Editorial

Does Leptin Cause Vascular Disease?

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In the past two decades, there has been a 2- to 4-fold increase in childhood obesity in the United States. The current epidemic of childhood obesity in the United States can be expected to cause a surge in cardiovascular disease in this generation.1,2 Already, obesity-related illnesses account for nearly 300 000 deaths and about $100 billion in economic costs per year in the United States. Therefore, understanding the mechanisms by which obesity accelerates vascular disease has become ever more important.

Leptin is a circulating peptide hormone produced by adipose cells that regulates body weight by effects on food intake and metabolism.9 By acting on hypothalamic receptors, leptin increases energy expenditure by enhancing sympathetic nervous activity and lipolysis. Leptin deficiency and resistance to the effects of leptin are each associated with weight gain. Leptin resistance, which is associated with hyperleptinemia, is much more common than leptin deficiency in human obesity.10

In addition to hypothalamic receptors, there are receptors for leptin on the endothelium11 and on vascular smooth muscle cells.12 Accordingly, leptin can exert receptor-mediated influence on vessel tone and growth. In cell culture, leptin stimulates vascular smooth muscle proliferation and migration.12 Vascular calcification is also accelerated by leptin in experimental models.13 Additionally, leptin induces oxidative stress in endothelial cells; this action triggers the transcription of oxidant-sensitive genes that participate in atherogenesis, including monocyte chemotactic protein.14 Furthermore, leptin increases sympathetic nervous activity, and chronic administration of leptin increases blood pressure in experimental models.15 Accordingly, it is possible that the high levels of leptin observed in obesity could contribute to its adverse effects on cardiovascular health.

Leptin and Vascular Compliance

This issue of Circulation features an intriguing study that comes from a group that has contributed much to our understanding of human vascular function and its alteration by risk factors. Singhal and colleagues16 studied vascular function of the brachial artery in a healthy group of adolescents that had a broad range of body mass indexes. Using high-resolution ultrasound and a wall-tracking system, they assessed flow-mediated vasodilation (the increase in brachial artery diameter with increases in blood flow) and vascular distension (the increase in brachial artery diameter that occurs with the systolic pulse wave). The former is a reflection of endothelium-mediated vasodilation, and the latter is a measure of vascular compliance. The salient finding of this study16 was that high leptin levels are predictive of poor vascular compliance in adolescents. This effect of leptin was independent of the traditional risk factors and metabolic abnormalities that are observed in obesity. In fact, in these healthy adolescents, leptin was a better predictor of vascular compliance than the traditional risk factors, as well as fasting insulin and CRP.

Leptin and Endothelial Function

Curiously, plasma leptin levels were not correlated with flow-mediated vasodilation (FMVD). The investigators (incorrectly) concluded that “...the effect of leptin on arterial distensibility was independent of the short-term availability...
of endothelial nitric oxide.” One must be cautious in drawing conclusions from observations of FMVD in the brachial artery. Although in healthy individuals, NO plays a major role in this phenomenon, FMVD is not a direct measurement of the activity of endothelial nitric oxide synthase. Indeed, several endogenous vasodilators may contribute to FMVD in conduit vessels. These include prostacyclin and endothelium-dependent hyperpolarizing factor. Moreover, when NO elaboration is suppressed because of genetic or metabolic abnormalities, these secondary factors may assume a primary role in FMVD, compensating for any reduction in NO synthesis. Thus, early in the disease process, FMVD may appear normal at a time that NO synthesis or bioactivity is reduced. Therefore, it is possible that the adolescents in this study with high leptin levels had impairment of the NO synthase pathway, which was masked by compensatory increase in the synthesis of endothelium-derived hyperpolarizing factor and/or prostacyclin. A lack of correlation with FMVD does not exclude a deleterious effect of leptin on the NOS pathway.

Alternatively, it is possible that leptin has opposing effects on vascular smooth muscle and endothelial function. Leptin has been shown to increase NO release from endothelial cells in vitro. When infused into leptin-deficient ob/ob mice, leptin enhances endothelium-dependent vasodilation ex vivo. Leptin stimulates angiogenesis, an effect that is known to require NO synthesis. The release of leptin by adipocytes may cause a local NO-mediated vasodilatation in fatty tissue that enhances lipid metabolism. The effect of leptin to acutely trigger NO-mediated vasodilation is reminiscent of the effects of insulin on vascular reactivity. Acutely, insulin infused into the brachial artery of humans causes an increase in forearm blood flow and vasodilation. However, it is important to note here that the acute effects of insulin (and leptin) may be quite different from long-term elevations of these hormones. Both insulin and leptin are known to increase oxidative stress in endothelial cells. The long-term consequences of oxidative stress may include reductions in NO bioactivity and/or synthesis and an increase in the expression of adhesion molecules and chemokines that mediate vascular inflammation and atherogenesis. Furthermore, the associated metabolic changes that occur in a setting of resistance to insulin and to leptin (eg, increased levels of plasma fatty acids) are also known to impair endothelial function.

**Summary**

To conclude, the study by Singhal and colleagues reveals that elevated levels of leptin (often observed in overweight individuals) are associated with increased vascular stiffness. To strengthen a causal link between leptin and vascular stiffness, it will be important to determine the mechanism by which leptin impairs vascular compliance and to determine if nutritional or pharmacological interventions to reduce leptin levels and/or reduce leptin resistance can improve vascular compliance in these individuals. Nevertheless, Singhal and colleagues have added to our understanding of the association between leptin and cardiovascular disease. Perhaps more importantly, the study represents yet another harbinger of the epidemic to come, as widespread childhood obesity gives rise to an unwelcome epidemic of cardiovascular disease in this generation.

**References**

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