

Obesity-Related Hypertension: Pathogenesis, Cardiovascular Risk, and Treatment—A Position Paper of the *The Obesity Society* and the *American Society of Hypertension*

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In light of the worldwide epidemic of obesity, and in recognition of hypertension as a major factor in the cardiovascular morbidity and mortality associated with obesity, The Obesity Society and The American Society of Hypertension agreed to jointly sponsor a position paper on obesity-related hypertension to be published jointly in the journals of each society. The purpose is to inform the members of both societies, as well as practicing clinicians, with a timely review of the association between obesity and high blood pressure, the risk that this association entails, and the options for rational, evidenced-based treatment. The position paper is divided into six sections plus a summary as follows: pathophysiology, epidemiology and cardiovascular risk, the metabolic syndrome, lifestyle management in prevention and treatment, pharmacologic treatment of hypertension in the obese, and the medical and surgical treatment of obesity in obese hypertensive patients.

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The United States is currently facing a very real obesity epidemic. The most recent National Health and Nutrition Examination Survey indicates that approximately two thirds of US adults are presently classified as overweight or obese (body mass index [BMI] ≥ 25) and one third as obese (BMI ≥ 30) (1,2). While the numbers alone are formidable, they leave unaddressed the medical costs associated with obesity and obesity-related comorbidities, not the least of which is obesity-related hypertension. Given the frequent concurrence of obesity and hypertension, it is no coincidence that as the rate of obesity continues to rise, so too does the rate of hypertension. It is estimated that at least 75% of the incidence of hypertension is related directly to obesity (1). It is essential, therefore, to develop treatment strategies for the management of obesity in order to reduce the development of obesity-related hypertension as well as to effectively manage high blood pressure (BP) in the obese.

Recent publications have estimated that the annual medical burden of obesity and obesity-related diseases in the United States totaled roughly \$147 billion in 2008 (1) and that projected obesity-related medical expenses will more than double by 2018, topping \$344 billion, or about 21% of total healthcare spending (1). Although lifestyle changes aimed at prevention, especially in childhood, are the ultimate solution to the societal problem of obesity and its complications, the scope of illness caused by obesity demands immediate attention and therapeutic intervention in the obese population. Given the important role that obesity plays in the pathogenesis of hypertension, the leadership of both The Obesity Society and The American Society of Hypertension have commissioned this position paper for the purpose of providing the membership of both societies, as well as the community of clinicians in practice, with a current and timely summary on the relationship between weight and BP, on the cardiovascular (CV) risk imposed and on the management of obesity-related hypertension.

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TABLE I Pathogenesis of Obesity-Related Hypertension

Central (abdominal) obesity
Insulin resistance (hyperinsulinemia)
↑ Leptin levels
↑ Sympathetic nervous system (SNS) activity
Insulin
Leptin
↑ Renin-angiotensin-aldosterone system activity
SNS stimulation of renin release
↑ Angiotensinogen from intra-abdominal adipocytes
↑ Aldosterone production (in excess of angiotensin stimulation)
Salt sensitivity (↑ renal sodium reabsorption)
SNS
Insulin
Angiotensin (all)
Aldosterone
Intra-renal blood flow redistribution

The Pathophysiology of Obesity-Related Hypertension

The association of obesity and hypertension has been recognized since the beginning of the 20th century, when BP was first measured in populations (Table I) (3). This relationship between body weight and BP was demonstrated prospectively in the Framingham Heart Study in the 1960s (4). The nature of the linkage between BP and body weight remained obscure until the mid-1980s when basic clinical and population-based research significantly clarified many aspects of the relationship between these two common and complex regulatory disturbances. Appreciation of the clinical significance of obesity-related hypertension has grown substantially over this same time period, to the point where obesity is recognized as a major cause of high BP, and the combination of obesity and hypertension is recognized as a pre-eminent cause of CV risk.

