Insulin and Blood Pressure
Connected on a Circumference?

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Hypertension has long been known to be more prevalent among obese subjects or in patients with diabetes, i.e., in states of insulin resistance. After the demonstration that essential hypertension is an insulin-resistant state in its own right, it was logical to include hypertension in the insulin resistance syndrome, later transmuted into the metabolic syndrome. A large number of studies, both epidemiological and physiological, have explored this association and, more in general, the interrelationships between blood pressure and insulin action. Summarizing the available evidence—and critically analyzing its merits and pitfalls—is beyond the scope of this brief commentary. It may be nevertheless useful to recall a few general points.

First, the association between insulin resistance and hypertension extends into the normal state as an association between insulin resistance and hypertension exists. This clearly speaks for the existence of multiple cross-talk between the 2 homeostatic systems. Second, longitudinal studies have confirmed that insulin resistance (as measured by its surrogate, fasting hyperinsulinemia) may precede the development of frank hypertension. The reverse temporal sequence, i.e., hypertension antedating insulin resistance, has not been documented. Third, associations, even if fairly consistent, do not mean necessarily one-on-one relationships (such that every insulin-resistant individual is, or will become, hypertensive); most commonly, they stand for overlapping clinical phenotypes. Fourth, contrary to habitual disclaimers, consistent associations do imply mechanisms; however, mechanisms need not be unique or direct; they may be multiple and/or indirect, and they must be identified experimentally. For example, hyperinsulinemia activates the adrenergic nervous system but adrenergic overactivity may beget hyperinsulinemia via insulin resistance: a 2-way, partly indirect physiological mechanism. As a corollary, in any given hypertensive individual the insulin resistance/hyperinsulinemia may have a diverse origin and a differential impact on blood pressure homeostasis. Finally, insulin resistance from any cause is usually accompanied by compensatory hyperinsulinemia: at the cellular or organ level, either insulin resistance (e.g., regulation of intracellular calcium metabolism in smooth muscle cells) or hyperinsulinemia (e.g., renal sodium reabsorption, stimulation of adrenergic activity) may be the mechanism interfering with blood pressure control.

To this general background of complex interactions, what new information can we add? In this issue, Poirier et al report an association between blood pressure levels and waist circumference in a sample of the general population of Quebec, Canada. In particular, in both men and women, waist circumference explained a higher proportion of individual blood pressure variability than did body mass index, fasting plasma insulin concentrations or HOMA (or homeostatic model assessment, an index of insulin resistance based on fasting plasma glucose and insulin measurements). These findings are in line with previous observations that in Japanese Americans visceral adiposity (as measured by computed tomography) segregates with prevalent hypertension, and that expanded visceral fat mass (as measured by multisegment magnetic resonance imaging) and insulin resistance cluster in men with essential hypertension. Compared with previous cohort studies, the findings by Poirier et al have the advantage of being representative of a whole population. However, the extent to which they can be extrapolated to other populations is limited, among other circumstances, by the odd finding in this cohort that hypertension had a very low prevalence and was more frequent among women (3.4%) than men (4.8%). Also, the prevalence of diabetes or impaired glucose tolerance was not reported. We do not know whether the predictivity of waist circumference for the presence of higher blood pressure levels was affected by the glucose tolerance status. In fact, higher blood pressure and increased waist circumference are characteristic of overt diabetes and impaired glucose tolerance; thus, the association between blood pressure and waist circumference in the whole population might have been driven by the subjects with altered glucose tolerance. A further limitation, common to large-scale studies, is the use of fasting plasma insulin concentration or HOMA as surrogates for insulin resistance. Had insulin resistance been measured directly (by the euglycemic insulin clamp technique or the frequently sampled intravenous glucose tolerance test), it is possible that the pattern of associations with blood pressure might have been different. Finally, we do not know whether the waist circumference is a marker for future hypertension (or stable increase in blood pressure) over time. In other words, it is not known whether in the normotensive segment of this population a large waist circumference confers enhanced risk for the subsequent development of clinical hypertension. In a more recent cohort study in Japanese Americans, intraabdominal fat (by computed tomography) predicted incident hypertension even after adjusting, among
other potential confounders, for waist circumference itself.\textsuperscript{11} Needless to say, waist circumference is a proxy for intraabdominal fat; however, what factors (such as gender, age and body mass index) determine how closely the waist circumference marks for the amount of visceral fat—and the corresponding thresholds that signal enhanced risk—are still a matter of debate.

Granted all these caveats and provisos, here we do have supportive evidence for the general concept that localization and quality of adipose tissue matter in terms of intermediate clinical phenotype (hypertension but also dyslipidemia and glucose intolerance\textsuperscript{4}) and, ultimately, atherosclerotic cardiovascular disease. Potential mechanisms abound.\textsuperscript{12} Among them of obvious interest are those that link adipose tissue biology and blood pressure homeostasis directly, such as increased generation of angiotensinogen\textsuperscript{12} and a reduced release of adiponectin\textsuperscript{13} by visceral versus subcutaneous adipose tissue. Just how much the relatively small visceral fat depots can contribute to systemic changes in vasoactive peptides remains an unsolved issue. With regard to this, we should not neglect the possibility that visceral fat accumulation and hypertension may be parallel consequences of one or more common progenitor abnormalities. Clearly, there is much research to perform before we fully understand how traveling along a wide circumference gets us to high blood pressure.

References

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