Hypertension is a public health challenge of increasing importance because of its high frequency and concomitant risk of cardiovascular and renal disease. It has been estimated that the worldwide prevalence of hypertension was 972 million in 2000, and this number will increase by 60% by the year 2025.1 A large body of evidence indicates that the increasing prevalence of hypertension is sustained by the escalation of overweight and obesity. Actually, most hypertensive patients are also overweight or obese,2 and this may contribute to further deteriorate their cardiovascular risk profile. Similar to hypertension, obesity is independently associated with numerous adverse cardiovascular outcomes, and, most importantly, adipose tissue expansion and hypertension have a synergistic negative impact on cardiovascular prognosis. Hence, the hypertension–obesity pandemic imposes today a considerable burden on societies and healthcare systems that one can reasonably expect to increase further in the next years. The importance of preventing hypertension underscores the critical role of a better understanding of the most common mechanisms underlying its development.

The association between obesity and hypertension has been recognized for many decades,2 and an almost linear relation appears between body mass index and systolic and diastolic blood pressures, at least over a body mass index range from 16 to 31 kg/m².3 Also, risk estimates from the Framingham Heart Study suggest that about 78% of the hypertension cases in men and 65% in women can be directly attributed to obesity.4 Further evidence for a consistent link between adiposity and hypertension comes from studies showing that weight gain is almost invariably associated with an increase in blood pressure. The increase in blood pressure is closely related to the magnitude of weight gain, and even moderate weight gain is associated with an increased risk of developing hypertension.5 In addition, even modest weight loss is associated with a reduction in blood pressure in overweight and obese individuals.6,7

Since its discovery in the mid-1990s, the adipocyte-produced peptide adiponectin has attracted the interest of many researchers as a tool for investigating the function of the adipose tissue and its clinical implications. The rationale for investigating adiponectin as a potential predictor of the development of hypertension is 2-fold. On the epidemiological point of view, many studies suggest that abdominal adiposity is more closely associated with blood pressure and/or the presence of hypertension than total adiposity.8 In a community-based study population of normotensive nondiabetic Chinese adults followed for 10 years after their baseline examination, Chuang et al9 found that abdominal obesity and its progression are predictors of future blood pressure and hypertension incidence, independent of the effects of general obesity. Also, the extent of visceral fat reduction, not subcutaneous fat reduction, was associated with blood pressure lowering after weight loss.10 Body mass index is at most a very imprecise measure of visceral adiposity, and also waist circumference is a rough approximation of visceral fat. Thus, there is a need for biomarkers of expanded visceral fat, and low serum adiponectin is an attractive candidate, given its strong inverse relation with visceral adiposity. Indeed, although adiponectin is produced by the adipose tissue, its secretion is powerfully inhibited by fat accumulation, especially at the visceral level.11

Under a pathophysiological perspective, the relation between obesity and hypertension is complex and incompletely understood. Sympathetic nervous and renin–angiotensin–aldosterone system activation appear to play an important role in sodium and water retention, the rightward shift of the pressure–natriuresis curve, and the blood pressure elevation, which have been observed in obese individuals.12 More recently, it has become evident that obesity is invariably accompanied by a significant decrease in plasma adiponectin levels13 and that adiponectin has many defensive properties against obesity-related diseases, such as hypertension. A growing body of evidence now indicates that low serum adiponectin may be contributing to the abnormalities of the metabolic syndrome.13

Several studies had previously shown a cross-sectional inverse relation between adiponectin levels and blood pressure.14,15 In the current issue of Hypertension, Chow et al16 add another important observation to the relation between adipose tissue and high blood pressure by demonstrating for the first time an inverse relation between plasma adiponectin concentration and the future development of hypertension. In this case–control study, which was nested in a population-based prospective investigation of ≥2800 Chinese subjects, 70 normotensive, nondiabetic subjects who will develop hypertension within the next 5 years were compared with 140

**Hypoadiponectinemia**

A Novel Link Between Obesity and Hypertension?

