Journal of the American College of Cardiology Vol. 47, No. 11, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.03.003

EDITORIAL COMMENT

Obesity and the Heart

A Weighty Issue*

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Obesity has been recognized as an important risk factor that contributes to the development of many different disease states worldwide. The World Health Organization (WHO) has implemented a definition that subjects with a body mass index (BMI) of 25 kg/m^2 or above should be diagnosed as *overweight* and those with a BMI of 30 kg/m^2 or greater as *obese* (1). The WHO states that obesity is one of the most blatantly visible, yet most neglected, public health problems. Recent data suggest that the waist-to-hip ratio may even better predict cardiovascular illnesses than BMI (2). The prevalence of overweight in the U.S. is increasing in recent years with 64.5% of the adult population being overweight and 30.5% being obese (3). These figures have led comedian and television host Jay Leno to observe that ". . . there are more overweight people in America than average-weight people. So overweight people are now average" (4). And there may be some truth in this statement.

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The problem of obesity is not restricted to the U.S., and the prevalence of overweight is increasing at an alarming rate worldwide. The International Obesity Task Force has estimated that at present at least 1.1 billion adults are overweight (5). The risk of developing diabetes, hypertension, or dyslipidemia starts to increase from a BMI of as low as 21 kg/m^2 (5). The rise in the plasma level of low-density lipoprotein in obese patients leads to an increase in the risk of coronary artery disease by a factor of 3.6 (5), and approximately 50% of cases of hypertension are secondary to obesity (6).

The prevalence of obesity in children and adolescents is rapidly growing as well. The presence of the perturbation at this age appears to program adult obesity (7). Risk factors such as obesity during childhood and the duration of exposure lead to premature signs of cardiovascular disease (6). Indeed, obesity leads to a number of structural changes of the myocardium. Obesity-related hypertension and elevated blood viscosity yield growth of the cardiac wall and thus induce concentric left ventricular (LV) hypertrophy (8). If hypertension is absent, the heart may also be harmed by chronic volume-overload as a consequence of an elevated cardiac output. Thus, LV dilation and LV hypertrophy are also common in normotensive patients (9).

In this issue of the *Journal*, Chinali et al. (10) have investigated the impact of obesity on cardiac geometry and function in a population of adolescents from the Strong Heart Study (SHS). The SHS is a trial of cardiovascular disease and its risk factors among American Indian men and women (11). It was set up in 1988 as the largest epidemiologic study of American Indians ever undertaken. The SHS trial was designed to estimate cardiovascular mortality and morbidity and to determine cardiovascular disease risk factors in American Indians (11). A total of 13 American Indian tribes and communities in three geographic areas were included. Three different substudies were undertaken, and a total of 4,500 tribal members age 45 through 74 years were clinically examined for the original study between 1993 and 1995. The participants are being followed up to the present day. An additional substudy was started between 2001 and 2003. As part of this substudy of SHS, a total of 460 unselected adolescent participants age 14 through 20 years were enrolled.

In the adolescent population from the SHS trial investigated by Chinali et al. (10), LV mass as assessed by echocardiography was 132 ± 30 g in normal weight, 149 ± 37 g in overweight, and 165 ± 41 g in obese subjects (both $p < 0.05$ vs. normal weight). Not surprisingly, LV hypertrophy was more common in obese (33.5%, $p < 0.05$ vs. normal weight) than in overweight (12.4%, $p < 0.05$ vs. normal weight) and normal weight (3.5%) participants. The stroke volume was 79.5 ± 12.8 ml in obese participants and thus increased ($p < 0.05$ vs. overweight and normal weight) compared with both normal weight (73.1 ± 10.4 ml) and overweight participants (76.5 ± 10.8 ml) indicating increased cardiac workload.

