

## EDITORIAL

## Obesity and Hypertension

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The link between obesity and hypertension is well known, but there are still many questions to be answered: Is abdominal adiposity rather than overall obesity more closely associated with high blood pressure? Is obesity an independent cardiovascular risk factor even if not combined with hypertension? Can obesity be metabolically benign? To what extent weight reduction is expected to contribute to the management or the primary prevention of hypertension? Are there compelling indications and/or contraindications to the use of specific classes of antihypertensive drugs for the pharmacological treatment of obesity hypertension? Consequently, the present editorial seeks to answer these questions by briefly reviewing the current state of knowledge of the association of obesity with hypertension.

Several tools are used to estimate obesity. The body mass index (BMI), or Quetelet index, is a statistical measurement which compares a person's weight and height. BMI is body weight in kilograms divided by the height in meters squared, expressed as weight (in kg)/height (m<sup>2</sup>). Overweight is defined as a BMI >25, obesity as a BMI >30, and morbid obesity is a BMI >35. Abdominal obesity is the accumulation of visceral fat resulting in an increase in waist size. It is often referred to as central, visceral, male-type or android obesity vs. female-type or gynoid obesity with a preferential gluteofemoral distribution. Abdominal obesity is diagnosed by a waist circumference >102 cm in men, and >88 cm in women or by a waist-to-hip ratio >0.95 in men and >0.85 in women.

As early as in 1980, in the second National Health and Nutrition Examination Survey (NHANES II), it was noted that the prevalence of hypertension was 2.9 times higher in obese than in non-obese adult Americans.<sup>1</sup> The Third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994 revealed a similar linear relationship despite a lower prevalence of hypertension.<sup>2</sup> BMI was recently found to be positively associated with blood pressure even in active, American veteran football players.<sup>3</sup> In a cross-sectional analysis of adults enrolled in NHANES 1999-2004, the odds ratio for hypertension for every 5-unit increase in BMI was 1.45 (95% CI 1.39-1.52). Although obesity was associated with hypertension in all age groups and both sexes, the odds for hypertension associated with obesity were relatively higher in younger people. With regard to hypertension subtypes, increasing BMI was a significant predictor of isolated diastolic hypertension or systodiastolic hypertension as opposed to isolated systolic hypertension. Isolated systolic hypertension represented a minority of hypertension cases in obese men, but remained the most prevalent type in obese women.<sup>4</sup>

There is substantial evidence that in addition to BMI, both waist circumference and waist-to-hip ratio are correlated with blood pressure, even after adjustment for BMI.<sup>5</sup> The associations of BMI and waist circumference with systolic and diastolic blood pressure and their possible interactions with gender and age were assessed in a cohort of 10,928 non-smoking and never treated for hypertension adults, recruited from all regions of Greece during 1994–1999, within the context of the European

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Prospective Investigation into Cancer and nutrition (EPIC).<sup>6</sup> Both BMI and waist circumference were found to be important predictors of systolic and diastolic blood pressure among both men and women. Among men, however, waist circumference appeared to be more important than BMI, whereas the opposite was apparently true for women. The differential effects of BMI and waist circumference on blood pressure by gender were evident among individuals older than 55 years, while among younger individuals BMI and waist circumference had comparable effects in both sexes. On the other hand, when waist-to-hip ratio was used instead of waist circumference and hip circumference, BMI became considerably more important than waist-to-hip ratio among both men and women.

Overweight and obese individuals of both genders have an increased risk of coronary heart disease and heart failure.<sup>7</sup> Nevertheless, since obesity is associated with an increased incidence of hypertension, dyslipidemia and type 2 diabetes, it has been postulated that the increased risk among obese subjects is related primarily to the influence of the associated risk factors and not to the obesity per se. In a French cohort of 139,562 men and 104,236 women, aged 18 to 95 years, overweight subjects without associated risk factors did not have an increased risk of cardiovascular mortality when compared with subjects with a body mass index <25 kg/m<sup>2</sup>. Mortality data for a mean follow-up period of 14.1±0.2 years were available for this population. The risk of cardiovascular death increased significantly when overweight was associated with hypertension alone. By contrast, the association of overweight with diabetes alone or hypercholesterolemia alone did not increase the risk. The authors conclude that the only reason for considering overweight as a major cardiovascular risk determinant is because it increases the prevalence of associated risk factors, especially hypertension.<sup>8</sup>