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age- and sex-matched individuals who remained normotensive at year 5. A low serum adiponectin at baseline was a powerful predictor of future hypertension. Although low serum adiponectin had a cross-sectional relation with high blood pressure, obesity, and other factors of the metabolic syndrome, the relation between hypo adiponectinemia and future hypertension remained significant also after adjustment for several potential confounders, including mean arterial pressure, C-reactive protein, and body mass index or waist circumference. Even after adjusting for the effect of these variables, subjects in the bottom sex-specific tertile of serum adiponectin had an almost triple probability of becoming hypertensive than subjects in the top tertile.

Several limitations of the study by Chow et al16 should be acknowledged. The low number of observations limits the precision of the estimates, and the nested case–control design requires prudence in judging the study results. Nested case–control studies should always be considered with caution because of the inherent risk of overemphasizing the role of individual factors, and case–control matching should be done very carefully to avoid such risks. Even if the authors tried to take into account the effect of some confounding variables, the study might not have the statistical power to appropriately control for all of the relevant variables potentially associated with both adiponectin and hypertension. The applicability of the present findings to the general population is also questionable. Among the 2875 subjects drawn from the general population who formed the original population, only 322 subjects with impaired glucose tolerance and 322 with normal glucose tolerance were considered for the present study. This overrepresentation of impaired glucose tolerance makes it difficult to extend the results of the study to the general population. Finally, commercially available ELISA methods are unable to distinguish between the lower-weight forms of adiponectin and the high-molecular complexes, which might have different biological actions.11

The results of the present study raise several questions. First, what mechanisms lead from hypo adiponectinemia to hypertension? The potential links between low adiponectin levels and the future development of hypertension are summarized in the Figure. Hypoadiponectinemia has been proposed recently by Matsuzawa17 as a novel clinical entity, with a genetic or acquired background. The genetic form (primary hypo adiponectinemia) has been implicated in the pathogenesis of a rare form of hereditary insulin resistance syndrome.18 More frequently, low adiponectin levels arise from a positive energy balance and an expansion of visceral fat (secondary hypoadiponectinemia), which are related to the phenotype of the metabolic syndrome. Hypoadiponectinemia has several metabolic and cardiovascular adverse effects, which have been reviewed recently.11 Low adiponectin levels are associated with increased plasma concentration of free-fatty acids and hepatic fat content and have been linked to the development of insulin resistance, which might, in turn, represent a fertile soil for the development of hypertension. However, in the study by Chow et al16 the association between low adiponectin and future hypertension was independent from homeostasis model assessment-insulin resistance, thus suggesting that hypoadiponectinemia might influence blood pressure also through other mechanisms, including endothelial dysfunction and the activation of the inflammatory cascade.11 Moreover, adiponectin attenuates growth factor–induced proliferation of vascular smooth muscle cells,15 and this may lead to hypertension through the development of vascular hypertrophy and stiffness.20

A second question raised by the study by Chow et al16 is whether hypoadiponectinemia is a bystander or a causal factor in the development of future hypertension. Observational studies like the present one disclose associations, not necessarily causation, and are not best suited to address such questions. Notably, in adiponectin-knockout mice, a high-salt diet induced hypertension even in the absence of insulin resistance, and adenovirus-mediated adiponectin therapy lowered blood pressure.21 In Japanese men, it has been found that the TC genotype of the 1164T polymorphism of the adiponectin gene has been associated with both low adiponectin concentration and high blood pressure.15 Taken together, these findings strongly suggest the possibility that hypoadiponectinemia might be on the causal pathway from visceral fat accumulation to hypertension.

Despite the above limitations, the study by Chow et al16 suggests for the first time the hypothesis that low adiponectin levels may play an important role in the pathogenesis of human hypertension. More work is clearly indicated to establish the mechanisms whereby the expansion of adipose tissue and the associated hypo adiponectinemia induce hypertension. The time is probably not yet ripe for including hypoadiponectinemia among the established risk factors for hypertension and associated diseases. However, the provocative findings of the present study should stimulate further prospective research to address the value of hypoadiponectinemia for the prediction of hypertension and related organ damage.
Disclosures
None.

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