Until the 1980s there was no cogent explanation for the documented association between weight and BP. Trivial attributions, such as small cuff/large arm artifact, or excessive salt intake, have been excluded as a cause for this association. Similarly, a purely hemodynamic explanation, based on increased plasma volume and increased cardiac output, are not sufficient explanations since the latter do not account for the increase in peripheral resistance noted in obese hypertensive patients when compared with normotensive obese patients. Clues to the basic mechanisms involved in the link between obesity and hypertension first appeared in the 1940s and 1950s with the important observations by Vague (5). Based on observations made in his own obesity practice, Vague noted that the CV and metabolic complications of obesity were more common in patients with the upper body obesity phenotype, which he called “android,” as compared with lower body obesity, which he referred to as “gynoid.” These prescient observations attracted little attention until the 1980s when population-based studies in Scandinavia, using waist to hip ratio as a quantifiable surrogate for the upper body phenotype, demonstrated significant CV risk (hypertension, myocardial infarction, and type 2 diabetes mellitus) in association with a high waist to hip ratio (6-8). Parallel lines of research showed that insulin resistance was also associated with the upper body phenotype (9-11), and many subsequent clinical and population-based studies showed an association of insulin levels and/or insulin resistance with hypertension in both obese and nonobese people (12,13). Thus, insulin

hypertension; and the android or central obesity phenotype tracked together in population-based and clinical studies. These observations formed the basis for our current understanding of the pathophysiology of obesity-related hypertension (14). Pathogenetic factors are reviewed here since they provide the basis for a rational therapeutic strategy.

Insulin and Sympathetic Activity

The relationship of insulin to BP, although controversial at first, has a plausible explanation, and insulin is now generally acknowledged to play a role in the pathophysiology of obesity-related hypertension (15). Since insulin stimulates the sympathetic nervous system (SNS) (16,17), and since obese patients have increased SNS activity, (18-20) a role for insulin-mediated SNS stimulation seems a likely factor in the pathogenesis of high BP in the setting of central obesity. This is supported by studies demonstrating concomitant decreases in BP and SNS activity when insulin is lowered by low energy diets in obese patients (21) Insulin also has a direct action on the kidney to stimulate sodium retention (22).

Leptin and the SNS

Leptin, the polypeptide product of the *ob/ob* gene, is produced in adipocytes and secreted into plasma where the circulating concentration reflects the fat mass of the individual (23). Leptin is a potent appetite suppressant and, like insulin, stimulates the SNS (24,25). Although leptin deficiency causes severe obesity in animals and humans, all but a vanishingly small minority of obese humans have elevated leptin levels (23,26). When infused into animals, leptin raises the BP (27), stimulates the SNS, (28) and has been shown to correlate with BP, in at least some human populations (29,30). Both insulin-mediated and leptin-mediated SNS activation may be viewed as mechanisms recruited in obese patients to stabilize weight and restore energy balance by stimulating sympathetically mediated thermogenesis with consequent enhancement of energy output (15,31).

Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is activated in obesity (32-36). Aldosterone levels may be increased out of proportion to the increase in renin activity (33). Several mechanisms have been thought to underlie RAAS activation, including SNS stimulation of renin release (33) with the generation of angiotensin II; angiotensinogen production in adipose tissue, especially intraabdominal adipocytes (34,35) with the generation of angiotensin II and aldosterone; and effects of free fatty acids, along with other poorly defined factors, on aldosterone production and release (33)

Sodium Excretion, Pressure Natriuresis, and Salt Sensitivity

Obesity predisposes the kidney to reabsorb sodium by neural (SNS), hormonal (aldosterone and insulin), and renovascular (angiotensin II) mechanisms (37). This enhanced sodium avidity shifts the pressure natriuresis curve to the right (38), thereby necessitating higher arterial pressure to excrete the day's salt intake and maintain sodium balance and volume homeostasis. This is the basis for the documented salt sensitivity of obesity-related hypertension (39) and underlines the need for diuretics in the therapeutic regimen.

Other Potential Mechanisms

Other factors that may be implicated in the pathophysiology of obesity-related hypertension include a decrease in natriuretic peptides (33,34)

with consequent impairment in salt excretion; a decrease in adiponectin; (40) obstructive sleep apnea, which stimulates the SNS (41-44); low birth weight, which is associated with excessive weight gain in childhood and adolescence, along with increased risk of hypertension and stimulation of the SNS (45-47) in adulthood; and endothelial dysfunction (48) with consequent blunting of physiological vasodilation (49).

Implications for Therapy

The goal of therapy is to address the CV risk factors attendant upon obesity-related hypertension. This involves lifestyle changes, pharmaceutical agents, and sometimes surgery. Treatment should address the underlying pathophysiology and modify the surrogate markers and risk factors for CV disease (CVD) toward desirable levels in the apparently justifiable belief that this will translate into decreased CV morbidity and mortality.

