Hypertension: Shall We Focus on Adipose Tissue?

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Adipose tissue is an active endocrine organ that produces substances having local and systemic actions on blood vessels, kidneys, and the heart. Leptin, adiponectin, resistin, angiotensin II, adipin, TNF-α, IGF-1, plasminogen-activator inhibitor 1, and prostaglandins compose an incomplete list.1

Resistin, an adipokine belonging to the cysteine-rich secretory protein family, was described as an adipocyte-derived polypeptide that links obesity and insulin resistance in mice2; however, striking differences in the genomic organization and cellular source of resistin in rodents versus humans and the highly contrasting results of human studies raise doubt about its role as a mediator of human insulin resistance.3 Indeed, human resistin expression is higher in mononuclear blood cells and other nonadipocyte cells of adipose tissue than in adipocytes.4

This protein might be involved in inflammation, either being induced by increased cytokine levels or directly stimulating the production of proinflammatory cytokines, suggesting that inflammation may be a hyperresistinemic state.5,6 Resistin associates with several markers of inflammation, including C-reactive protein, TNF-α, and IL-6.5 Resistin accumulates in the inflamed joints of patients with rheumatoid arthritis, and its inflammatory effects are mediated by NF-κB signaling pathways.7 Furthermore, resistin activates human endothelial cells, which are therefore resistin-sensitive cells, leading to increased expression of adhesion molecules, and reduces endothelium-dependent and independent vasorelaxation.3,5,9 Moreover, this protein stimulates smooth muscle cell proliferation,10 and hypoxia enhances resistin expression in vascular smooth muscle cell, suggesting that resistin is implicated in the pathogenesis of atherosclerosis under hypoxia.11 These effects could explain the association found between higher circulating resistin levels and increased prevalence of cardiovascular diseases and heart failure in humans.5,12

A few studies have reported an association between hyperresistinemia and hypertension, in patients both with and without diabetes.13,14 Zhang et al.15 now report in this issue of JASN that increased levels of resistin are significantly associated with incident hypertension among women without diabetes. The authors prospectively studied 872 women without diabetes or hypertension from the Nurses’ Health Study. After a follow-up of 14 years, 361 (41.4%) women developed hypertension. Plasma resistin values were significantly associated with incident hypertension: The highest resistin tertile conferred a 75% higher risk for hypertension than the lowest (relative risk 1.75; 95% confidence interval 1.19 to 2.56). The relative risk did not substantially change after adjustment for multiple potential metabolic and nutritional confounding factors and for other adipokines. The risk was greater among older women. In a secondary analysis, inflammatory and endothelial biomarkers were measured in a subset of women. Resistin levels were significantly associated with both groups of biomarkers. After further adjustment for C-reactive protein, IL-6, soluble TNF receptor 2, intercellular adhesion molecule 1, vascular adhesion molecule 1, and E-selectin, resistin concentrations remained positively associated with an increased risk for incident hypertension.

Increased resistin concentration may determine hypertension by its vasoconstrictive properties; the ability to promote smooth muscle cell proliferation; and the increased expression of adhesion molecules, endothelin 1, metalloproteinases, and other mediators leading to endothelial dysfunction.3,5,10,13 Moreover, in vitro analysis of gene expression in endothelial cells from human coronary arteries showed that resistin is able to induce fatty acid–binding protein, a key molecule of insulin resistance, diabetes, and atherosclerosis.13 Resistin may also reduce vasorelaxation by pro-oxidant mechanisms: It could increase superoxide radical production and decrease endothelial nitric oxide synthase expression, and these effects are reversed by treatment with antioxidants.9 Imbalance in the production and regulation of oxygen radicals lead to oxidative stress, which is known to contribute to atherosclerosis.9 The participation of resistin in oxidative processes has been suggested by the impact of oxidative stress on the regulation of adipokine gene expression and the effect of antioxidants on resistin expression and concentrations in animals and humans.9,16

Zhang et al.15 conclude that increased levels of resistin may exist in their nondiabetic population before the occurrence of clinical hypertension; however, patients within the highest resistin tertile showed significantly higher body mass index values, and it cannot be excluded that they also had higher BP values at baseline, because hypertension in this cohort was self-reported. Individuals with high-normal BP, even when healthy, show reduced levels of adiponectin, increased resistin concentrations, and early signs of endothelial dysfunction and oxidative stress.14,17

Hypertension results from a complex interaction of several pathophysiologic mechanisms. Among them, endothelial dysfunction, oxidative stress, increased vascular reactivity, and vascular remodeling may be causes or consequences of increased BP. The chicken or the egg is an old question; there-
fore, it is difficult to determine whether increased concentrations of resistin are the cause or the consequence of inflammation within the vascular wall, oxidative stress, or vascular dysfunction associated with hypertension.

Much needs to be learned about the relationship among adipokines, inflammation, hypertension, and the cardiovascular system. Nevertheless, the study of Zhang et al.\textsuperscript{15} adds a piece to the emerging evidence that adipokines may contribute to the pathogenesis of chronic conditions. In the future, we should focus much more on the role of adipose tissue. Obesity is a causative factor in the development of hypertension and is linked to inflammation and chronic kidney disease.\textsuperscript{18,19} Among implicated mechanisms such as increased sodium retention, sleep disturbance, activation of the renin-angiotensin system and sympathetic nervous system, and insulin resistance, the release of adipokines may play an adjunctive role in the increased risk for hypertensive diseases. These molecules may provide incremental value in the prediction of cardiovascular risk beyond current schemes and approaches.

DISCLOSURES

None.

REFERENCES


See related article, “Plasma Resistin Levels Associate with Risk for Hypertension among Nondiabetic Women,” on pages 1185–1191.

Neighborhoods, Race, and Nephrology Care

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Access to nephrology care is essential to mitigating the progression of renal failure. There is some evidence of racial disparities with regard to this care, disparities whereby black individuals are less likely to received timely care compared with their white counterparts. The underlying causes of these racial differences are not fully understood but most likely include a combination of socioeconomic and social factors. In this issue

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