studies are usually appropriate, but realistically speaking, why would industry fund studies that have an excellent chance of showing what a number of smaller studies have already shown, especially since they are making a lot of money in that market already? And, if a larger study were negative, wouldn't there be cries to do even larger ones? After all, one can really never prove a negative. There is always the possibility that another slight twist or an even larger study could be positive. If it takes a very large number of subjects to show a significant positive result, the clinical benefit must be difficult to uncover. At some point, one has to conclude that enough is enough and we have to accept the results at hand. In the meantime, large amounts of money are being diverted from better uses in our health care system.

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An Evaluation of the Efficacy of Methods Used in Screening for Lower-Limb Arterial Disease in Diabetes

Response to Williams et al.

We have read with interest the report by Williams et al. (1) on diabetic limbs without critical ischemia. We have recently performed a similar study in 106 diabetic patients with polyneuropathy, 61 of whom had critical ischemia (2), which confirms the poor performance of ankle-brachial pressure index in these patients (1,2). At variance to Williams et al. (1), we were, however, able to demonstrate the usefulness of the pulsatility index to predict critical ischemia. A pulsatility index <1.2 recorded at the ankle arteries predicted critical limb ischemia with reasonably good sensitivity (0.87) and specificity (0.62); the positive and the negative predictive values were 0.64 and 0.86, respectively. We explain our differences to the findings of Williams et al. by the different Doppler devices that were employed. While Williams et al. had used a 8-MHz Doppler probe (1), we used a 10-MHz linear ultrasound probe with a color-flow duplex machine (Accuson 128XP10; Acuson, Mountain View, CA) in our study.

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An Evaluation of the Efficacy of Methods Used in Screening for Lower-Limb Arterial Disease in Diabetes

Response to Janssen and Chantelau

We thank Janssen and Chantelau (1) for their interest in our study (2), which analyzed the efficacy of several commonly used lower-limb arterial screening modalities in diabetes. We demonstrated that qualitative, operator interpretation of the continuous Doppler waveform at the ankle for limbs without critical ischemia was more sensitive than quantitative analysis in detecting peripheral arterial occlusive disease. In our hands, qualitative waveform analysis achieved a sensitivity of 94% and specificity of 66% in the presence of clinically detectable peripheral neuropathy. Pulsatility index and other quantitative waveform analyses invariably failed to detect more severe peripheral arterial occlusive disease, with an overall sensitivity of 52%. In your study of limbs with and without critical ischemia, pulsatility index was demonstrated to achieve greater sensitivity at 87% (3).

There appear to be two fundamental differences between the respective studies. First, this study focused on the ability of commonly used screening methods to detect hemodynamically significant arterial disease not their ability to predict the presence of critical ischemia. Patients with critical ischemia were therefore excluded from our study. Further, we employed a relatively simple, single-crystal, continuous waveform analyzer and not a more complex device with a linear crystal array and color-flow facility. Color duplex imaging with waveform analysis of the lower limb has been demonstrated to be effective in detecting peripheral arterial occlusive disease (4). Our study used this modality as a gold standard not as a screening modality.

It is not surprising, therefore, that the results of quantitative analysis differ between the two studies.

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Association Between Cigarette Smoking and Metabolic Syndrome

Response to Oh et al.

In the August 2005 issue of *Diabetes Care*, Oh et al. (1) reported that, in a representative population-based sample of 3,452 Korean men, cigarette smoking is associated with the metabolic syndrome. They also show a dose-dependent effect, with prevalence of the syndrome progressively increasing with the number of cigarettes smoked. Of the components of the syndrome, dyslipidemia (high triglycerides and low HDL cholesterol) and abdominal obesity are shown to be the main contributors to this association. The underlying mechanisms of this association are not explored. Insulin resistance and compensatory hyperinsulinemia are considered central features of the metabolic syndrome, yet neither factor is measured in this study.

We have explored this same issue in a large population-based sample of 2,370 nondiabetic men, aged 35–65 years, in whom the components of the metabolic syndrome, defined according to Adult Treatment Panel III criteria, were evaluated together with fasting plasma insulin; homeostasis model assessment of insulin resistance index was also calculated as a validated surrogate measure of insulin resistance.

In agreement with Oh et al., we find that chronic smoking is associated with higher triglycerides and lower HDL cholesterol with a dose effect. However, other key components of the metabolic syndrome, such as hypertension and hyperglycemia, were less common in smokers. These results were not modified after correction for BMI, alcohol and coffee consumption, and use of antihypertensive medication. Furthermore, fasting plasma insulin concentrations were very similar in smokers and never-smokers (8.02 ± 4.63 vs. 8.34 ± 3.35 μU/ml), whereas homeostasis model assessment of insulin resistance index was significantly lower in smokers (1.99 ± 1.12 vs. 2.12 ± 0.91, $P < 0.01$) due to the lower glucose values observed in this group.

Our data therefore confirm the finding by Oh et al. of an increased prevalence of the metabolic syndrome in smokers but suggest that this is mainly driven by higher prevalence of dyslipidemia. Furthermore, our findings expand the interpretation by providing evidence that smoking-associated dyslipidemia may be mediated by mechanisms other than insulin resistance.

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Association Between Cigarette Smoking and Metabolic Syndrome

Response to Masulli and Vaccaro

We thank Massulli and Vaccaro (1) for their interest and comments regarding our article (2). Moreover, we are pleased to hear that they found results similar to ours in a population-based study of Italian men. They reported that, like Korean smokers, Italian smokers had higher triglycerides and lower HDL cholesterol levels than those who had never smoked. They also showed that smoking is not associated with high fasting glucose or high blood pressure, which is similar to our findings. It is a general belief that insulin resistance is the main mechanism underlying the development of metabolic syndrome. Therefore, they tested the association between smoking and insulin resistance using the homeostasis model assessment of insulin resistance index (HOMA-IR). Contrary to their expectation, they could not find an association with HOMA-IR and they suggested that smoking-associated dyslipidemia is mediated by mechanisms other than insulin resistance.

We agree with their suggestions; however, we would like to comment on some points that must be considered. First, both their study and our own used cross-sectional observational data. As we mentioned in our article, the cross-sectional observational design has inherent limitations. Patients with type 2 diabetes and hypertension are more likely to be taking medicines that influence insulin sensitivity. Furthermore, the lifestyles, diet, and other behavioral factors that can influence insulin sensitivity may have differed. Second, HOMA-IR and fasting insulin values have an inherent limitation for predicting insulin resistance. Third, previous cohort data, which investigated temporal associations to identify causal relationships, have demonstrated that smoking increases the risks of diseases such as type 2 diabetes (3,4), which are known to have insulin resistance as their underlying mechanism. From these findings, although we agree with their suggestion, we cannot be totally confident that the association between smoking and metabolic syndrome is not mediated by insulin resistance. Further well-designed study of the temporal relationships is needed to evaluate this hypothesis.

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