Epidemiology of Obesity-Related Hypertension and CV Risk

Data from recent US National Health and Nutrition Examination Surveys (NHANES) from 2005 to 2008 indicate that the prevalence of hypertension among adults 18 years older in the United States was 30.9%, or nearly 1 in 3 adults. In the context of the entire population, more than 76 million US adults are estimated to have hypertension (50). At the same time, nearly 70% of American adults are overweight or obese (51). Given the important pathophysiologic links between weight and BP described above, we can expect a significant increase in the prevalence of hypertension in coming years if trends of increasing weight in the population are not stabilized and reversed.

Epidemiological data unequivocally support the link between body weight and BP. Indeed, greater body weight is one of the major risk factors for high BP. Recent data from NHANES indicate that the prevalence of hypertension among obese individuals, with a BMI ≥ 30 kg/m² (2, is 42.5% compared with 27.8% for overweight individuals (BMI 25.0-29.9 kg/m²) and 15.3% for those with BMI < 25 kg/m² (52).

Likewise, higher BMI is also associated with increased risk for development of hypertension over time. Data from the long-standing Framingham Heart Study revealed that compared with normal weight adult men and women, the multivariable-adjusted relative risks for development of hypertension in long-term follow-up were 1.48 and 1.70 for overweight men and women and 2.23 and 2.63 for obese men and women, respectively (53). With the current obesity epidemic extending into its third decade, prevalence rates of hypertension, which had been falling in the 1970s and 1980s, are again rising.

Numerous studies have also demonstrated the important role of *weight gain* in BP elevation and of *weight reduction* in BP lowering. As a general rule, in Western societies, systolic BP (SBP) and diastolic BP (DBP) tend to rise with age beginning at around age 25 in most adults (54,55). This is a “normative” process of aging, but it may not be inevitable or “normal.” In fact, recent data suggest that these “age-related” increases in SBP and DBP may be avoided in young adults who maintain stable BMI during long-term follow-up into middle age. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, young adults (mean age 25 years at baseline) who maintained a stable BMI (within 2 kg/m² of baseline) at 6 examinations during 15 years had no significant changes in

SBP or DBP, whereas those who had an increase in their BMI ≥ 2 kg/m² had substantial increases in BP (56). For example, women who maintained stable BMI in this study had nonsignificant declines in SBP, whereas women whose BMI increased had statistically significant average increases in SBP of 9.8 mm Hg to 12.5 mm Hg. Of note, this weight gain was more important than the baseline weight, since the same patterns were observed for those who were at normal weight or overweight at baseline. Hence, age-related changes in BP may not be inevitable, and may be caused more by age-related weight gain than aging per se. These data have important implications for healthcare and public health, since weight maintenance may be a strategy that is easier to achieve than substantial weight loss for preventing or controlling hypertension (56).

The influence of weight gain on BP and the benefits of maintaining stable weight or losing weight extend down even to young children. One large birth cohort study of children examined BMI at ages 5 and 14 and the association with SBP and DBP at age 14. Children who were overweight at age 5 but had normal BMI at age 14 had similar mean SBP and DBP to those who had a normal BMI at both time points. Conversely, children who were overweight at both ages or who had a normal BMI at age 5 and were overweight at age 14 had higher SBP and DBP at age 14 than those who had a normal BMI at both ages, even after adjustment for potential confounders (57).

Risks Associated With Hypertension

Hypertension is a complex phenotype that arises from numerous genetic, environmental, behavioral, and even social origins. As discussed above, obesity is one of the most prevalent risk factors for its development. Regardless of its etiology, however, hypertension is a highly prevalent and highly significant risk factor for the development of all manifestations of CVD, including coronary heart disease (CHD), stroke, heart failure (HF), aortic and peripheral arterial disease, and valvular heart disease.

