Obesity, Leptin, and Incident Heart Failure*

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Obesity has been established as a risk factor for the development of heart failure (HF), independent of the established risk factors for HF such as diabetes and hypertension. Studies have demonstrated a continuous gradient of HF risk with increasing body mass index (BMI) (1,2). Although waist circumference (WC) or waist-hip ratio measurements are more representative of central or abdominal obesity, not all studies substantiate a significant incremental benefit of using these measures as opposed to BMI in predicting the risk of incident HF (3).

The contributions of mechanisms other than coexistent comorbidities and hemodynamic stressors associated with excess body fat have been proposed in the pathogenesis of overweight/obesity-related HF. Obesity-related inflammatory, metabolic, and hormonal changes have been postulated to contribute to the development of HF with obesity. The role of adipose tissue with its secretory products (adipokines) as an active endocrine organ is gaining importance in the investigation of obesity-associated diseases. One of the adipokines that has been postulated as a link between obesity and HF is leptin.

In this issue of the *Journal*, Wannamethee et al. (4) report on the association of plasma leptin levels with incident HF in a large prospective cohort of men with and without coronary heart disease (CHD) at baseline. The study was conducted on 4,080 men (>99% Caucasian), age 60 to 79 years, followed over a mean of 9 years in the British Regional Heart Study, a prospective study of cardiovascular disease in men. Of note, the presence or absence of pre-existing CHD was defined by asking the men whether a physician had ever told them that they had angina or myocardial infarction. The investigators confirmed findings from previous studies that increasing BMI was significantly associated with an increased risk of HF in men with and without pre-existing CHD after adjustment for established cardiovascular risk factors. The novel finding in this study was that in men without pre-existing CHD, higher leptin levels at baseline were associated with an increase in the risk of incident HF even after adjustment for multiple risk factors including BMI or WC. In men with pre-existing CHD, leptin showed only a weak positive association with incident HF, which was completely abolished after adjustment for BMI. Of note, plasma leptin levels were highly correlated with obesity measures (BMI and WC), as they were with measures of insulin resistance. Also, men with pre-existing CHD had significantly higher mean plasma leptin levels at baseline compared with men without CHD, which may be explained in part by the higher BMI in patients with CHD compared with those without CHD.

Leptin is a 16-kDa adipocyte-derived protein hormone, encoded by the ob (obesity) gene (reviewed in references 5 and 6). It was traditionally viewed as a product of adipocytes that can exert endocrine effects. However, several peripheral tissues including the heart are now known to also produce leptin, which can mediate autocrine or paracrine effects. Leptin exerts an inhibitory effect on food intake and increases energy expenditure through thermogenesis and physical activity. In humans, plasma leptin levels typically correlate with fat mass and the majority of obese individuals are hyperleptinemic. Leptin was initially thought to be an antiobesity hormone, but the discovery of leptin resistance suggests this belief may be simplistic. It has been hypothesized that leptin resistance results in defective hypothalamic regulation of food intake in obese humans.

Extensive investigation into whether leptin exerts beneficial or detrimental effects on cardiovascular function has yielded paradoxical observations, some of which are summarized in the following text (reviewed in references 5 and 6). Acute increases in leptin levels protect the heart and other tissues from ectopic lipid deposition by limiting dietary intake, up-regulation of fatty acid oxidation and down-regulation of lipogenesis in peripheral tissues. However, long-term exposure to elevated leptin levels leads to an overall decrease in fatty acid oxidation and increased cellular uptake, leading to cardiomyocyte fatty acid loading (7). Increased levels of intracellular free fatty acids can initiate the pathways of programmed cell death, termed lipoapoptosis. However, other studies suggest that leptin confers cardioprotection via attenuating cardiomyocyte apoptosis (8,9). In rat ventricular myocytes, leptin has been shown to directly affect cardiomyocyte contraction by depressiing ventricular myocyte shortening (10). Leptin has also been shown to directly induce hypertrophy of cardiomyocytes (11). In contrast, another study demonstrated that leptin-deficient mice may have an exaggerated hypertrophic re-

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sponse that is mitigated by the infusion of leptin (12). Leptin may mediate obesity-associated hypertension through central sympathetic activation (13), although in vitro studies have also shown that leptin evokes direct vasodilatory effects by inducing nitric oxide production (14). Similarly, data supporting the role of leptin in both accelerating and protecting against atherosclerosis are available (15,16). Inflammation has been another proposed link between obesity and HF. Leptin may be an important pathophysiologic mediator of inflammation, which in turn may be a significant factor in the development of cardiac and vascular dysfunction. The release of proinflammatory cytokines (such as interleukin-6) by adipose tissue can be influenced by leptin (17).

In view of the evidence available at present, a number of unanswered questions remain about the balance between the beneficial and harmful effects of leptin on the cardiovascular system in general and on the progression to obesity-related HF in particular.

In light of the study by Wannamatthee et al. (4), can we postulate that in obesity, leptin may be an intermediary in causing HF in patients without CHD? First, it is important to examine the consistency of these findings in the context of previous observations. Only a few prospective studies have investigated the association of leptin with obesity and incident HF. In a study of 775 participants in the Framingham study free of HF at baseline, the association between leptin levels and incident HF was not evident after adjustment for BMI (18). Because >30% of this cohort had CHD at baseline, any association present only in patients free of CHD could have been obscured. In another cohort of only CHD patients, enrolled in the Heart and Soul Study, central obesity as measured by waist-hip ratio predicted the risk of HF independent of several risk factors including adipokines such as leptin as well as markers of inflammation and insulin resistance (19).

Although the interesting observations by Wannamatthee et al. (4) could represent a true stronger association of leptin with the development of HF in a non-CHD population, we cannot rule out a chance finding in the examination of the clinically defined subgroups of CHD and non-CHD in the overall cohort. These findings need to be validated in other prospective cohorts. Future studies should include patients with greater ethnic and sex diversity. Both the Framingham study and British Heart Study cohorts were exclusively Caucasian, although the burden of HF may be greater in black men and women (3). It is already known that leptin levels vary by sex (18), raising interesting issues about differences in the distribution and metabolic activity of adipose tissue by sex.

The next question of whether leptin has a causal relationship with the development of HF in the non-CHD obese population is more difficult to examine in clinical studies. The experimental evidence provides conflicting data regarding the beneficial and detrimental effects of leptin on the cardiovascular system. On the basis of available data, we do not have a clear explanation of why leptin could be invoked as a mediator in the development of HF in non-CHD but not in CHD patients. Overall plasma leptin levels may just be a better marker of body fat compared with BMI or WC and therefore may be more strongly associated with the development of HF. Alternatively, leptin levels may be elevated in conjunction with activation of various other causal pathways of HF in obesity, such as inflammation, insulin resistance, and other adipokine activation. Furthermore, due to postulated autocrine/paracrine effects, plasma levels of leptin may not correlate with effects seen at the tissue level. Last, the occurrence of leptin resistance further complicates the evaluation of elevated plasma leptin levels, more so given the fact that leptin resistance may also be selective in certain tissue/organ systems. Therein lies the uncertainty about whether the elevated leptin levels are likely to be causing harmful biological effects in certain organ systems or whether they just represent increases in response to resistance.

Clearly, more research is needed to enhance our understanding of the pathophysiologic pathways involved in the development of HF in obesity. The study by Wannamatthee et al. (4) provides some clues for further investigation.

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