Ankle-brachial Index, Peripheral Arterial Disease, and Diabetic Retinopathy

Dear Editor

We read with interest the article by Yun et al. [1], who reported that the frequency of diabetic retinopathy was associated with the presence of arterial stiffness as measured by the brachial ankle pulse wave velocity, but not with common carotid artery intima-media thickness, carotid plaque, or peripheral arterial disease (PAD), in a Korean sample of type 2 diabetic patients. They suggested that the association between macroangiopathy and microangiopathy may be due to a functional rather than structural process within the vascular system, although arterial stiffness is widely accepted as a structural phenomenon characterized by medial calcium accumulation in the vessel wall.

Yun et al. [1] found no relation of PAD as diagnosed by ankle brachial index (ABI) measurement to the presence of retinopathy in their diabetic participants. They successfully discussed this finding in light of the previous studies that had displayed conflicting data with respect to an association with microangiopathy and clinical or subclinical atherosclerotic diseases. They also linked their "negative condition" findings to several factors such as selective survival, discordant sample sizes in the tested groups, population characteristics, image magnification limitations, or the age distributions in their study population. At this point, we needed to make some more contribution by going through the diagnosis of PAD by ABI measurement in people with diabetes mellitus.

Use of ABI measurement in the diagnosis of PAD in subjects with diabetes, especially in those with long-standing disease, requires caution with regard to recent findings in large trials and recommendations inserted into the guidelines. Diabetes has been linked not only to accelerated atherosclerosis and plaque formation but also to earlier initiation of arterial stiffness [2], as was also shown in the study by Yun et al. [1]. However, it is well known that arterial stiffness often causes inversely increased ABI values due to incompressible vessels [3], masking the presence of occlusive disease in the lower extremities that could be identified by ABI testing. Consistent with this, diabetes was clearly found to be a risk factor for a high ABI [4]. Moreover, diabetic individuals with ABI <0.90 and ABI >1.40 were demonstrated to display similar patterns of abnormalities in different diagnostic tests for lower extremity ischemia, and a high ABI was suggested to be PAD-equivalent [4]. Therefore, it is possible that the true prevalence of PAD might have been underestimated by determining a low ABI in the study by Yun et al. [1], resulting in insufficient statistical power as well. Indeed, Table 1 of the study shows that the frequency of PAD was detected to be 20.45% lower in those subjects with retinopathy compared to those without, which is not consistent with the knowledge that the duration of diabetes is positively associated with the prevalence of cardiovascular diseases. In order to improve the understanding of our readers, it would be helpful if the authors could re-evaluate their data for high ABI (>1.4) or collectively with ABI ≤0.9 because, Papanas et al. [5] reported a significantly higher prevalence of a low ABI in diabetics with microvascular complications when the subjects with medial arterial calcification were specifically excluded.

CONFLICT OF INTEREST

The authors have no conflicts of interest with the material presented in this paper.

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Author Response

We appreciate your excellent opinions after having read the research article [1]. Our response to the thoughts of the authors mentioned in the letter is as follows.

Ankle-brachial index (ABI) is a convenient and simple method of measuring peripheral arterial disease (PAD) in clinical examination and research. The ABI measurement method has been introduced and been enforced since the 1960s, and a decrease in ABI (<0.9) has been applied as a powerful indicator of PAD diagnosis. The severity of PAD is generally classified as normal (0.91-1.30), mild occlusion (0.70-0.90), moderate occlusion (0.40-0.69), severe occlusion (<0.40), or poorly compressive vessels (>1.30).

Diabetes induces not only structural changes (i.e., increased intima-media thickness, plaque formation) but also arterial stiffness. Just as you have said, when one tries to measure ABI in the state of arterial stiffness, ABI is measured as higher than expected due to improper vessel compression. Because diabetes and medial artery calcification have a strong association [2], ABI results come out to be higher than expected because ankle pressure rises due to arterial stiffness. Therefore, PAD (defined as ABI <0.9) that is calculated by measuring ABI can show a much lower prevalence rate than the reality. In particular, there have been reports that

asserted, in the case where a patient has peripheral neuropathy related to diabetes, PAD diagnostic efficiency by ABI measurement decreases [3]. Recently, when defining the PAD of diabetic patients, some epidemiologic studies have claimed that one should include a high ABI group of not only 'ABI <0.9' but also 'ABI >1.40' [4,5].

Yun et al. [1] reported the results of having defined PAD as 'ABI <0.9.' The difference in the PAD prevalence rate between subjects with retinopathy and without retinopathy (10.6% vs. 8.8%) was not significant. Also, no significant association between PAD and retinopathy (odds ratio, 0.77; 95% confidence interval, 0.34 to 1.73) was found. After that, in addition to the analysis of PAD, just as you have suggested in the letter, additional analysis of 'high ABI (>1.40)' and of 'PAD equivalent (ABI <0.9 or >1.4)' were done. However, no significant association was observed in any of these studies (Tables 1 and 2). In addition, 'high ABI' and 'PAD equivalent' were re-classified and analyzed based on an ABI of 1.3 as a standard, but the result was similar to the case where an ABI of 1.4 was set as the standard. Findings such as these, just as suggested in the existing report [1], are assumed to be the result of selective survival, discordant sample sizes, population characteristics, image magnification limitations, certain age distributions, and so on.

It is necessary to analyze and interpret the ABI measured from a diabetic patient very carefully in consideration of clinical symptoms, and it is necessary to diagnose PAD while keeping in mind the limitations of ABI measurement of diabetic patients, and by utilizing other noninvasive examination methods. Furthermore, it will be important to clarify the association between retinopathy and PAD of diabetic patients through additional research in the future.

CONFLICT OF INTEREST

The authors have no conflicts of interest with the material presented in this paper.

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Table 1. PAD, high ABI, and PAD equivalent prevalence of study group with and without retinopathy

Variables	Without retinopathy (n=491)	With retinopathy (n=114)	p-value
PAD (ABI <0.9)	52 (10.6)	10 (8.8)	0.56
High ABI (ABI >1.4)	4 (0.8)	2 (1.8)	0.36
PAD equivalent (ABI <0.9 or >1.4)	55 (11.2)	12 (10.5)	0.84

Values are presented as number (%).
PAD, peripheral arterial disease; ABI, ankle-brachial index.

Table 2. OR for diabetic retinopathy according to ABI level

Variables	Crude OR (95% CI)	Model 1[1] OR (95% CI)	Model 2[2] OR (95% CI)
PAD (ABI <0.9)	0.81 (0.40, 1.65)	1.01 (0.49, 2.10)	0.77 (0.34, 1.73)
High ABI (ABI >1.4)	2.17 (0.39, 12.02)	2.01 (0.35, 11.49)	2.23 (0.32, 15.73)
PAD equivalent (ABI <0.9 or >1.4)	0.93 (0.48, 1.81)	1.13 (0.57, 2.24)	0.89 (0.42, 1.91)

OR, odds ratio; ABI, ankle-brachial index; CI, confidence interval; PAD, peripheral arterial disease.
[1] Adjusted for age and sex.
[2] Adjusted for age, sex, duration of diabetes, HbA1c, total cholesterol, log-transformed triglycerides, high-density lipoprotein cholesterol, estimated glomerular filtration rate, body mass index, and history of hypertension.