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between cigarette smoking and cardiovascular disease?**

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VIEWPOINT

Insulin Resistance and Compensatory Hyperinsulinemia

The Key Player Between Cigarette Smoking and Cardiovascular Disease?

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Hyperinsulinemia, dyslipidemia, and endothelial dysfunction are characteristic findings in insulin-resistant individuals, and all of these abnormalities have been identified as increasing cardiovascular disease (CVD) risk. Smokers tend to be relatively insulin resistant, hyperinsulinemic, and dyslipidemic, with evidence of endothelial dysfunction, as compared with nonsmokers, and recent epidemiologic data have suggested that CVD in smokers is primarily seen in those individuals who also have the characteristic findings of insulin resistance. Based on these observations, it is argued that insulin resistance and its consequences represent a major mechanistic link between cigarette smoking and CVD. It is also postulated that the enhanced CVD risk in smokers, resulting from hyperinsulinemia, abnormalities of lipoprotein metabolism, and endothelial dysfunction, will primarily be present in those smokers who are insulin resistant. As a corollary, it is suggested that CVD risk in individuals who cannot, or will not, stop smoking can be reduced by therapeutic efforts aimed at attenuating the adverse effects of insulin resistance and its consequences. (J Am Coll Cardiol 2003;41:1044-7)
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Smoking is a major risk factor for atherosclerosis and cardiovascular disease (CVD), with a dose-response correlation between CVD morbidity and mortality and the number of cigarettes smoked (1). Although this relationship is well recognized, the pathophysiologic links between smoking and CVD have not been resolved. For example, the results of studies to be reviewed subsequently have demonstrated that smokers have abnormalities in lipoprotein metabolism and endothelial function known to be associated with increased CVD risk. Although these changes in lipid metabolism and endothelial function provide attractive mechanistic links between smoking and CVD, neither one need be an independent risk factor for CVD in smokers. More specifically, there is evidence that smokers are insulin resistant and hyperinsulinemic, as compared with nonsmokers (2-9), and these changes can lead to both the dyslipidemia (10) and endothelial dysfunction (11) shown to be present in smokers. Furthermore, recent data from the Copenhagen male study indicated that only those smokers who have the characteristic dyslipidemia associated with insulin resistance/compensatory hyperinsulinemia were at greatly increased CVD risk (12). Thus, it can be argued that a major defect leading to increased CVD risk in smokers is insulin resistance and compensatory hyperinsulinemia, and that the multiple adverse consequences associated with these changes in insulin metabolism, including dyslipidemia and endothelial dysfunction, are responsible for the accelerated atherogenesis in these individuals. If this formulation is

correct, the prevalence of these abnormalities will be increased primarily in those smokers who are also insulin resistant. The untoward effects of insulin resistance and compensatory hyperinsulinemia provide a mechanistic link between smoking and CVD that is consistent with available data, as well as offering a new and clinically relevant approach to decreasing CVD risk in those smokers who cannot, or will not, stop smoking.

SMOKING AND INSULIN RESISTANCE

In 1992, we demonstrated that smokers were insulin resistant and hyperinsulinemic, as compared with a matched group of nonsmokers (2). The initial report that smokers were relatively more insulin resistant than nonsmokers was soon confirmed, and evidence was subsequently published indicating that smoking 1 cigarette per h for 6 h was associated with a decrease in insulin sensitivity (3). In addition to these studies showing smoking to be associated with direct measures of insulin resistance, other population-based reports have indicated that smokers have higher insulin levels (a surrogate marker of insulin resistance) than nonsmokers (4-6). Furthermore, despite the observation that smoking cessation was associated with weight gain, it was possible to document an improvement in insulin sensitivity at the same time (7). Finally, smoking has been shown to accentuate the degree of insulin resistance in patients with type 2 diabetes (8,9). However, in one population-based study, smokers did not have higher plasma insulin concentrations than did nonsmokers (13). Also, in another study using the minimal model to quantify insulin action, no difference in insulin sensitivity was noted

