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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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The Effectiveness of β-Blockers After Myocardial Infarction in Patients With Type 2 Diabetes

Response to McDonald et al.

In the September 2005 issue of *Diabetes Care*, McDonald et al. (1) showed that β-blocker therapy after myocardial infarction (MI) was not associated with reduced mortality or fewer recurrent events in people with type 2 diabetes in routine practice. This contrasted with studies performed before intervention with drugs such as ACE inhibitors and statins were available. These studies showed a significant decrease in mortality and reinfarction post-MI in diabetic subjects (2,3). The authors conclude that the benefits of β-blockers are attenuated in the era of multiple interventions.

I believe that there is another reason for the decreased effectiveness of β-blockers in the modern era. When the older studies were preformed, the majority of β-blockers used were nonselective β-blockers that blocked both the β_1 and the β_2 receptors. Selective β_1 blockers, unless used intravenously at the time of the MI, have never been shown to decrease reinfarction or mortality post-MI (4). In contrast, nonselective β-blockers (propranolol and pindolol) with normal ventricular function, as well as carvedilol with decreased ventricular function, have been shown to decrease cardiac events and mortality post-MI.

Therefore, I believe that the shift in effectiveness of β-blockers post-MI is not due to multiple other interventions but to utilization of β_1-blockers, which—especially at lower doses—have not been shown to decrease mortality or reinfarction. A reanalysis based on the use of β_1 selective and nonselective β-blockers could prove or disprove this theory.

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The Effectiveness of β-Blockers After Myocardial Infarction in Patients With Type 2 Diabetes

Response to Bell

We thank Dr. Bell (1) for his interest in and insightful comments about our study. Dr. Bell proposes that the use of lower doses of cardioselective β-blockers could have reduced the effectiveness of this class of agents after myocardial infarction (MI) in diabetic subjects, a reasonable hypothesis. Another hypothesis is that short-acting cardioselective β-blockers lead to periods of withdrawal and decreased efficacy (2).

As in previous studies (3,4), we assumed a class effect among β-blockers. Unfortunately, we could not differentiate the type of β-blockers that were prescribed, although our sample size would have been precipitously reduced if we had done so. However, atenolol and metoprolol are the most commonly prescribed β-blockers in Canada (5).

Dr. Bell asserts that cardioselective β-blockers have never been shown to reduce mortality post-MI unless used intravenously. However, meta-analyses have demonstrated a 25% reduction in mortality with long-term β-blockade after MI (including cardioselective agents) (6,7); cardioselectivity or membrane-stabilizing activity did not predict mortality. Rather, Yusuf et al. (6) demonstrated decreased effectiveness when trials using agents with intrinsic sympathomimetic activity (ISA) were pooled (odds ratio [OR] for agents with ISA 0.90 [0.77–1.05]; OR without ISA 0.69 [0.61–0.79]). Freemantle et al. (7) also failed to demonstrate a significant effect of cardioselectivity, although the OR for the protective effect of β-blockers with ISA was 1.19 (0.96–1.47). Moreover, older observational studies of β-blockers (as a class) post-MI, conducted in an era when metoprolol and atenolol were frequently prescribed, have found no effect of cardioselectivity (3,4,8). For example, in the Bezafibrate Infarction Prevention (BIP) study, mortality was similar in patients who received propranolol or a cardioselective β-blocker (4), and in the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study, metoprolol was an independent predictor of reduced mortality after MI (relative risk ratio 47%) (8). If Dr. Bell's hypothesis is correct, it seems unlikely that these earlier studies would have shown mortality benefit.

Therefore, we believe that the putative benefits of β-blockade were less in our study because of cointerventions that also reduce mortality. Future studies should include the type of β-blocker as a covariate rather than assuming a class effect, as we and others have done. The answer to this question is clinically