Cardiovascular Outcomes in Patients With Hypertension
Phenotype Versus Genotype, There Is No Small Risk

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Obesity-associated comorbidities, such as diabetes mellitus, atherogenic dyslipidemia, and systemic hypertension, have undoubtedly contributed to create an atherosclerosis prone environment which contributes to the development to cardiovascular diseases (CVDs). It is well known that there is a greater prevalence of hypertension in obese than among normal weight subjects. It is estimated that between 65% and 78% of systemic hypertension is attributed to obesity and hypertension is about 6× more frequent in obese subjects than in lean men and women.

In the Multi-Ethnic Study of Atherosclerosis (MESA), Colangelo et al. studied the interaction of adiposity indices with hypertension on CVD events using body mass index (BMI)–based definitions of overweight and obesity, as well as waist circumference (WC), to refine at risk obesity. The authors classified 3657 nonsmoking men and women, free of baseline clinical CVD, diabetes mellitus, and cancer, into 7 BMI-WC combinations defined by ethnicity-specific BMI (normal, overweight, class 1 obesity, and class 2/3 obesity), as well as ethnicity and sex-specific WC categories (optimal or nonoptimal). Adjusted absolute event rates per 1000 person-years and relative risks (RRs; 95% confidence intervals) for CVD events for hypertension (blood pressure ≥140/90 mm Hg or taking medication) versus no hypertension were assessed within BMI and WC categories. Sample included non-Hispanic white, black, Chinese-American, and Hispanic men and women from 6 US communities. In the end, 3687 subjects who were classified into 5 categories of BMI and 2 categories of WC were included. Incident CVD events were recorded over a mean follow-up of 10.3±2.7 years. All CVD events included myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), coronary heart disease death, stroke, death, other atherosclerotic death, and other CVD death. Information on participant demographics, smoking status, alcohol intake, physical activity, medical history, and medication usage was collected with standardized questionnaires. Not surprisingly, the event rates were lower in who hypertension was absent than in individuals in who hypertension is present. Although the relative risks suggest a stronger association of hypertension with CVD events among the lean/normal weight than among the obese subjects, the absolute adjusted event rates show that among hypertensive subjects, subjects with obesity have as high CVD risk as the lean/normal weight subjects. More precisely, in the hypertensive subjects, the adjusted event rates per 1000 person-years were—normal BMI and optimal WC: 9.3, normal BMI and nonoptimal WC: 13.2, overweight BMI and optimal WC: 9.0, overweight BMI and nonoptimal WC: 8.4, Class 1 obesity and optimal WC: 14.1, Class 1 obesity and nonoptimal WC: 10.1, Class 2/3 obesity: 9.9 event rate/1000 person-years. Of clinical interest, the authors documented a strong association of hypertension with CVD events for normal BMI participants without abdominal obesity. Absolute adjusted event rates were similarly high for both hypertensive normal BMI and hypertensive obese BMI individuals emphasizing the notion that hypertension in nonobese individuals is not benign.

Pathophysiological mechanisms linking obesity to hypertension are numerous (stimulation of the sympathetic nervous system, renal sodium retention, decreased heart rate variability, hemodynamic effects, perirenal fat, fat infiltration into the kidney, etc). Activation of the renin-angiotensin system, increment in sympathetic nervous system activity which mediates an increase in leptin secretion, as well as an involvement of microvascular dysfunction, has been implicated in the pathogenesis of hypertension. These mechanisms may contribute to the increase in blood pressure resulting from increasing levels of adiposity independently of insulin resistance. Sympathetic nervous system activation associated with obesity and molecules released by hypertrophied fat cells are 2 factors with the potential to promote the formation of angiotensin II and aldosterone. These have a direct vasopressor and antiinflammatory effect. A local renin-angiotensin system is present in human adipose tissue and may act as a distinct system from the plasma renin-angiotensin system. WC may be central in the association between insulin resistance and hypertension. It is plausible that crosstalks exist between visceral adipose tissue, angiotensin II, and insulin in the overweight/obesity state in humans, in an independent and facilitative manner, depending on a permissive genetic background. This process may contribute to conditions, such as the development of CVD and metabolic complications. Ectopic fat deposition involves also the kidney by inducing perirenal fat, as well as fat infiltration, into the kidney. These processes have been associated with increased intrarenal pressures,
impaired pressure natriuresis, and hypertension.\textsuperscript{5} The importance of this phenomenon is yet to be clinically demonstrated in human because obesity-related comorbidities like hypertension is associated with a smaller rate of long-term remission/ improvement in severely obese patients after bariatric surgery in comparison with diabetes mellitus or sleep apnea.\textsuperscript{6}

