Is leptin protective against heart failure with preserved ejection fraction? A complex interrelationship among leptin, obesity, and left ventricular hypertrophy

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The U.S. has experienced an epidemic of heart failure with preserved ejection fraction (HFpEF), which currently affects at least 3 million American adults [1]. The prognosis after a hospitalization for HFpEF is dismal, with a 5-year survival of 35%—this is worse than most malignancies [1]. HFpEF is especially prevalent in African-Americans [2], and this can be attributed to a high prevalence of hypertension and obesity in this population [3]. Thus far, no therapy has been shown to provide mortality benefits in patients with HFpEF. An important knowledge gap exists in the underlying molecular pathways that lead to the development of left ventricular (LV) hypertrophy, stiff LV, and resultant HFpEF. Without a deeper understanding of the pathophysiology through which risk factors of HFpEF lead to adverse LV remodeling and diastolic dysfunction, it is unlikely that primary prevention efforts to avoid HFpEF will succeed.

Leptin is a hormone excreted from adipose tissue (thus its concentration positively correlates with body mass index [BMI]) and is known to have complex effects on the cardiovascular system [4, 5]. Leptin results in hypertrophy of cardiomyocytes in vitro [6]. In physiological studies in rats, it has been shown that leptin leads to unfavorable neurohormonal changes via activation of the sympathetic nervous system [7]. The resultant elevation in blood pressure may cause LV hypertrophy and HFpEF. However, using a mouse model of obesity, investigators have shown that leptin may be protective against LV hypertrophy [8, 9]. For instance, obese mice lacking leptin developed LV hypertrophy, which was reversed with the administration of leptin

[9]. As another example, a mouse model of leptin resistance (i.e., lacking the leptin receptor) showed a reduction in LV hypertrophy only after heart-specific expression of the leptin receptor [8]. Moreover, leptin decreases appetite and increases energy expenditure, both of which can result in weight loss and an improvement in hypertension, sleep apnea, and metabolic derangements such as hyperinsulinemia and lipotoxicity [10, 11]. Given recent studies reporting the preventive effects of substantial weight loss against the development of new-onset HF and associated morbidities [12, 13], leptin may act as a protective factor against HFpEF through weight reduction. However, the overall effects of leptin with regard to HFpEF in humans are largely unknown.

In this context, the cross-sectional study by Kamimura et al. [14], which was published in the prior issue of *Hypertension Research*, examined the relationship between plasma leptin concentrations and indices of LV structure and function in 1172 African-Americans with preserved EF using a community-based database. Stratified analyses were performed according to sex and BMI quartiles. Interestingly, leptin concentrations were significantly and inversely associated with LV mass only in women within the 3rd BMI quartile but not in the other subpopulations after adjusting for potentially confounding factors. Similarly, the association between leptin concentrations and diastolic wall strain—an indicator of LV stiffness—was significant only in women within the 4th BMI quartile. These findings are in line with those of the aforementioned studies in obese mice in which a high leptin concentration was protective against LV hypertrophy only in obese subjects [8, 9]. An intriguing hypothesis generated from these findings would be that obese patients with resistance to the weight-reduction effects of leptin have higher leptin concentrations, which in turn exerts direct effects on the heart to prevent the development of hypertrophied and stiff LV.

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These observations need to be interpreted with caution given the eight multiple comparisons (i.e., two sex categories and four BMI quartiles). It should also be noted that the generalizability of these findings is limited to obese African-American women. Additionally, due to the cross-sectional study design, the present study does not provide information on the temporal relationship or causality between leptin concentration and the incidence of HFpEF. This study should encourage further research on the molecular basis of the sex-specific and BMI-specific effects of leptin and its predictive value, i.e., whether leptin concentration predicts HF incidence and/or HF-related morbidities such as acute exacerbation.

In conclusion, the relationships among leptin concentration, BMI, and LV hypertrophy/stiffness are complex and warrant further investigation to determine whether leptin has protective effects against the development of HFpEF.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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