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Original Article

Correlation between diabetic lower-extremity arterial disease and diabetic neuropathy in patients with type II diabetes: an exploratory study

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Abstract: The lower-extremity vascular injuries and neuropathy are the most salient complications of diabetes which could lead to the poor prognosis, especially for the type II diabetes. The lower extremity vascular injuries and neuropathy usually coexist, yet their correlation in the pathogenesis of lower extremity lesions has received little attention in previous studies. To investigate the correlation between the degree of lower-extremity arterial injuries and lower-extremity neurological functional status in patients with type II diabetes, 32 patients with type II diabetes were examined for the mean flow velocity of the femoral artery and popliteal artery of lower extremeties, while the motor nerve conduction velocity (MCV) and sensory nerve conduction velocity (SCV) of the bilateral common peroneal nerve, sural nerve and posterior tibial nerve were simultaneously examined. Results showed that there was moderate correlation between the mean flow velocity of lower-extremity arteries and MCV/SCV. In particular, the MCV of the right tibial nerve was strongly correlated with the average velocity of the right popliteal artery ($P < 0.05$).

Keywords: Diabetes, lower extremity arterial disease, diabetic neuropathy, motor nerve conduction velocity, sensory nerve conduction velocity

Introduction

The lower-extremity vascular injuries and neuropathy are the most salient complications of diabetes which could lead to the poor prognosis, especially for the type II diabetes. These chronic complications have prominent clinical symptoms, which severely affect the quality of life of the afflicted, with rather high rates of morbidity and mortality. Up until 2008, the prevalence rate of diabetes in China has surged to 9.7 percent, and the population of current diabetic patients in China has reached 100 million. The lower extremity vascular injuries and neuropathy usually coexist, yet their correlation in the pathogenesis of lower extremity lesions has received little attention in previous studies.

In this study, we examined the vascular blood flow in the lower extremities of diabetic patients, and the changes in the sensory nerve conduction velocity (SCV) and motor nerve conduction velocity (MCV) of lower extremities, the indicators that reflect the degree of nerve damage of peripheral neuropathy, by which investigating the link between lower extremity vascular injuries and neuropathy in patients with diabetes.

Material and methods

32 patients were recruited from October 2011 to March 2012 at the in-patient and out-patient sections of the Department of Endocrinology in The Second Hospital Affiliated to Tianjin Medical University. Among the patients, there were 20 male and 12 female, with a mean age at 56.3 years old (ranging from 33 to 78 years old). They had varied length of disease history ranging from 2 to 22 years. The diagnostic criteria of all patients were complying with the standard of WHO in diabetes. The inclusion criteria of the participants include: i) There were clinical symptoms of cold, numb or pain in the lower extremities, diagnosed as diabetic vascular disease and/or diabetic neuropathy; ii) Patients were

Table 1. Subject characteristics

Subject Characteristics	Explanation (n = 32)	95% CI
Age (years)	56.25 ± 10.56	52.44-60.06
Sex (%)		
Male	20 (62.5%)	
Female	12 (37.5%)	
Body Mass Index (kg/m^2)	25.25 ± 3.74	23.91-26.6
Total cholesterol (mmol/L)	5.39 ± 0.995	5.03-5.74
TG (mmol/L)	2.07 ± 2.41	1.2-2.94
HDL (mmol/L)	1.22 ± 0.32	1.10-1.34
LDL (mmol/L)	3.24 ± 0.83	2.94-3.54
VLDL (mmol/L)	0.93 ± 0.46	0.76-1.09
Glycation (%)	9.18 ± 2.28	8.36-10
Atherogenic index	2.8 ± 0.9	2.48-3.13
Medical history (years)	6.97 ± 4.0	5.53-8.41

TG: triglycerides; HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein; CI: confidence interval.

excluded who had previous histories of lower extremity trauma, lower extremity vascular disease, or lower extremity vascular surgery, which could possibly affect the results of hemodynamic test; iii) Patients were excluded who had past or current neurological diseases, cerebrovascular diseases or diseases in the cervical spine or lumbar; iv) Patients with no history of neurological medications three months prior to the study. This study was approved by the ethics committee of The Second Hospital Affiliated to Tianjin Medical University. Written informed consent was obtained from all subjects.

The measurement of some clinical parameters was performed for each diabetic patient admitted in the hospital, including mean flow velocity and maximum blood flow of the femoral artery and popliteal artery of bilateral lower extremities which were conducted with Philips IE33 Multicolor Ultrasonic System (Philips Medical Systems), electroneurogram examination of lower extremities, and the sensory nerve conduction velocity (SCV) and motor nerve conduction velocity (MCV) of peroneal common nerve, posterior tibial nerve, sural nerve and posterior tibial nerve using Haishen NDI-200P+ evoked potentials equipment (Shanghai). All the examination procedures were carried out when the patients were in a peaceful state in the early morning, with room temperature of 24-26°C.

All clinical parameters were analyzed with Pearson product-moment correlation coefficient and processed by SPSS19.0.

