

Diabetic Peripheral Neuropathy Is Associated With Increased Arterial Stiffness Without Changes in Carotid Intima-Media Thickness in Type 2 Diabetes

EUN SOOK KIM, MD¹
 SUNG-DAE MOON, MD, PHD¹
 HUN-SUNG KIM, MD²
 DONG JUN LIM, MD²
 JAE HYOUNG CHO, MD²
 HYUK SANG KWON, MD, PHD²

CHUL WOO AHN, MD, PHD³
 KUN HO YOON, MD, PHD²
 MOO IL KANG, MD, PHD²
 BONG YUN CHA, MD, PHD²
 HO YOUNG SON, MD, PHD²

OBJECTIVE—This study was conducted to investigate the association of diabetic peripheral neuropathy (DPN) with both arterial stiffness and intima-media thickness (IMT).

RESEARCH DESIGN AND METHODS—We conducted a cross-sectional analysis of 731 subjects with type 2 diabetes. DPN was diagnosed on the basis of neuropathic symptoms, insensitivity to a 10-g monofilament, abnormal pin-prick sensation, and abnormal current perception threshold. Arterial stiffness was assessed by cardio-ankle vascular index (CAVI), and IMT was assessed by B-mode ultrasonography.

RESULTS—Patients with DPN had higher CAVI than those without DPN in multivariate-adjusted models, whereas no differences in IMT were observed between patients with and without DPN after adjustment for age and sex. In the multivariate analysis, CAVI was a significant determinant of DPN (odds ratio 1.36 [95% CI 1.13–1.65], $P = 0.001$).

CONCLUSIONS—DPN is significantly associated with arterial stiffness without carotid intimal changes in patients with type 2 diabetes.

Diabetes Care 34:1403–1405, 2011

The leading cause of death in patients with diabetes is cardiovascular disease (CVD) (1); recent studies have reported that microvascular disease is also associated with excess mortality (2). Although the underlying mechanism is unclear, some evidence suggests that the effects of microvascular disease on mortality may be linked to subclinical atherosclerosis, considering atherosclerotic vascular changes in parallel with microvascular complications, including retinopathy (3),

nephropathy (4), and autonomic neuropathy (5).

Diabetic peripheral neuropathy (DPN) is a common microvascular complication with high mortality rates (6), but little is known about the association between DPN and atherosclerotic vascular changes. Thus, we investigated the association between DPN and vascular wall properties in patients with type 2 diabetes by measuring cardio-ankle vascular index (CAVI) and carotid intima-media thickness (IMT).

RESEARCH DESIGN AND

METHODS—We retrospectively recruited subjects with type 2 diabetes, aged 20–80 years, who visited Seoul St. Mary's hospital between May 2008 and June 2009. Subjects were excluded if they had peripheral vascular disease; an ankle-brachial pressure index <0.9 ; or severe illness, such as acute infectious disease, progressive malignancy, or severe renal impairment.

DPN was diagnosed in subjects displaying two or more of the following features: neuropathic symptoms, insensitivity to a 10-g monofilament, abnormal pin-prick sensation, and abnormal current perception threshold (CPT). Neuropathic symptoms were assessed by a total symptom score, CPT using a Neurometer CPT/C (Neurotron, Inc., Baltimore, MD), and autonomic neuropathy by heart rate variability to the Valsalva maneuver, deep breathing, and standing (7).

CAVI was measured using a CAVI-VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan), as described previously (8). Carotid IMT was measured using high-resolution B-mode ultrasonography (Logiq S6, General Electric Medical Systems, Wauwatosa, WI) in 681 subjects. The average IMT value on one side was calculated, and the thicker of the sides was used for analysis.

Comparisons were made using the Student t test or χ^2 test. ANCOVA was used to compare CAVI and IMT. Logistic regression analyses were performed to estimate the odds ratios (ORs) and 95% CIs for DPN or abnormal CAVI. A P value <0.05 was considered to indicate statistical significance.

RESULTS—Of the 731 subjects (aged 57.5 ± 11.2 years), 127 (17.4%) were diagnosed with DPN. Subjects with DPN were older, had a longer duration of diabetes, had higher systolic blood and pulse pressure, and were more likely to have albuminuria and retinopathy than subjects without neuropathy. However,

From the ¹Division of Endocrinology, Department of Internal Medicine, Incheon St. Mary's Hospital, The Catholic University of Korea, Incheon, Korea; the ²Division of Endocrinology and Metabolism, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea; and the ³Division of Endocrinology and Metabolism, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.

Corresponding author: Ho Young Son, hys@catholic.ac.kr.

