Obesity, Metabolic Syndrome, and Coronary Atherosclerosis

Scott M. Grundy, MD, PhD

The relationship between obesity and coronary atherosclerosis (and coronary heart disease [CHD]) has been a subject of some dispute for many years. Data from early investigations suggested that obesity is not an important contributing cause of coronary atherosclerosis and CHD. For example, results of the Seven Countries Study revealed little correlation between body weight and incidence of CHD. Moreover, in the massive autopsy study called “The Geographic Pathology of Atherosclerosis,” edited by Henry C. McGill, Jr., the relationship between body weight and atherosclerosis was weak at best. This study included a detailed examination of arteries from a large number of autopsies carried out in New Orleans, Sao Paulo, Puerto Rico, Lima, and Santiago; by and large, the results uncovered no association between extent of arterial fatty streaks or raised atherosclerotic lesions in either the coronary arteries or the aorta for any measure of body weight, height, or obesity. It was noted that this study had the advantage of including several groups that differed greatly in geographic origin, ethnicity, CHD morbidity, and severity of atherosclerosis. Although the authors conceded that obesity is a factor contributing to risk factors for CHD such as hypertension, they surmised that the relationship between obesity and other risk factors is too weak for obesity to have a detectable effect on the severity of atherosclerosis.

In spite of these earlier negative findings, the Framingham Heart Study in the United States has consistently shown that increasing degrees of obesity are accompanied by greater rates of CHD. Even so, multivariate analysis of Framingham data strongly suggests that most of the relationship between body weight and CHD risk is mediated through the standard risk factors, ie, blood pressure, total cholesterol, HDL cholesterol, and diabetes. Their own data led Framingham investigators to question whether obesity is truly independent of the standard risk factors. If so, part of the relationship between obesity and CHD risk could be mediated by the emerging risk factors.

Returning to the question of the impact of obesity on coronary atherosclerosis, the present issue of Circulation contains an article by McGill et al in which body fat was correlated with the severity of coronary atherosclerosis in the Pathological Determinants of Atherosclerosis in Youth (PDAY) study. This study included autopsies carried out in approximately 3000 persons aged 15 to 34 years dying of external causes. Gross atherosclerotic lesions were graded in...
the right coronary artery and in the left anterior descending coronary artery. Adiposity was estimated by body mass index (BMI) and by thickness of the panniculus adiposus. In young men, BMI was positively associated with both fatty streaks and raised atherosclerotic lesions in both coronary arteries. A thick panniculus adiposus was also significantly associated with greater lesions of the right coronary artery when BMI was $>30$ kg/m$^2$. Thus, obesity appeared to be a contributor to coronary atherosclerosis in adolescent and young adult men. In young women, BMI was not associated with coronary atherosclerosis, but in those with a thick panniculus adiposus, there was a trend toward greater coronary lesions.

In the PDAY study, a portion, but not all, of the association between adiposity and coronary atherosclerosis could be explained by the standard, major risk factors. The latter were estimated from postmortem blood for lipid concentrations (non-HDL cholesterol and HDL cholesterol), thiocyanate (for smoking), glycohemoglobin (for recent, average plasma glucose levels); also medial thickness of renal arteries was assessed to identify hypertension. With increasing adiposity, non-HDL cholesterol (LDL $+$ VLDL cholesterol), glycohemoglobin, and prevalence of hypertension were higher, whereas HDL-cholesterol levels were lower. As might be expected smokers had less adiposity. When the authors adjusted their data for the presence of the standard risk factors, the effects of adiposity on coronary fatty streaks and raised lesions was diminished but not eliminated. The standard risk factors reduced the effect of adiposity on fatty streaks by an average of 15% and on raised lesions by 12%. Although the impact of standard risk factors on coronary lesions may have been underestimated, the findings nonetheless strongly suggest that obesity is a risk factor for coronary atherosclerosis beyond and independent of the standard risk factors, at least for young men.

If obesity is an independent risk factor for coronary atherosclerosis over and above standard risk factors, this relationship implies that much of the influence of obesity is mediated through the emerging risk factors—insulin resistance, a proinflammatory state, and a prothrombotic state. In the PDAY study, higher levels of glycohemoglobin in persons who were more obese reflect the presence of insulin resistance. The findings of this study thus support the hypothesis that the emerging risk factors, which are common in obese persons and are characteristic of the metabolic syndrome, are independently atherogenic. The failure to find a positive relationship between adiposity and coronary atherosclerosis in women may have two explanations. First, premenopausal women generally have a delay in progression of atherosclerosis; and second, excess adipose tissue in men, which tends to accumulate abdominally, carries a higher risk for atherosclerotic disease than it does in women. These 2 factors may be interrelated.