These findings are in line with earlier reports from other ethnic groups. The Bogalusa Heart study (12), for example, showed that there is a strong association between LV mass in childhood and young adults across BMI quartiles in both whites ($n = 334$) and blacks ($n = 133$). Linear regression analysis showed a strong relationship between the degree of obesity and LV mass ($r = 0.52$, $p < 0.001$). Moreover, this study demonstrated that obesity in childhood significantly predicts LV mass in adulthood (12). Another multiethnic study in 46.5% white, 38.0% black, and 15.5% Hispanic children and adolescents age 4 to 22 years found similar results (13). In the latter population, 41% were diagnosed with LV hypertrophy. Children with LV hypertrophy were more likely to be overweight than those without (odds ratio 5.02, 95% confidence interval 2.17 to 11.61, $p = 0.0002$) (13). However, LV hypertrophy appeared to be more prevalent in Hispanics than in the other ethnic groups.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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Chinali et al. (10) note that an increase in LV mass may to some degree result from an increased hemodynamic workload. Hence, it may represent a physiologic response of the cardiovascular system. This explanation does not account for the disproportional further LV hypertrophy in obese subjects. In such patients, pathophysiological vicious circles are being activated that lead to *maladaption* of the myocardium. Indeed, not only structural but also functional parameters are being hampered in obesity. The mechanisms underlying this finding deserve closer scrutiny, as they shed light on a shifting paradigm of cardiovascular pathophysiology. Our understanding has shifted away from a mere hemodynamic disorder to a broader approach involving hormonal metabolic and immunologic derangements (14). In this context, increasing insulin resistance might be of pivotal importance. Unfortunately, the study by Chinali et al. (10) did not evaluate associations between insulin resistance parameters and echocardiographic assessments.

Insulin is one of the most powerful protein-anabolic hormones and controls a multitude of pathways beyond glucose control. Hyperinsulinemia may play an important part in the development of myocardial hypertrophy. This may also be regarded as an early aspect of the development of diabetes-associated cardiomyopathy that may ultimately yield chronic heart failure (CHF) (14). Obesity-related increases in fatty acids impair glucose utilization in a metabolic cycle that involves imbalanced substrates for energy metabolism (15). The resulting insulin resistance accounts for a variety of effects including but not limited to increased oxidative stress, immune activation, tissue fibrosis, and impaired microvascular homeostasis, all of which contribute to the heart failure syndrome (14,16). Only recently, insulin resistance received increasing attention as part of the development and progression of CHF: it impacts on patients' symptomatic status and represents an independent marker of impaired survival (17).

Chinali et al. (10) suggest that metabolic derangements may contribute to myocardial abnormalities. Thus, CHF may develop independent of hemodynamic impairment from hypertension or ischemia. However, it is interesting to note that obesity, other than involuntary weight loss or cachexia, shows beneficial prognostic associations once CHF has developed. Cachexia is a well-recognized risk factor and an independent predictor of impaired survival in advanced CHF (18,19). In a study in 525 unselected consecutive CHF patients without evidence of weight loss who were subdivided according to ascending quintiles of BMI, on the other hand, survival was greatest among those in the fourth quintile with a mean BMI of 29.2 ± 0.8 kg/m^2 (20). Thus, obesity leads to metabolic and myocardial changes that may trigger the development and the progression of CHF. But patients with CHF, who have a poor prognosis per se, appear to benefit from being overweight.

The most intriguing question in this respect is to define a time point after which obesity does *not* pose as a risk factor anymore. Indeed, data from patients after complicated myocardial infarction in the Optimal Therapy In Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) (21) and retrospective data from 22,666 patients undergoing coronary artery bypass grafting with or without valve surgery (22) suggest that a higher body weight is beneficial once cardiovascular disease is present (Fig. 1). For young people with presence of established risk factors for future cardiovascular illness (like hypertension, hyperlipidemia or diabetes), it seems very likely that obesity confers a somewhat higher risk for death compared to people with normal weight. Whether the same is true for older people is not known. We hypothesize that obesity carries no adverse mortality impact above the age of 60 years—possibly even from age 55 to 50 years. This remains to be tested.

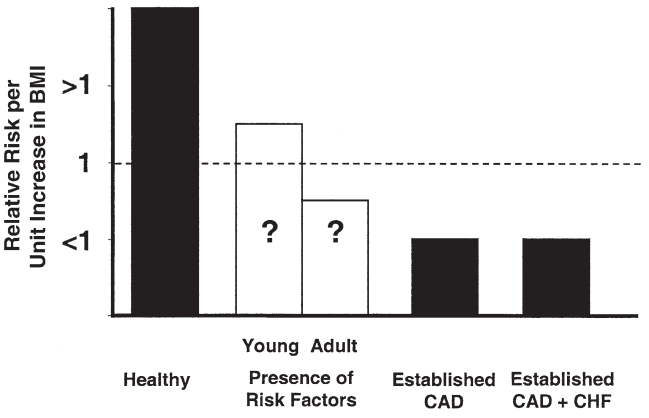

Figure 1. Estimated relative risk per unit increase in body mass index (BMI) in overweight and obese subjects. CAD = coronary artery disease; CHF = chronic heart failure.

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