Results

Among the patients received from October 2011 to March 2012, we found 32 eligible subjects. **Table 1** shows the subject characteristics, including the proportion of sex and mean ± standard deviation of each variables studied.

First we analyzed the correlation between the mean flow velocity of the left lower extremity arteries and left lower extremity nerve conduction velocity. As showed in **Table 2**, the Pearson correlation coefficient of the MCV of the left peroneal nerve (MCV-LPN) with the mean flow velocity of the left femoral artery (MFV-LFA) is 0.191 (P = 0.294), and with the mean flow velocity of the left popliteal artery (MFV-LPA) is 0.207 (P = 0.255); The Pearson correlation coefficient of the MCV of the left posterior tibia nerve (MCV-LPTN) with the mean flow velocity of the left femoral artery (MFV-LFA) is 0.193 (P = 0.290), and with the mean flow velocity of the left popliteal artery (MFV-LPA) is 0.144 (P = 0.433); The Pearson correlation coefficient of the SCV of the left peroneal nerve (SCV-LPN) with the mean flow velocity of the left femoral artery (MFV-LFA) is 0.128 (P = 0.484), and with the mean flow velocity of the left popliteal artery (MFV-LPA) is 0.197 (P = 0.281); The Pearson correlation coefficient of the SCV of the left posterior tibia nerve (SCV-LPTN) with the mean flow velocity of the left femoral artery (MFV-LFA) is 0.167 (P = 0.362), and the same with the mean flow velocity of the left popliteal artery (MFV-LPA) is 0.241 (P = 0.183).

Then we analyzed the correlation between the mean flow velocity of the right lower extremity arteries and right lower extremity nerve conduction velocity. As showed in **Table 3**, the Pearson correlation coefficient of the MCV of the right peroneal nerve (MCV-RPN) with the mean flow velocity of the right femoral artery (MFV-RFA) is 0.169 (P = 0.355), and the same with the mean flow velocity of the right popliteal artery (MFV-RPA) is 0.240 (P = 0.186); The Pearson correlation coefficient of the MCV of the right posterior tibia nerve (MCV-RPTN) with the mean flow velocity of the right femoral artery (MFV-RFA) is 0.282 (P = 0.117), and the same with the mean flow velocity of the right popliteal artery (MFV-RPA) is 0.496 (P = 0.004 < 0.05); The Pearson correlation coefficient of

Table 2. Correlation between the mean flow velocity of the left lower extremity arteries and left lower extremity nerve conduction velocity

		MCV-LPN	MCV-LPTN	SCV-LPN	SCV-LPTN
MFV-LFA	Pearson Correlation	.191	.193	.128	.167
	Sig. (2-tailed)	.294	.290	.484	.362
	N	32	32	32	32
MFV-LPA	Pearson Correlation	.207	.144	.197	.241
	Sig. (2-tailed)	.255	.433	.281	.183
	N	32	32	32	32

MFV-LFA: mean flow velocity of the left femoral artery; MFV-LPA: mean flow velocity of the left popliteal artery; MCV-LPN: motor nerve conduction velocity ofthe left peroneal nerve; MCV-LPTN: motor nerve conduction velocity of the left posterior tibia nerve; SCV-LPN: sensory nerve conduction velocity of the left peroneal nerve; SCV-LPTN: sensory nerve conduction velocity of the left posterior tibia nerve.

Table 3. Correlation between the mean flow velocity of the right lower extremity arteries and right lower extremity nerve conduction velocity

		MCV-RPN	MCV-RPTN	SCV-RPN	SCV-RPTN
MFV-RFA	Pearson correlation	.169	.282	.098	.176
	Sig. (2-tailed)	.355	.117	.595	.335
	N	32	32	32	32
MFV-RPA	Pearson correlation	.240	.496**	.299	.249
	Sig. (2-tailed)	.186	.004	.096	.169
	N	32	32	32	32

MFV-LFA: mean flow velocity of the right femoral artery; MFV-LPA: mean flow velocity of the right popliteal artery; MCV-LPN: motor nerve conduction velocity of the right peroneal nerve; MCV-LPTN: motor nerve conduction velocity of the right posterior tibia nerve; SCV-LPN: sensory nerve conduction velocity of the right peroneal nerve; SCV-LPTN: sensory nerve conduction velocity of the right posterior tibia nerve.

the SCV of the right peroneal nerve (SCV-RPN) with the mean flow velocity of the right femoral artery (MFV-RFA) is 0.098 (P = 0.595), and the same with the mean flow velocity of the right popliteal artery (MFV-RPA) is 0.299 (P = 0.096); The Pearson correlation coefficient of the SCV of the right posterior tibia nerve (SCV-RPTN) with the mean flow velocity of the right femoral artery (MFV-RFA) is 0.176 (P = 0.335), and the same with the mean flow velocity of the left popliteal artery (MFV-RPA) is 0.249 (P = 0.169).

