Obesity and Coronary Heart Disease
A Targeted Approach

For many years, investigators have known that obesity is associated with increased risk of mortality, much of which is due to cardiovascular disease. I propose that a significant portion of this risk is due to specific familial disorders that are associated with both obesity and premature coronary artery disease (CAD). This hypothesis attempts to reconcile the findings of cohort studies on normal populations with studies of selected families who have specific genetic disorders and is based on the following observations: the risk of obesity for CAD has been shown by multivariate analysis to be due to other known risk factors for CAD; the association of obesity with CAD is seen in persons under 45 years of age, thus, it is premature CAD; many of the known risk factors for premature CAD are highly prevalent in families with specific genetic disorders.

Many studies have used univariate analysis to show an increase in cardiovascular morbidity and mortality in obese individuals. In the large prospective screening study done by the American Cancer Society,1 much of the excess mortality rates in persons of higher than average weight was due to CAD. There was a stepwise increase in CAD for each weight index category. Larsson et al.2 reviewed numerous studies that confirm the univariate association between obesity and CAD.

While body weight may be related to the risk for premature cardiovascular disease, it has also been shown to be associated with most of the known risk factors for atherosclerosis, such as hypertension, cigarette smoking, low levels of high density lipoprotein (HDL) cholesterol, elevated plasma glucose levels, hypercholesterolemia, and hypertriglyceridemia. When multivariate analysis is used to consider all of these additional risk factors, the relationship between obesity and coronary heart disease is markedly attenuated or disappears entirely.3 The Framingham Study4 reported that after 26 years obesity was a significant predictor for coronary disease. This risk was independent of age, total cholesterol, systolic blood pressure, cigarette smoking, and glucose intolerance; however, plasma triglyceride and HDL cholesterol were not assessed. It is difficult to interpret multivariate analyses of CAD risk factors, which assume independence of variables, when many of these risk factors are obviously interdependent.

Elevated systolic and diastolic blood pressure appear to be associated with an increased risk for CAD at all ages and are also more prevalent in the obese. Similarly, cigarette smoking is associated with a marked increase in CAD at all ages. This association is complex, however, because smokers weigh less than nonsmokers and the effect of cigarette smoking on CAD risk may be reversible when smoking is stopped. Decreased HDL cholesterol levels are also associated with an increased risk for CAD in all age groups, and HDL cholesterol levels are lower in the obese. Elevated total plasma cholesterol levels are, similarly, related to premature CAD, and the obese have higher levels also. Elevated fasting plasma glucose levels are a risk factor for premature CAD and are seen in the obese individual with noninsulin-dependent diabetes mellitus. Finally, in some studies hypertriglyceridemia is associated with premature CAD, and obesity is also associated with elevated plasma triglyceride levels.

Thus, it may be argued that obesity is not an important independent risk factor for premature CAD because of the relationships between obesity and other CAD risk factors. However, weight loss does bring a normalization of blood pressure, increased HDL cholesterol levels, and lower plasma glucose cholesterol and trigly-


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1 American Cancer Society.
2 Larsson et al.
3 The Framingham Study.
4 The Framingham Study.

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ceride levels, suggesting that obesity may be a mediator of some of the other risk factors. While smoking, increased blood pressure, and increased total plasma cholesterol are independent risk factors for CAD, the complex interaction of these factors with the others mentioned here makes it very difficult to evaluate their relevance, together or independently.