Received 25 November 2010 and accepted 27 March 2011.

DOI: 10.2337/dc10-2222

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc10-2222/-/DC1>.

© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

subjects with DPN had a lower glomerular filtration rate, HDL cholesterol level, and BMI (Supplementary Table A1). No difference in glycosylated hemoglobin (HbA_{1c}) or fasting glucose levels was observed between subjects with and without DPN.

CAVI was significantly higher in subjects with DPN than in subjects without DPN, after adjusting for age, sex, diabetes duration, BMI, HbA_{1c}, pulse pressure, glomerular filtration rate, hyperlipidemia, CVD, autonomic neuropathy, and use of insulin or antihypertensive drugs (8.87 vs. 8.45, $P = 0.001$). In contrast, the difference in IMT between the groups lost significance after adjusting for age and sex. In multivariate logistic regression models, CAVI was a significant predictor of DPN (OR 1.36 [95% CI 1.13–1.65], $P = 0.001$, Table 1).

Moreover, subjects with DPN had an OR for abnormal CAVI of 2.54 (95% CI 1.52–4.26, $P < 0.001$) after adjusting for confounding factors. The association with abnormal CAVI remained significant after further adjusting for microvascular complications and even in subgroups divided by age, BMI, diabetes duration, and hypertension (Supplementary Table A2).

CONCLUSIONS—We showed that DPN was closely associated with CAVI independently of traditional cardiovascular risk factors. DPN remained a significant determinant of abnormal CAVI after

further adjusting for other microvascular complications and was significant in subgroups classified by age, BMI, diabetes duration, and hypertension.

Several studies have reported an increased risk for CVD and other microvascular diseases, including retinopathy and microalbuminuria (3–5,9). However, only two reported studies have investigated associations between DPN and CVD risk (9,10). Yokoyama et al. (10) found that diabetic neuropathy was associated with arterial stiffness assessed by brachial-ankle pulse-wave velocity in 294 patients with type 2 diabetes. However, in contrast with our study, they observed a positive relationship between DPN and IMT. This inconsistency may be due to different sample sizes and the diagnostic criteria they used (they included cases of autonomic neuropathy). Another study by Cardoso et al. (9), conducted on 482 patients with type 2 diabetes, also demonstrated a close relationship between DPN and aortic stiffness.

The significant association between DPN and increased CAVI observed in this study suggests that determinants of CVD principally affecting arterial stiffness may be potential risk factors for DPN. Accordingly, prospective cohort studies have demonstrated that CVD risk factors predict the development of DPN in patients with type 1 diabetes (11,12). Although the underlying mechanism linking DPN to arterial stiffness is not well understood, one possible

explanation is that large artery stiffness may cause microvascular damage via high pulse pressure, leading to diminished blood flow to nerve tissues vulnerable to hypoxic damage, and thereby to the development of neuropathy (13).

It is beyond the scope of this study to establish whether increased arterial stiffness is a causal risk factor for DPN or a concomitant finding developed by shared pathogenic mechanisms. Nevertheless, our results have clinical implications. Patients with DPN are at high risk of CVD because of their increased arterial stiffness (14) whether it has causal association or not. Therefore, careful assessment of the combined risks and intensive intervention may reduce the risk of CVD.

A major limitation of our study is its cross-sectional design; thus, we could not determine temporal or causal relationships between DPN and arterial stiffness. Another limitation is that the study subjects may not represent the general population.

In conclusion, DPN is significantly associated with arterial stiffness without changes in IMT in patients with type 2 diabetes. Further prospective studies could elucidate whether intensive management of CVD risk factors other than glycemic control can also prevent or delay the development of neuropathy.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

E.S.K. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. S.-d.M. contributed to discussion and reviewed and edited the manuscript. H.-S.K. researched data and contributed to discussion. D.J.L., J.H.C., and H.S.K. researched data. C.W.A., K.H.Y., M.I.K., and B.Y.C. researched data and contributed to discussion. H.Y.S. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript.

Parts of this study were presented in abstract form at the 70th Scientific Sessions of the American Diabetes Association, Orlando, Florida, 25–29 June 2010.

The authors thank Hyeon-Woo Yim, MD, PHD, and Seung-Hee Jeong, MPH (Catholic Medical Center Clinical Research Coordinating Center), for invaluable advice on statistics.