CVD Risk Across the Spectrum of BP

Individuals with hypertension, currently defined as untreated SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or use of therapy for elevated BP, have a 2- to 3-fold increased risk for all CVD events combined compared with nonhypertensive individuals. When CVD endpoints are considered individually, *relative* risks with hypertension are greatest for stroke and HF, and somewhat lower for CHD. Nonetheless, because overall absolute CHD incidence is greater than incidence of stroke and HF, the *absolute* impact of hypertension on CHD is greater than for other manifestations of CVD. Although much of the focus on CVD risk has been on frank hypertension, it is clear that risks for CVD increase at higher BP levels, even within the so-called normal range. A recent epidemiologic pooling study of nearly 1 million men and women, which included data on more than 56,000 decedents, revealed that risk for CVD death increases in a continuous fashion at SBP levels starting as low as 115 mm Hg and DBP 75 mm Hg, as discussed in detail below (58).

Other studies provide confirmation of these findings. Data from more than 347,000 middle-aged men (35 to 57 years) screened for the Multiple Risk Factor Intervention Trial (MRFIT) provide precise estimates of incremental risks with higher BP levels. There is a continuous, graded effect of BP on the multivariable-adjusted relative risk for CHD mortality beginning at pressures well below 140 mm Hg (59,60). Although *relative* risks were clearly highest for men with SBP ≥ 180 mm Hg, these data help make an important point about BP levels in the population of which the majority of CVD events are

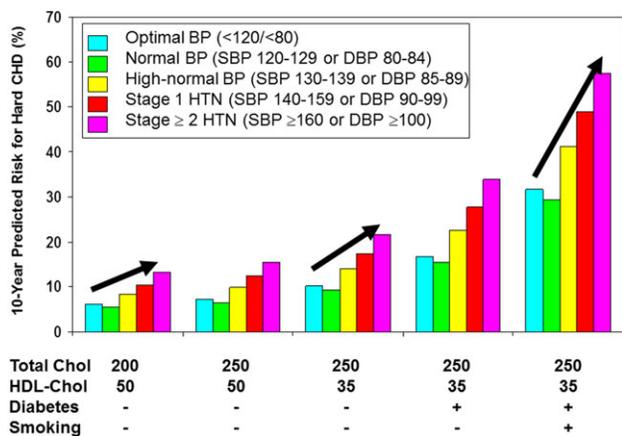


FIGURE 1 Predicted 10-year risk for hard coronary heart disease events for a 50-year-old man with selected levels of risk factors and blood pressure (BP) stages. Note that risk increases dramatically with greater risk factor burden and with higher BP level at any given risk factor burden. The increase in risk across BP strata is more pronounced when other risk factors are at more adverse levels. Data calculated from reference.63 SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; HDL, high-density lipoprotein; CHD, coronary heart disease; Chol, cholesterol.

occurring. Because the majority of the population had lower BP levels, this is where most of the events occurred. Thus, nearly two thirds of excess CHD deaths occurred in men with baseline SBP between 130 and 159 mm Hg, relatively “mild” levels of elevated BP.

For many CVD endpoints, there is effect-modification by sex, with hypertensive men being at higher absolute risk for CVD events than hypertensive women. HF is a notable exception to this generalization. There is also substantial effect-modification by age, with older hypertensive patients being at similar or higher relative risk but much greater absolute risk than younger patients (61). Hypertension rarely occurs in isolation, (62) and it confers increased risk for CVD across the spectrum of overall risk factor burden, with increasing importance in the setting of other risk factors. As shown in Figure 1, absolute levels of predicted hard CHD risk (including CHD death or nonfatal myocardial infarction) increase substantially with increasing risk factor burden, and risk is augmented still further by increases in BP levels from optimal to marked hypertension in men and similarly for women (63). Thus, BP levels, and the risk they confer, must always be considered in the context of other risk factors and the patient’s global risk for CVD.

BP and CHD

Elevated BP is one of the major risk factors contributing to the estimated 1.4 million CHD events that occur in the United States annually (51). Numerous studies have documented the graded and continuous risk for CHD endpoints associated with higher BP levels. Risk for CHD mortality is not limited to patients with frank hypertension, however. There is a linear, graded risk for CHD death that extends down even to optimal levels of BP. The Prospective Studies Collaboration observed that beginning at 115 mm Hg, the risk for CHD death doubles for each increase of 20 mm Hg in SBP. Similarly, CHD death risk doubles for each increase of 10 mm Hg in DBP beginning at 75 mm Hg (58).