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Abbreviations and Acronyms

ADMA	= asymmetric dimethylarginine
ATP-III	= Adult Treatment Panel III
CVD	= cardiovascular disease
HDL	= high-density lipoprotein
LDL	= low-density lipoprotein
TG	= triglycerides

between smokers and nonsmokers (14), but this latter finding is confounded by the fact that although active smoking was not associated with insulin resistance, exposure to environmental tobacco smoke was. Consequently, there is considerable support for the view that smokers are insulin resistant and hyperinsulinemic as compared with nonsmokers. On the other hand, although smokers, as a group, are more insulin resistant than nonsmokers, not all smokers are insulin resistant (2). Perhaps the best way to view the metabolic effect of smoking is as a modulating factor that will adversely affect insulin-mediated glucose disposal, and the more intrinsically insulin resistant an individual is, the greater will be the untoward effect of smoking.

SMOKING, DYSLIPIDEMIA, AND INSULIN RESISTANCE

The fact that smokers have higher plasma triglyceride (TG) and lower high-density lipoprotein (HDL) cholesterol concentrations than nonsmokers has been apparent for many years (15-17). Indeed, it was the similarity between the dyslipidemia described in smokers and that characteristic of insulin resistance (10) that led to the initiation of our study showing that smokers were insulin resistant as compared with nonsmokers (2). In that study, we were also able to demonstrate that insulin resistance, compensatory hyperinsulinemia, and high TG and low HDL cholesterol concentrations appeared together as a cluster in smokers. The association between smoking, insulin resistance, and dyslipidemia has also been observed in subsequent studies showing the powerful impact of the combined effects of smoking and hyperinsulinemia on plasma TG and HDL cholesterol concentrations in patients with combined hyperlipidemia (18), and that the cluster of metabolic abnormalities associated with insulin resistance and compensatory hyperinsulinemia was increased sixfold in smokers (19). Thus, there is substantial evidence that the combination of insulin resistance, hyperinsulinemia, and the dyslipidemia characteristic of insulin resistance occurs together in smokers more commonly than in nonsmokers. The clinical relevance of this association has been emphasized by evidence showing that the increased prevalence of CVD in smokers was almost entirely confined to those individuals who also had high TG and low HDL cholesterol concentrations (12).

SMOKING, ENDOTHELIAL DYSFUNCTION, AND INSULIN RESISTANCE

Several lines of evidence have shown that endothelial function is abnormal when smokers are compared with nonsmokers. For example, endothelial-dependent blood flow following venous occlusion is decreased in smokers (20-24), as was the vasodilatory response to bradykinin in the perfused hand vein (25) and the vasomotor response of epicardial coronary arteries to cold pressor testing (26). In addition to these apparent changes in endothelial function, mononuclear cells from smokers bind with greater adherence to cultured endothelium (27), and plasma concentrations of cellular adhesion molecules are increased in these individuals, in association with higher plasma insulin concentrations (28).

The possibility that insulin resistance and/or compensatory hyperinsulinemia mediates the association between smoking and endothelial dysfunction is consistent with several lines of evidence. There are significant relationships between insulin resistance and/or compensatory hyperinsulinemia and markers of endothelial dysfunction, including enhanced binding of mononuclear cells isolated from peripheral blood to cultured endothelium (29), increased plasma concentrations of several cellular adhesion molecules (30), partially oxidized low-density lipoprotein (LDL) particles (31), and decreased plasma concentrations of antioxidant vitamins (32). More recently, we have demonstrated a highly significant relationship between the degree of insulin resistance and plasma concentrations of asymmetric dimethylarginine (ADMA) (33). Asymmetric dimethylarginine is an endogenous inhibitor of nitric oxide synthase, recently shown to predict CVD in patients with renal failure (34), as well as acute coronary events in a population-based study in Finland (35). The potential importance of elevated ADMA levels as a CVD risk factor has recently been emphasized in a *Lancet* editorial (36). Finally, endothelial dysfunction is associated with reduced arterial compliance, and increased arterial stiffness has been described in smokers, as well as in two clinical conditions characterized by insulin resistance type 2 diabetes and hypertension (37).