References

- Rydén L, Standl E, Bartnik M, et al.; Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC); European Association for

Table 1—ORs and 95% CIs for diabetic peripheral neuropathy

	Unadjusted		Multivariate adjusted*	
	OR (95% CI)	P	OR (95% CI)	P
CAVI ^a	1.37 (1.20–1.56)	<0.001	1.36 (1.13–1.65)	0.001
Age (years)	1.02 (1.01–1.04)	0.010	0.98 (0.95–1.01)	0.110
Male sex	1.25 (0.86–1.84)	0.247	0.57 (0.35–0.93)	0.024
Duration (years)	1.05 (1.02–1.07)	<0.001	1.04 (1.01–1.07)	0.005
BMI (kg/m ²)	0.92 (0.87–0.98)	0.010	0.96 (0.90–1.04)	0.323
HbA _{1c} (%)	1.00 (0.91–1.11)	0.936	0.98 (0.86–1.11)	0.691
Pulse pressure (mmHg)	1.02 (1.00–1.03)	0.021	1.01 (0.99–1.03)	0.388
GFR (mL/min per 1.73 m ²)	0.99 (0.98–1.00)	0.012	1.00 (0.99–1.01)	0.533
Hyperlipidemia ^b	0.96 (0.59–1.57)	0.884	1.01 (0.57–1.79)	0.964
CVD	1.83 (1.01–3.31)	0.045	2.09 (1.01–4.32)	0.048
Autonomic neuropathy	1.26 (0.80–2.00)	0.324	0.89 (0.51–1.54)	0.575
Current smokers	1.05 (0.43–2.60)	0.912	1.34 (0.48–3.74)	0.679
Insulin therapy	1.32 (0.90–1.94)	0.161	1.05 (0.62–1.77)	0.856
ACE inhibitor/ARB	0.76 (0.51–1.12)	0.163	0.63 (0.38–1.03)	0.067
Calcium channel blocker	0.80 (0.49–1.29)	0.628	0.81 (0.45–1.47)	0.489
β-Blocker	0.85 (0.45–1.63)	0.624	0.86 (0.39–1.88)	0.701

ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate. ^aCAVI is a continuous measure. ^bHyperlipidemia was defined as a triglyceride concentration ≥ 150 mg/dL, low-density lipoprotein concentration ≥ 100 mg/dL, or taking cholesterol-lowering medication. *Adjusted for all other variables in the first column.

- the Study of Diabetes (EASD). Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. *Eur Heart J* 2007;28:88–136
2. Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH; EURODIAB Prospective Complications Study Group. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). *Diabetes Care* 2008;31:1360–1366
 3. Ogawa O, Hayashi C, Nakaniwa T, Tanaka Y, Kawamori R. Arterial stiffness is associated with diabetic retinopathy in type 2 diabetes. *Diabetes Res Clin Pract* 2005;68:162–166
 4. Smith A, Karalliedde J, De Angelis L, Goldsmith D, Viberti G. Aortic pulse wave velocity and albuminuria in patients with type 2 diabetes. *J Am Soc Nephrol* 2005;16:1069–1075
 5. Meyer C, Milat F, McGrath BP, Cameron J, Kotsopoulos D, Teede HJ. Vascular dysfunction and autonomic neuropathy in type 2 diabetes. *Diabet Med* 2004;21:746–751
 6. Forsblom CM, Sane T, Groop PH, et al. Risk factors for mortality in type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. *Diabetologia* 1998;41:1253–1262
 7. Viswanathan V, Prasad D, Chamukuttan S, Ramachandran A. High prevalence and early onset of cardiac autonomic neuropathy among South Indian type 2 diabetic patients with nephropathy. *Diabetes Res Clin Pract* 2000;48:211–216
 8. Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *J Atheroscler Thromb* 2006;13:101–107
 9. Cardoso CR, Ferreira MT, Leite NC, Barros PN, Conte PH, Salles GF. Microvascular degenerative complications are associated with increased aortic stiffness in type 2 diabetic patients. *Atherosclerosis* 2009;205:472–476
 10. Yokoyama H, Yokota Y, Tada J, Kanno S. Diabetic neuropathy is closely associated with arterial stiffening and thickness in type 2 diabetes. *Diabet Med* 2007;24:1329–1335
 11. Tesfaye S, Chaturvedi N, Eaton SE, et al.; EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. *N Engl J Med* 2005;352:341–350
 12. Elliott J, Tesfaye S, Chaturvedi N, et al.; EURODIAB Prospective Complications Study Group. Large-fiber dysfunction in diabetic peripheral neuropathy is predicted by cardiovascular risk factors. *Diabetes Care* 2009;32:1896–1900
 13. Dyck PJ. Hypoxic neuropathy: does hypoxia play a role in diabetic neuropathy? The 1988 Robert Wartenberg lecture. *Neurology* 1989;39:111–118
 14. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236–1241