BP and Stroke

Hypertension is well established as the dominant risk factor in contributing to the 700,000 strokes that occur each year in the United

States (51), even when considered in the context of other known risk factors, such as cigarette smoking, atrial fibrillation, myocardial infarction, and diabetes. Hypertension confers a threefold relative risk for stroke compared with BP levels <140/<90 mm Hg, and approximately 80% of individuals who experience a stroke have antecedent hypertension. The population-attributable risk (PAR) for stroke associated with hypertension varies between 33% and 53% in different age groups, suggesting that this proportion of strokes would be avoided if hypertension were not present (64). In adults aged 55 in the Framingham Heart Study, the lifetime risk for stroke was >1 in 6, but it was twice as high among those with hypertension compared with those who had BP <120/<80 mm Hg (65).

As is true for CHD risk prediction, a risk prediction algorithm has been developed to estimate the absolute 10-year risk of an atherothrombotic brain infarct using standard CVD risk factors plus the presence of atrial fibrillation, HF, and coronary disease. In these equations, hypertension represents the predominant risk factor for stroke, but the risk in people with elevated BP varies over as much as a 10-fold range depending on the degree of exposure to the other risk factors (66).

Just as with CHD, risk for stroke is not limited to patients with frank hypertension. There is a linear, graded risk for stroke that extends down even to optimal levels of BP. Beginning at 115 mm Hg, the risk for stroke mortality doubles for each increase of 20 mm Hg in SBP. Likewise, stroke mortality risk doubles for each increase of 10 mm Hg in DBP beginning at 75 mm Hg (58). Thus, at any given age, an individual with SBP of 135 mm Hg is at approximately twice the risk and one with SBP of 155 mm Hg is at four times the risk as someone at the same age with an SBP of 115 mm Hg.

BP and HF

With the aging of the population, the concomitant increase in the prevalence of hypertension, and improved survival after myocardial infarction, HF has become an emerging public health concern. National surveillance data indicate that approximately 5.7 million Americans are living with HF currently, with 670,000 incident cases each year. HF is the leading cause of hospitalization for people 65 years and older in the United States, with 990,000 hospital discharges in 2007 (51).

As with stroke, hypertension is also the dominant risk factor for HF. The overall remaining lifetime risk for HF is 1 in 5 for men and women 40 years and older, but at every age there is a stepwise increase in lifetime risk for HF with increasing BP, with approximately a twofold higher risk in patients with stage 2 or treated hypertension compared with those with BP <140/<90 mm Hg (67). From 75% to 91% of individuals who develop HF have antecedent hypertension (51,68). The PAR for hypertension in HF, ie, the fraction of HF in this population that would not occur in the absence of hypertension, was 59% in women and 39% in men. By contrast, the PARs for myocardial infarction were 13% and 34% for women and men, respectively (68).

BP and Renal Disease

Hypertension is also a major risk factor for the development of renal disease. African Americans have approximately four times the risk of whites of developing end-stage renal disease (ESRD), in part due to their significantly higher prevalence of hypertension (51). Data from a large insured population of 316,675 adults with a normal glomerular filtration rate (>60 mL/min/1.73 m²) and no evidence of

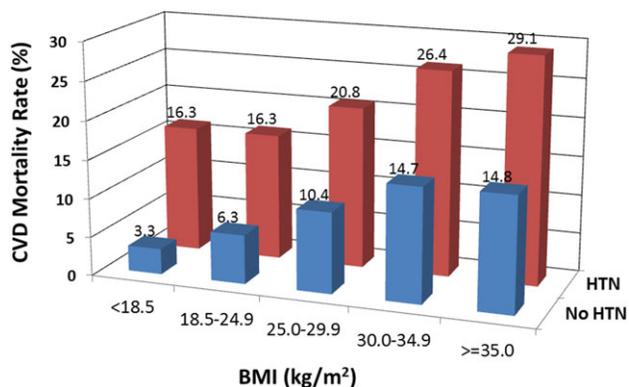


FIGURE 2 Thirty-two year rates of death due to cardiovascular disease in participants of the Chicago Heart Association Detection Project in Industry cohort, stratified by baseline body mass index (BMI) and hypertension (HTN) status. CVD indicates cardiovascular disease.