Discussion

Peripheral arterial disease and neuropathy are the most common complications of diabetes. Peripheral arterial disease (PAD) is manifested as the progressive decrease of the arterial blood supply to the extremities. Peripheral vascular disease has a high incidence rate in diabetic patients, with rather poor prognosis that would seriously affect the quality of life of the patients. Diabetic vascular disease is mainly attacking the medium to small arteries, clinically manifested as, by patient complaints, the multiple symptoms in the lower extremities. The exact pathogenesis of diabetic neuropathy has not yet been elucidated, and at present it is believed to be the synergistic effects of metabolic, vascular and autoimmune factors. Microvascular disease may play an important role in the pathogenesis and aggravation of diabetic neuropathy. But it has not been concluded, at least from a statistical basis, that whether nerve damage emerges immediately following the presence of vascular sclerosis, which one of them happens first, and whether there is a correlation between them.

The pathological phenomenon lies at the intersection of diabetic vascular damage and diabetic neural damage is the complication of diabetic retinopathy. Numerous investigators have suggested that the pathogenesis of diabetic retinopathy includes glucose-mediated microvascular damage. Previously implicated pathways related to excess glucose include oxidative stress, activation of protein kinase C (PKC), and activation of advanced glycation end products and their receptor [1-5]. Mechanisms of vascular injury include increased vascular permeability due to tight junction disassembly [6] and endothelial cell-mediated leukostasis [7]. These studies have led to potential therapeutic approaches, including PKC inhibitors, corticosteroids, and soluble receptor for advanced glycation end product inhibitors [1]; of these, PKC inhibition has been shown to be effective in randomized clinical trials [8]. However, recent work strongly suggests that diabetic retinopathy involves more than elevated glucose and microvascular lesions, and numerous reports using electroretinogra-

phy, dark adaptation, contrast sensitivity, and color vision tests have conclusively demonstrated that neuroretinal function is compromised before the onset of vascular lesions in humans [9-13]. In fact, loss of oscillatory potentials on electroretinograms predicts the onset of proliferative retinopathy better than vascular lesions seen on fundus photographs or capillary nonperfusion visualized by fluorescein angiograms [14]. If diabetes exerts its primary damage on vascular cells and increases permeability or vascular occlusion, neuronal and glial cell integrity would be compromised by the entry of circulating macrophages, antibodies, inflammatory cytokines/chemokines, excitotoxic amino acids, or fatty acids into the retina. On the other hand, if diabetes primarily affects the neural retina, it could compromise vascular integrity by loss of normal barrier-inducing functions of glia or increased expression of proinflammatory cytokines or reactive oxygen species that promote vascular leakage or occlusion. At this point, it is not known whether vascular or neural cell defects occur first; most likely they are interdependent. Thus, Antonetti et al. [15] propose a feed-forward concept of vascular-neural dysfunction that begins shortly after the onset of diabetes and increases over time, creating a widening vortex of retinal injury. Eventually, accumulated injury and failing reparative responses lead to the clinically evident features of diabetic retinopathy. Although retinopathy is at the center of diabetic vascular damage and neural damage, which has been investigated to a great extent, the relation of diabetic vascular damage and neural damage in the lower extremities has regretfully been greatly neglected in the current research debate. This lack of interest is regretful particularly considering the fact that diabetic artery disease and diabetic neuropathy are two of the most common complications of diabetes, yet the molecular mechanisms of this diabetic vascular-neural damage in lower extremities can be similar to those of the diabetic retinopathy.

The patients included in this study all have, in varying degrees, lower extremity atherosclerosis. There are lower extremity artery stenosis of varying progression in these patients, resulting in decreased blood flow in more or less degrees, which is clinically manifested as chills and/or pain in the lower extremity skin, and weakened arterial pulse in the lower extremities. Lower extremity neuropathy is manifested as paresthesias and decreased ability to walk. MCV and SCV, the two parameters indicating the lower extremity nerve conduction velocity were monitored in our study, and then their correlations with the lower extremity vascular injury and blood flow velocity were evaluated using Pearson product-moment correlation coefficient. Results show that the blood flow velocities of the femoral artery and popliteal artery were weakly to moderately correlated with the nerve conduction velocity, where the blood flow velocity of the popliteal was more strongly correlated with the sensory-motor conduction velocity, in particular, the blood flow velocity of the right posterior popliteal artery was absolutely positively correlated with the MCV of the right tibial nerve, suggesting that there is a correlation between the decreased artery blood flow velocity of the lower extremities and nerve damage.

However, the above results did not show a strong correlation. This can be explained that firstly, nerve damage and vascular damage are complex pathological processes which are influenced by various factors such as the metabolic, the vascular and autoimmune factors. And these complexities have not been modeled into our analysis. Secondly, the sample size is relatively small in our study, which we shall improve in the future studies, in the expectation to achieve more accurate results and patterns. This exploratory study aims to provide an introduction to ignite further interest of the broader academic communities in this issue.

Disclosure of conflict of interest

None.

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