This conclusion, however, was based on analysis of the influence of body weight over a rather short period of follow-up and may not have conveyed the true impact of disease risk. When the influence of relative weight (the ratio of actual weight to desirable weight x100) on the 26-year incidence of cardiovascular disease was examined in the 2,252 men and 2,818 women of the original Framingham cohort, ages 28-62 years, who were free of clinically recognizable cardiovascular disease at the first study examination, the degree of obesity was found to be an important long term predictor of the incidence of coronary disease (both angina and coronary disease other than angina), coronary death and congestive heart failure in men independent of age, cholesterol, systolic blood pressure, cigarette smoking, left ventricular hypertrophy and glucose intolerance. Relative weight in women was also positively and independently associated with coronary artery disease, stroke, congestive heart failure, and coronary and cardiovascular disease death. The impact of weight on the incidence of cardiovascular disease was similar in those younger than 40 years and 40-49 years, but greater in these two age groups

combined than in those older than 50 years. In a subgroup of 629 men and women younger than 50 years who were normotensive, had cholesterol levels less than 250 mg/dl, did not smoke cigarettes, and had no evidence of glucose intolerance or electrocardiographic left ventricular hypertrophy, the incidence of cardiovascular disease rose with increasing weight in both genders, but the gradient of risk was clearly steeper in males than females.<sup>9</sup>

On the basis of evidence from early studies indicating that abdominal adiposity, as measured by waist circumference or waist-to-hip ratio, is an independent risk factor for cardiovascular disease,<sup>10-12</sup> waist circumference >102 cm in men, and >88 cm in women has been advocated as risk factor by recent hypertension treatment guidelines.<sup>13,14</sup> INTERHEART, a case-control study of acute myocardial infarction, conducted in 52 countries, including Greece, with 15,152 cases and 14,820 controls, was designed to examine the relationship of smoking, diabetes, hypertension, blood apolipoproteins, obesity, waist circumference, and psychosocial factors to myocardial infarction. In this study, the age- and region-adjusted odds ratios (95% CI) for risk of acute myocardial infarction for a change of 1 SD in waist circumference adjusted for BMI measurement was calculated to be 1.24 (1.19-1.25) for men and 1.21 (1.17-1.25) for women. The odds ratios (95% CI) for a change of 1 SD in BMI adjusted for waist circumference was relatively lower, especially for men (1.13 [1.09-1.17] as contrasted to 1.20 [1.16-1.24] for women).<sup>15</sup>

The concept of "benign obesity" has been used for more than 20 years to suggest that a considerable proportion of overweight and obese adults may not be at increased cardiovascular risk from their excess weight. Recent analysis of the data from 5,440 participants in the National Health and Nutrition Examination Surveys (NHANES) 1999-2004 showed that 23.5% of normal-weight adults were metabolically abnormal, as evidenced by the presence of hypertension, insulin resistance, raised triglycerides, fasting plasma glucose, and C-reactive protein, and low high-density lipoprotein, whereas 51.3% of overweight adults and 31.7% of obese adults were metabolically healthy. Factors associated with hypertension and metabolic abnormalities among normal-weight individuals were older age, lower physical-activity levels, and larger waist circumference, and factors associated with lack of such abnormalities among overweight and obese individuals were younger age, non-Hispanic black race/ethnicity, higher leisure-time physical-activity levels, and smaller waist circumference.<sup>16</sup>