proteinuria or hematuria at baseline, risks for ESRD increased dramatically with higher baseline BP level. Individuals with hypertension were 2.5 to more than 4 times as likely to develop ESRD, depending on the severity of their hypertension, even after adjustment for other factors (69). In addition to its contribution to ESRD, elevated BP also occurs in and exacerbates milder forms of chronic kidney disease and worsens proteinuria. Data from the same population indicate that, compared with patients with lean body mass, risk for ESRD was higher with greater baseline weight, with adjusted relative risks of 1.87, 3.57, 6.12, and 7.07 for those with BMI in the overweight, class I (BMI 30-34.9), class II (BMI 35-39.9), and class III (BMI >40) obesity ranges, respectively (70). Thus, greater baseline weight is also associated with a markedly increased risk for incident ESRD, both through its association with hypertension and independent of this association.

Joint Effects of Obesity and Hypertension on CVD Risk

The association of hypertension with CV risk in the short- and long-term is thus unequivocally established. The association of obesity with short-term CVD event rates (eg, in the next 10 years) is more difficult to establish, largely because the major effects of obesity appear to act through more proximal risk factors such as diabetes, dyslipidemia, and hypertension. However, longer-term studies of obesity and CVD do indicate risk for CVD associated with obesity independent of these other risk factors. In addition, several lines of evidence data suggest that obesity and hypertension may have additive effects in increasing risk for CVD over long-term follow-up.

Data from the long-standing Chicago Heart Association Detection Project in Industry (71), which enrolled more than 38,000 individuals from 1967 to 1973, serve as an example to highlight these joint risks. As shown in Figure 2, 32-year CVD death rates were higher (and increased in a stepwise fashion) for patients with higher BMI at baseline and no hypertension. For those with hypertension at baseline, CVD death rates were substantially higher overall, and increased in a stepwise fashion for patients with higher baseline BMI levels. A similar pattern of results was observed for individual outcomes of CHD death and stroke death rates, as well as for hospitalizations for CHD, stroke, and HF during follow-up using Medicare data.

Clinically Relevant Risk Assessment

Given the above data on the prevalence, risks, and sequelae of hypertension and the likelihood that hypertension will be clustered with obesity and other major CVD risk factors (the metabolic syndrome), it is imperative that patients with hypertension be identified and appropriately managed. Risk assessment for individuals with hypertension should take into account global CVD risk based on the presence and severity of these other risk factors. Widely available multivariable risk equations, such as the Framingham CVD risk score or the Reynolds risk score, are means for assessing such risk and identifying individuals who may benefit from more intensive preventive therapy and efforts at lifestyle modification. Adjunctive therapy beyond antihypertensive therapy must be considered, especially in light of clinical trial results indicating significant and substantial reductions in risk for CVD events in treated hypertensive patients with fairly average levels of low-density lipoprotein (LDL) cholesterol who were randomized to low-dose statin medication (72). Likewise, the benefits of adjunctive low-dose aspirin therapy for CVD risk reduction clearly appear to outweigh the potential risks when specifically targeted to hypertensive patients (73).

Impact of Obesity on Diabetes and CV Risk

An additional important factor in the CV risk associated with obesity and hypertension is the role played by obesity in the development of type 2 diabetes. Obesity, and particularly central adiposity, is the dominant risk factor for the development of type 2 diabetes, which routinely clusters with hypertension because of common underlying pathophysiology. Diabetes exerts a substantial independent and amplifying effect on the CV risks associated with both obesity and hypertension (74,75). Efforts aimed at diminishing the incidence and impact of diabetes, therefore, including both lifestyle changes and the appropriate use of antihypertensive and anti-obesity therapies, are an essential part of the overall therapeutic plan.

The Metabolic Syndrome

Obesity-related hypertension frequently occurs in association with other CV risk factors, forming a constellation referred to as the metabolic syndrome (Table II) (76). Although the concept of a metabolic syndrome has achieved widespread acceptance over the past 2 decades, no consensus has developed over the precise definition of

TABLE II Metabolic Syndrome

Many sets of diagnostic criteria
Critical components
Hypertension
Central obesity
Insulin resistance (hyperinsulinemia)
Characteristic dyslipidemia
High triglycerides
Low high-density lipoprotein cholesterol
Other associations
Impaired glucose tolerance; type2 diabetes mellitus
Microalbuminuria; chronic renal disease
Prothrombotic diathesis
Small dense low-density lipoprotein
↑ Inflammatory markers

the syndrome, nor over the criteria required to establish the diagnosis. No less than five sets of diagnostic criteria have been proposed by different international and national panels including the International Diabetes Federation (IDF), the World Health Organization (WHO), and the US National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), among others (77). The differences in criteria, although small and overlapping, point to the imprecision in defining the metabolic syndrome, and to the differences in the perceived importance of the various manifestations. Using the NCEP-ATP III criteria and the NHANES III survey it has been estimated that about 30% of the US population has the metabolic syndrome (78). The prevalence increases with age so that by 60 years, more than 40% of people meet criteria for the diagnosis.