CLINICAL IMPLICATIONS

The most effective way for smokers to decrease the risk of CVD is to stop smoking. However, not all smokers are either willing or able to make this behavioral change. The information outlined in this Viewpoint provides the experimental background that can help decrease the CVD risk in those individuals who cannot stop smoking. At the simplest level, it is essential that health care professionals realize that insulin resistance and its consequences are accentuated in smokers, that these abnormalities increase the CVD risk, and that smokers should be evaluated for evidence of insulin resistance and its consequences. Perhaps the simplest was to do this is to use the recent criteria suggested by the Adult

Treatment Panel III (ATP-III) for identifying individuals with the metabolic syndrome (38). Although somewhat arbitrary, the ATP-III criteria provide a useful approach to decide which smokers also appear to be insulin resistant and in whom efforts should be initiated aimed at improving insulin sensitivity, as well as addressing the adverse manifestations of insulin resistance.

A complete discussion of the therapeutic interventions to decreasing the CVD risk in insulin-resistant smokers is outside the scope of this Viewpoint, but a few general comments appear to be appropriate. To begin with, it is necessary to differentiate between efforts focused on improving insulin sensitivity, per se, and those aimed at treating the specific manifestations of insulin resistance/compensatory hyperinsulinemia. Both adiposity and the level of physical activity are powerful modulators of insulin-mediated glucose disposal (39) and, in contrast to the other factors that affect insulin action, they are modifiable by safe, straightforward lifestyle changes. Thus, weight loss of 5% to 10% of body weight in overweight or obese individuals who are also insulin resistant significantly enhances insulin sensitivity, lowers ambient plasma insulin concentrations, and improves the associated CVD risk factors (40). An increase in physical activity in insulin-resistant individuals is also of considerable utility and provides two benefits. At the simplest level, any increase in energy expenditure will help insulin-resistant individuals maintain or lose weight. The greater the magnitude of the increase in energy expenditure, the greater will be the benefit to the individual. It is also possible to directly enhance insulin sensitivity if an individual is able to exercise for approximately 30 to 40 min, 4 times/week. The beneficial effects of the combination of modest weight loss and increased physical activity were clearly demonstrated in studies showing that these lifestyle changes decreased the rate at which type 2 diabetes developed in patients with impaired glucose tolerance (41,42).

Although macronutrient composition of the diet, by itself, has little or no direct effect on insulin-mediated glucose disposal, it modulates the dyslipidemic changes seen in insulin-resistant smokers. Of greatest importance in this context is the avoidance of low-fat/high-carbohydrate diets, unless weight loss is also occurring. The more insulin resistant an individual is, the more insulin he or she must secrete to maintain normal glucose homeostasis. In the absence of weight loss, the untoward manifestations of insulin resistance/hyperinsulinemia will be accentuated when insulin-resistant persons increase the amount of carbohydrate in their diet (43). A simple alternative, and one consistent with efforts to minimize the intake of saturated fat, is to replace saturated fat with unsaturated fat, rather than with carbohydrate, thus maintaining a moderate carbohydrate intake. Parenthetically, this dietary manipulation is as effective as low-fat/high-carbohydrate diets in lowering LDL cholesterol concentrations (44,45).

Given the difficulty in changing one's lifestyle, it could be argued that the ideal treatment of insulin-resistant cigarette

smokers would be drug(s) that could significantly enhance insulin sensitivity, as well as its related adverse consequences. In this context, the use of thiazolidinedione compounds is of particular interest in that they are capable of improving insulin sensitivity (46). However, thiazolidinedione compounds are currently approved by the Food and Drug Administration only for the treatment of hyperglycemia in patients with type 2 diabetes, and at the present time, there are no compelling experimental data to establish their clinical utility in other clinical situations.

Finally, it seems reasonable to consider pharmacologic treatment of the characteristic dyslipidemia of insulin-resistant smokers (high TG and low HDL cholesterol concentrations), an approach that has been useful in decreasing the CVD risk in a secondary CVD prevention trial (47). Although a high LDL cholesterol concentration is not associated with insulin resistance/hyperinsulinemia, evidence from the Heart Protection Study (48) that simvastatin administration decreased the CVD risk, irrespective of smoking status, makes it seem reasonable to aggressively treat hypercholesterolemia in smokers to the same degree as is recommended for patients with type 2 diabetes (49).

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