An entirely different approach to the study of risk factors associated with premature CAD has been the research on highly selected families or populations in which premature atherosclerosis is unusually prevalent. In studies of the survivors of myocardial infarction (MI) and their families, hyperlipidemia was found in 60% of persons with MI under the age of 40 years, in 50% of those 40 to 49 years, and in 40% of those 50 to 60 years old. In each group, one-half of the hyperlipidemia was thought to be familial because of the elevated lipid levels in the family members of the MI survivors, a minimal estimate because many survivors had no or very few relatives. Goldstein et al. have suggested that familial elevated lipid levels could be due to three common monogenic disorders: familial hypercholesterolemia, familial hypertriglyceridemia, and familial combined hyperlipidemia. They found that these disorders in young individuals with acute MI were 20 to 40 times more prevalent than in a random population, indicating that each disorder was an important factor in premature CAD. In studies of the families of hypertriglyceridemic probands who had elevated lipid levels but no CAD, evidence again was found that familial combined hyperlipidemia is an important risk factor for premature CAD, although no evidence was found to suggest that familial hypertriglyceridemia leads to CAD.

Subjects with familial combined hyperlipidemia (FCHL) are more obese than normal in association with elevated plasma cholesterol and triglyceride levels. In this disease, the apparent risk for CAD with hypertriglyceridemia was similar to the risk for hypercholesterolemia. The HDL cholesterol levels of persons with FCHL tended to be low and of abnormal composition. Elevated blood pressure was more prevalent in the hyperlipidemic relatives of these families as compared to the nonblood relatives.

Noninsulin-dependent diabetes was previously thought to be caused by environmental factors. However, recent studies of identical twins indicate that noninsulin-dependent diabetes is entirely inherited. When one twin developed diabetes, 92% of the second twins developed the disease within 1 year, and 100% had developed it within 3 years. Individuals with noninsulin-dependent diabetes mellitus are more obese than the nondiabetic population and have elevated blood pressures. Those individuals who independently inherit both familial combined hyperlipidemia and noninsulin-dependent diabetes show a cumulative effect of obesity with each disorder.

If the abnormalities in relative body weight in each of these apparently familial disorders is inherited as part of their respective diseases, then the obesity seen with familial combined hyperlipidemia and with noninsulin-dependent diabetes may be a different form of obesity than that seen in the otherwise normal obese population. Epidemiological studies indicate that there is increased mortality at both extremes of the spectrum of relative body weight. Obesity seems to be related to the risk of premature CAD, but an increase in the risk for CAD was also noted in some lean individuals. These extremes of relative body weight comprise only a small fraction of a total population. Although familial disorders contribute in a minor way to the total risk for cardiovascular disease, they are much more significant for cardiovascular disease in the young.

While insulin-dependent diabetes is easy to diagnose and exclude, there are difficulties in determining who has familial combined hyperlipidemia and noninsulin-dependent diabetes that make evaluation of these factors in the relationship between obesity and cardiovascular disease more difficult. The selection of only those individuals who meet strict criteria for the familial disease studied introduces a bias. On the other hand, these familial disorders get lost in the multitude of data in large epidemiological studies. Perhaps continued studies of the offspring of the Framingham cohort or similar epidemiological studies will provide some answers.

We need to know: Is obesity a risk factor for premature cardiovascular disease independently of familial combined hyperlipidemia and noninsulin-dependent diabetes? Does the low HDL cholesterol and elevated blood pressure in the obese account for premature cardiovascular disease or is the disease caused by the high
prevalence of familial combined hyperlipidemia and noninsulin-dependent diabetes? The importance of these questions is reflected in the final report of the Pooling Project Group:9 “Since it has been shown that overweight and gain in weight are associated with a worsening of atherogenic traits, the limited role of overweight as a risk factor in middle age remains an enigma needing further investigation. Its significance for young adults, probably greater, also merits additional research.”

In studies of the effects of weight reduction in obesity on lipoprotein risk factors, the heterogeneity of obesity has not been considered, nor has the lack of long-term success of maintenance of reduced weight. While it is usually not difficult for a subject to lose weight, the inability to maintain weight loss is exceedingly discouraging. Using all parameters of therapy, Drenick and Johnson10 found that successful maintenance of weight loss in both childhood-onset and adult-onset obesity was less than 5% after 9 years of follow-up.

If it can be proved that the relationship between extremes of body weight and CAD is due in part to specific genetic disorders, efforts to modify body weight can be directed specifically toward individuals with these disorders.

References

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