Critical Components

The four fundamental components of the metabolic syndrome are central obesity, insulin resistance, hypertension, and a characteristic dyslipidemia (high triglycerides and low high-density lipoprotein cholesterol). Reaven has identified the importance of insulin resistance as a critical component of the syndrome, which he originally designated “syndrome x” and which was also called the “insulin resistance syndrome,” although these earlier designations have given way to the term metabolic syndrome (14,77). Central or android obesity is the usual although not the exclusive cause of the insulin resistance. Insulin resistance and the consequent hyperinsulinemia drive the hypertension (as described above) and the dyslipidemia (stimulation of hepatic very LDL production).

Other Associated Features

In addition to the four principal components, a variety of other abnormalities have been associated with the metabolic syndrome, including type 2 diabetes mellitus, impaired glucose tolerance, renal functional impairment and microalbuminuria, hyperuricemia, prothrombotic coagulation diatheses, small dense LDL cholesterol, and markers of inflammation (79). All of these abnormalities have been associated with increased CV risk.

Additional Pathogenetic Factors

Although abdominal obesity and insulin resistance are the major threads that connect the various features of the metabolic syndrome, two other factors of potential importance should be mentioned: dietary fructose and disordered sleep. The consumption of high fructose corn syrup has increased dramatically in the past 3 decades, paralleling the increase in obesity and hypertension. Sweetened beverages, such as non-diet soda, account for 70% of the intake of high fructose corn syrup (80,81), and recent evidence suggests a link between sweetened sodas, hyperuricemia, and the manifestations of the metabolic syndrome (82,83).

Another recently described factor that may contribute to the development of the metabolic syndrome is shortened or interrupted sleep. Obstructive sleep apnea, a well-recognized complication of obesity, is associated with increased SNS activity, which persists during daytime wakefulness (42,43). The SNS overactivity is associated with hypertension. Both the SNS stimulation and the hypertension are reversed with effective treatment of the sleep apnea. Sleep debt, a consequence of shortened or disordered sleep, or night shift work, is also associated with obesity, insulin resistance, and hypertension,

TABLE III Lifestyle Management of Obesity-Related Hypertension

Weight loss
Dietary Approaches to Stop Hypertension (DASH) diet
Salt restriction
↑ Physical activity; exercise
Alcohol moderation
Behavioral modification

raising the possibility that disturbances of normal sleep patterns may play a role in the pathogenesis of the metabolic syndrome (44,84-86). Insufficient sleep may also antagonize weight loss in response to caloric restriction (87).

Is the Metabolic Syndrome a Distinct Entity?

Considerable debate has centered on whether the metabolic syndrome is in fact a discrete entity. Although the abnormalities characteristic of the metabolic syndrome are relatively common in the population at large, there is no doubt that these traits occur together much more commonly than predicted by chance alone. This, however, may reflect the central role of insulin resistance and hyperinsulinemia in the pathogenesis of the different manifestations, rather than a direct linkage of the associated traits. The argument has been advanced, with some merit, that the concept of a metabolic syndrome may alert clinicians to look for associated manifestations when obesity and hypertension coexist and to recognize the CV risk associated with this constellation.

Lifestyle in the Prevention and Management of Obesity and Hypertension

The importance of lifestyle management in the treatment of patients with obesity-related hypertension cannot be overemphasized (Table III). Adoption of a healthy lifestyle facilitates weight loss, increases responsiveness to antihypertensive medications, and produces independent beneficial effects on cardiac risk factors.