The link between insulin resistance and blood pressure suffers from a lack of consistency and ethnicity may be an important potential confounder. Because the first description of hyperinsulinemia in hypertensive patients,\textsuperscript{7} a meta-analysis supported the role of hyperinsulinemia in the pathogenesis of essential hypertension.\textsuperscript{8} The strength of relationship between insulinemia, insulin resistance, and hypertension varies widely according to ethnic groups.\textsuperscript{9–11} Thus, ethnicity/genetic background may be an important potential confounder in the study of Colangelo et al. Even if the authors used robust statistical approaches, data were insufficient in term of power to permit reliable evaluation of ethnicity-specific associations in some BMI-WC categories. Undeniably, the strength of the relationship between insulinemia, insulin resistance, and hypertension varies widely according to ethnic groups: (1) no racial difference in the Insulin Resistance Atherosclerosis Study (IRAS) study,\textsuperscript{12} (2) weak associations in black versus white Americans in the Atherosclerosis Risk in Communities Study (ARIC)\textsuperscript{10} and the Coronary Artery Risk Development in Adults (CARDIA) study,\textsuperscript{11} and (3) a strong relationship observed in European individuals.\textsuperscript{13} Indeed, genetic background is almost certainly an important factor in the relationship between adiposity, insulin, and hypertension. Hypertension in lean and obese individuals may represent separate genetic entities because the results of kinship and inbreeding analysis demonstrate that in the French Canadian population of the Saguenay/Lac St-Jean region, the sharing of common genes is increased among families selected for hypertension versus families selected at random.\textsuperscript{14} Furthermore, the degree of relatedness is increased within but not between subsets of hypertensive families with high and low prevalence of obesity, indicating that hypertension with and without obesity may represent, at least partly, separate genetic entities with difference in total body water and activity of ions transporters.\textsuperscript{15} Pausova et al showed that a genome-wide scan performed in either hypertensive families or the subset of families with a high prevalence of obesity, identified most significant loci of hypertension in the same 2 chromosomal regions: 1p36 and 11p15. Findings indicate that the 1p36 locus may contain a gene that is specific to obesity-associated hypertension, and the 11p15 locus may include a gene of hypertension that, in contrast, acts independently of obesity. The 11p15 locus demonstrated suggestive linkage to hypertension that was not associated with obesity.\textsuperscript{15}

In the study of Colangelo et al,\textsuperscript{1} there was a lack of inclusion of dietary variables with strong linkages to adiposity indices and hypertension. However, additional adjustment for sodium, potassium, calcium, magnesium, and total energy intake was performed because these parameters are known to affect blood pressure\textsuperscript{16}. As underlined by the authors, cardiorespiratory fitness may have had a mediating role in the interaction between adiposity, hypertension, and CVD outcomes.

Notwithstanding the limitations, this study highlights the fact that the presence of hypertension is associated with deleterious CVD outcomes independently of the obesity phenotype. Even if hypertension is a heterogeneous disorder, it is important for the clinician that proper treatment should be aggressively instituted on the basis of phenotype and in the future the genotype when available. Ethnicity, genetic background, food habits, and cardiorespiratory fitness should be added in the algorithm of management of individuals with hypertension to decrease CVD outcomes.

### Disclosures

None.

### References

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