after the subjects had four-hour fast and rest in supine lying position for at least 15 minutes. Ankle brachial index (ABI) was calculated as ankle systolic blood pressure divided by brachial systolic blood pressure. Carotid and femoral artery pulse wave were recorded by arterial Applanation on carotid and femoral arteries. The time delay was measured automatically with the foot-to-foot method. The time it took for the wave to travel, and the distance between 2 tonometers were used to calculate PWV.

SPSS for window was used for analyze the data. The statistical significant was set at p-value less than 0.05 ($p<0.05$). The distribution of all data was tested by Kolmogorov-Smirnov Goodness of Fit test.

Results were showed as mean±standard deviation. The difference of variables among groups was tested by one-way ANOVA. If data showed significant difference, post hoc test was used to identify significant difference among mean values. The correlation and regression were used to determine factors that could contribute to vascular function.

Results

All data were obtained from September 2016 to August 2017. 62 participants were recruited in this study which consisted of 20 T2DM patients with DPN, 21 T2DM patients without DPN and 21 healthy control subjects. Demographic data and clinical characteristics of participants were shown in Table 1.

Table 1 Demographic data and clinical characteristics of participants

	Healthy n=21	Non DPN n = 21	DPN n = 20
Age (years)	55.5±8.6	57.6 ± 6.9	60.5 ± 6.1
Gender (male/female)	5/16	5/16	6/14
Body mass index (kg/m^2)	21.81±2.29	28.01 ± 3.95*	25.83 ± 3.37*
Waist circumference (cm)	77±5	93 ± 10*	88 ± 13*
Hypertension, n (%)	0	15 (71.4%)	13 (65%)
Dyslipidemia, n (%)	0	18 (85.7%)	17 (85%)
Laboratory variables			
Fasting blood glucose (mg/dL)	92 ± 15	130 ± 32*	155 ± 70*
Total cholesterol (mg/dL)	226 ± 39	171 ± 32*	213 ± 45†
High-density lipid cholesterol (mg/dL)	59 ± 13	48 ± 9*	52 ± 11
Low-density lipid cholesterol (mg/dL)	159 ± 36	104 ± 41*	133 ± 36
Triglyceride (mg/dL)	145 ± 88	136 ± 56	186 ± 104

Values are mean±SD.

* p<0.05 versus healthy controls. † p<0.05 versus non DPN group.

In diabetic patients, both brachial and ankle SBP, MAP and PP were significantly higher than healthy control subjects. T2DM with DPN had higher brachial-ankle and heart-femoral pulse wave velocity than those without DPN and healthy controls. Heart-carotid pulse wave velocity was significantly higher in DPN group when compared with healthy (Table 2).

Table 2 Comparison between healthy control, diabetes and diabetes with neuropathy

	Healthy n=21	Non DPN n = 21	DPN n = 20
Pulse wave velocity (index of arterial stiffness)			
baPWV (cm/s)	1477±181	1549±220	1703±161*†
faPWV (cm/s)	1070±107	1067±107	1084±136
hcPWV (cm/s)	885±215	942±185	1073±208*
cfPWV (cm/s)	901±144	941±176	1089±249*†
ABI	1.15±0.06	1.14±0.07	1.12±0.10
Brachial Blood pressure			
Systolic BP (mmHg)	120±12	134±14*	135±14*
Mean arterial pressure (mmHg)	91±10	100±10*	100±12*
Diastolic BP (mmHg)	74±8	79±7	80±9*
Pulse pressure (mmHg)	46±7	55±10*	56±9*
Ankle blood pressure			
Systolic BP (mmHg)	140±17	155±16*	154±18*
Mean arterial pressure (mmHg)	99±10	107±9*	105±10*
Diastolic BP (mmHg)	77±8	81±7	81±9
Pulse pressure (mmHg)	63±13	73±14*	73±15*

Values are mean±SD.

* p<0.05 versus healthy controls. † p<0.05 versus non DPN group.

baPWV = brachial-ankle pulse wave velocity, faPWV = femoral-ankle pulse wave velocity, hcPWV = heart-carotid pulse wave velocity, cfPWV = carotid-femoral pulse wave velocity, ABI = ankle-brachial index.

On multiple linear regression, the correlates of brachial-ankle PWV were age (p<0.05), DPN (p<0.05), gender (p<0.01), and brachial PP (p<0.01). Femoral-ankle PWV was associated with triglyceride (p<0.05), brachial PP (p<0.05) and ankle PP (p<0.01). The correlates of heart-carotid PWV were age (p<0.01) and ankle DBP (p<0.05). The correlates of carotid-femoral PWV were the presence of DPN (p<0.05), age (p<0.05) and HDL (p<0.05). Moreover, multiple linear regression analysis revealed that brachial-ankle PWV (r=0.429, p<0.001) and fasting blood glucose (r=0.409, p=0.001) were significant

determinants of neuropathy after adjustment for conventional cardiovascular risk factors such as age, gender, BMI, hypertension, hyperlipidemia.

Discussion

This study has two main findings: First, arterial stiffness as measured by PWV, has been found to be increased in type 2 diabetes compared to healthy control. Furthermore, it demonstrated that the presence of diabetic peripheral neuropathy was associated with increased central aortic (cfPWV) and peripheral arterial stiffness (baPWV) in type 2 diabetes.

Despite the cross-sectional design of this study could not establish a cause-and-effect relationship between diabetic peripheral neuropathy complication and arterial stiffness, the possible pathophysiological mechanisms should be mentioned. Large arteries play an important role to conduct the blood to peripheral arteries and buffer the pressure pulsations resulting from intermittent ventricular ejection (Laurent et al., 2006). In diabetic patient, long-term hyperglycemia could induce increased polyol pathway activity, dyslipidemia, formation of advanced glycation end products, and increased protein kinase C activity, leading to increasing oxidative stress, chronic low-grade inflammation and endothelial dysfunction. These mechanisms would affect large arteries loss of it buffering function, increase pulsatile pressure wave and directly damage large and small vessels, induced endoneurial hypoxia, which is considered to causing diabetic neuropathy (Stehouwer, Henry, & Ferreira, 2008).

Second, it confirmed that other predictors of increased vascular stiffness were older age, gender, presence of DPN, dyslipidemia and higher pulse pressure. The association with diabetic peripheral neuropathy is controversial: one study (Cardoso et al., 2009) reported that the presence of DPN was correlated to aortic stiffness only, not correlated to peripheral arterial stiffness, whereas another study (Yokoyama et al., 2007) found the association between DPN and peripheral arterial stiffness as brachial-ankle PWV, likewise, our findings.

As older age, gender, higher blood pressure and lipid profiles are considered to be the important determinants of increased PWV in type 2 diabetes and even in general population. Hence, we tried to control all confounding factors that could affect to the results, for instance; the using of age and gender matched method, and purposive sampling selection to balance baseline characteristics between 2 diabetic groups.

Limitation of this study was the cross-sectional study design could not reveal causal relationship between diabetic peripheral neuropathy complication and arterial stiffness. The sample selection is not randomized because of the specific inclusion criteria for diabetes, DPN, and healthy control.

Conclusion

According to our results, the researcher can conclude that first; it demonstrated the impairment of vascular function in type 2 diabetes mellitus, even in early uncomplicated phase and progressive phase as the presence of diabetic peripheral neuropathy complication. Second; the presence of diabetic peripheral neuropathy was significantly associated with increased central aortic and peripheral arterial stiffness in type 2 diabetic patient. Hence, type 2 diabetic patients especially with diabetic peripheral neuropathy complication should deserve actively approached to prevent development of cardiovascular disease.

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