Abdominal obesity has long been known to correlate with insulin resistance and many investigators have claimed that excess visceral fat is more strongly associated with insulin resistance than any other adipose tissue compartment. Results from another recent study, however, suggest that visceral fat, classically measured through its surrogate waist circumference, may in fact be a relatively weak predictor of insulin resistance.<sup>17</sup> The researchers investigated 314 subjects measuring

parameters, such as total body, visceral and subcutaneous fat with magnetic resonance tomography and fat in the liver and skeletal muscle with proton magnetic resonance spectroscopy, as well as insulin sensitivity and carotid intima thickness. They found that altogether, 10% of the study population and 25% of the obese subjects had a high insulin sensitivity phenotype or “metabolically benign obesity”. In the above study, obese but insulin-sensitive patients had a lower fat accumulation in skeletal muscle and particularly in the liver and lower intima-media thickness of the common carotid artery compared to obese, insulin-resistant patients. The authors conclude that a metabolically benign obesity that is not accompanied by insulin resistance and early atherosclerosis exists in humans. An accompanying editorial, however, points out that because risk factors and not outcomes were the end points in the above study (although carotid intima-media thickness is a reasonable surrogate measure of end-organ damage), insulin measurements are still not justified as a tool in the evaluation of the obese patient and assessment of cardiovascular risk should rely on BMI calculation and waist circumference.<sup>18</sup>

In hypertension treatment guidelines, weight loss is proposed as the most effective non-pharmacological means for lowering blood pressure in obese hypertensives, as well as for decreasing the dose of antihypertensive medications required to control blood pressure in overweight individuals.<sup>13,14</sup> Weight loss has also been advocated as an effective nonpharmacologic means for the primary prevention of hypertension in the population at large. In this respect, the results of an observational study on the surviving members of the Framingham cohort suggest that a weight loss of 6.8 kg or more can reduce the long-term risk of hypertension by 21% to 29%.<sup>19</sup> An early meta-analysis of 12 controlled intervention trials showed a reduction in systolic blood pressure and diastolic blood pressure of -2.4 and -1.5 mm Hg per kilogram weight loss, respectively.<sup>20</sup> However, only half of the studies in this meta-analysis were randomized. A more recent meta-analysis of 25 randomized controlled trials comprising 4,874 participants from different ethnic populations showed a blood pressure reduction of -4.4/-3.6 mm Hg (95% CI, -5.93 to -2.95/-4.88 to -2.25) for a net weight reduction of -5.1 kg (95% CI, -6.03 to -4.25) by means of energy restriction, physical activity, or both. The effect on diastolic blood pressure was significantly larger in populations taking antihypertensive drugs than in untreated populations (-5.31 mm Hg [95% CI, -6.64 to -3.99] vs -2.91 mm Hg [95% CI, -3.66 to -2.16]).<sup>21</sup>

In general, hypertension in obese patients is less responsive to various antihypertensive medications. Current guidelines for the management of hypertension make no specific recommendations for treatment of patients with obesity hypertension that go beyond recommending weight loss. The reason for this lack of compelling indications and contraindications is perhaps the fact that although there is some evidence that certain anti-

hypertensive drugs used as monotherapy may be more effective than others in lowering blood pressure in obese patients, no hard-endpoint studies in obese hypertensive patients have been reported to date.<sup>22</sup> In addition, in most large intervention trials the average BMI of participants barely exceeds 30 kg/m<sup>2</sup>, and although some of them may have included several overweight or obese patients, sub-analyses for these subgroups have not been presented so far.<sup>23</sup>

**In conclusion:** (a) the prevalence of hypertension is much higher in obese than in non-obese adults, particularly in younger people; (b) isolated systolic hypertension represents a minority of hypertension cases in obese men, but remains the most prevalent type in obese women; (c) among men older than 55 years waist circumference appears to be a more important predictor of hypertension than BMI, whereas the opposite is true for women of the same age group; (d) obesity as estimated by BMI, as well as abdominal adiposity as measured by waist circumference seem to be independent cardiovascular risk factors, especially in males; (e) about half of overweight and 30% of obese adults may be not at increased cardiovascular risk from their excess weight, but is uncertain whether this “benign obesity” phenotype is expressed by insulin sensitivity or by a particular body fat distribution; (f) a reduction of at least 4/3 mm Hg in the general population and a significantly larger effect in patients taking antihypertensive drugs can be expected by a weight reduction of about 5 kg; (g) there is lack of evidence from antihypertensive trials regarding the most appropriate antihypertensive drugs for the obese hypertensive patient.

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