Two important questions must be addressed. First, why did the Framingham Heart Study find a positive correlation between BMI and CHD risk, whereas no such relationship was found in the Seven Countries Study? And second, why did the PDAY study find a positive correlation between adiposity and coronary atherosclerosis in men, whereas the large Geographic Pathology of Atherosclerosis did not?

Regarding both questions, the Seven Countries Study and the Geographic Pathology Study may have included populations in which susceptibility to the adverse effects of obesity may have been too variable to detect a definite relationship. If some populations are less sensitive to the influence of adiposity, then an adverse effect in other populations may have been missed in the analysis. This possibility raises the issue of differences in susceptibility in different groups. This issue is important because it has implications for the approach to the problem of obesity in different populations.

One example of a difference in susceptibility appears to exist between men and women in the United States. As the PDAY study showed, adiposity has a greater effect on atherogenesis in men than in women. It is well known that men develop coronary atherosclerosis more rapidly than women. This difference in atherogenesis rates may be related in part to differences in body fat distribution. Men are more prone to abdominal obesity than are women; and abdominal obesity is widely held to have more impact on risk factors than does gluteofemoral adiposity, which is common in women. Whether abdominal obesity per se is a direct cause of risk factors or a reflection of an underlying metabolic abnormality of a more fundamental type is not certain, but the association with cardiovascular risk factors certainly is present.

Some populations as a whole appear to be more susceptible to the adverse effects of obesity than are others. For example, only moderate weight gain leads to a striking increase in risk for CHD in the South Asian population. Undoubtedly, there is individual variability in susceptibility in this population, but in aggregate, the risk is high. South Asians commonly develop insulin resistance when they experience only moderate weight gain. This propensity is seen in South Asians who have migrated to other regions or who have moved into urban settings and have become relatively affluent in their own countries. The increased risk for CHD in South Asians exceeds by about 2-fold that which can be explained by standard risk factors at least compared with other populations. This observation supports the concept that the emerging risk factors, which are secondary to overweight, also contribute to CHD risk. In the case of South Asians, insulin resistance seems to be the most important emerging risk factor. It might be noted that South Asians are prone both to premature CHD and to type 2 diabetes, both of which are related to a greater insulin resistance.

Indeed, there is racial and ethnic variability in susceptibility to the specific risk factors of the metabolic syndrome. The differences presented below represent impressions gleaned from limited information in the literature; to date systematic comparisons of susceptibility and patterns of the metabolic syndrome in different populations have not been carried out. In general, the white population of European origin appears to be more predisposed to atherogenic dyslipidemia than other populations. Blacks of African origin are prone to hypertension when they gain weight; they also appear to be susceptible to type 2 diabetes, possibly due to a relatively low reserve for insulin secretion. On the other hand, they develop less atherogenic dyslipidemia than do whites with the same degree of weight gain. In the United States, Native Americans
and Hispanics are especially susceptible to type 2 diabetes, but are less likely to develop hypertension than are blacks. East Asians likewise tend to express the metabolic syndrome first as insulin resistance and type 2 diabetes.\textsuperscript{31} Whereas people of South Asia and Southeast Asia also have a high frequency of insulin resistance and type 2 diabetes, they appear to be more susceptible to CHD than are East Asians.\textsuperscript{32} More systematic comparisons to verify these impressions would make an important contribution to our understanding of the metabolic syndrome. In addition, studies on patterns of cardiovascular disease and type 2 diabetes in different populations likely would shed light on the role of adiposity in the causation of coronary atherosclerosis.

Because of the relation of obesity to CHD and type 2 diabetes, the rising prevalence of obesity in the United States is a cause of great concern. In the wake of this epidemic of obesity is a corresponding increase in prevalence of the metabolic syndrome. A recent report\textsuperscript{33} indicated that 20% to 25% of the adult US population has the metabolic syndrome. In some older groups, this prevalence approaches 50%. The public health consequences for the nation project to be substantial.

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References


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