Developmental Origins of Obesity-Related Hypertension

The childhood origins of obesity-related hypertension are well illustrated in a study of 260,000 overweight and obese children in Germany and Switzerland, in which 35% had hypertension with increased ventricular mass or arterial stiffness (88). Studies of the Bogalusa childhood cohort who were prehypertensive or mildly hypertensive in adulthood showed that when they were tracked back to as young as 4 to 8 years old, they had higher BPs and were heavier and more insulin resistant than their normotensive counterparts (89). This is in accord with prospective studies showing tracking of adiposity, obesity, and BPs from childhood into adult life. In a recent analysis of four cohort studies followed for a mean of 23 years, overweight or obese children who remained obese as adults had substantially increased risk of hypertension, diabetes, dyslipidemia, and carotid atherosclerosis (90). Importantly, patterns of food consumption and physical activity also track from childhood to adulthood (91).

Stemming from Barker's work, there is substantial evidence for effects of intrauterine growth and early postnatal weight gain on adiposity and high BP (92). These effects are not restricted to low birth weight infants, as shown by the clustering of adiposity and BP along with impaired glucose tolerance and dyslipidemia in 8- and 14-year-olds born from the lowest and highest birth weight quintiles (93,94). Excessive postnatal weight gain in early childhood dominated over effects of birth weight, (94) especially in children of mothers who smoked in pregnancy or did not breastfeed (94). In the same Australian cohort, the trajectories for adolescent obesity were well established by the age of 5 (95). For all of these reasons, a consensus is developing that it may be necessary to tackle lifestyle-induced obesity-related hypertension at its source: in infancy and early childhood and in the parents.

Evidence that Childhood Obesity can be Prevented or Modified at a Population Level

There is an increasing number of randomized controlled trials attempting to modify childhood obesity in populations rather than in clinic settings. Most of these have been school-based. Few have also examined effects of the programs on BP. An extensive Cochrane review of lifestyle interventions to prevent obesity in childhood included 55 studies. A meta-analysis of 37 of these involved 27,946 children, of whom the majority were aged 6 to 12 years (96). The authors concluded that the "programs overall were effective at reducing adiposity, although not all individual interventions were effective, and there was a high level of observed heterogeneity and possible bias." Moreover, the effect was relatively small with children in the intervention group "showing a small standardized mean difference in adiposity (measured as BMI or zBMI) of -0.15 kg/m." Given the unexplained heterogeneity and the likelihood of small study bias, however, these findings must be interpreted cautiously. The authors were unable to distinguish which of the program components contributed to the beneficial effects and suggested that "childhood obesity prevention research must now move towards identifying how effective intervention components can be embedded within health, education and care systems and achieve long term sustainable impacts."

None of the above studies reported effects on BP or CV risk phenotypes other than obesity. However, two large randomized controlled trials of effects of home- and school-based nutrition and physical activity programs on CV risk factors have been reported from Australia. The first 1147 10- to 12-year-olds from 30 schools found improved BP, a reduction in fatness, and improved physical fitness (97). Decline in SBP was significantly greater with a fitness intervention for the boys and with a home nutrition intervention for the girls. The greatest improvements overall were with the combined fitness and home nutrition program.

The second study used cluster analysis to identify 29% of 800 11-year-old children at increased CV/metabolic risk. The children in both high- and low-risk clusters were then randomized to two semesters of family nutrition and school-based physical activity programs (98). High-risk children responded better in terms of fatness, fitness, nutrition, and blood cholesterol than did low-risk children. Boys responded better than the girls during the program but effects were more sustained after a further 6 months in girls.

The lifestyle factors contributing to the rising epidemic of obesity, and hence obesity-related hypertension, are embedded in changes in

society worldwide: increased sedentariness from the car, television, and computers; parental protectiveness in seemingly hostile urban environments; and increased consumption of calorie-rich foods in the form of soft drinks, fast foods, and sugar-enriched low-fat dairy products. Clustering of unhealthy behaviors in obese children, such as poor nutritional habits, high salt consumption, low levels of physical activity, and smoking and alcohol consumption (by adolescence) (99) dictate the need for multifaceted national-, school-, and family-based programs to tackle global CV risk at an early stage. Many such programs are underway worldwide, and are addressing issues relating to infancy (100), childhood (101), parents (102) and the community (103), and through international networks (104).

Prevention of Weight Gain and Hypertension

Lifestyle changes tend not to occur in isolation. Those who are obese tend to show clustering of behaviors predisposing to higher BP including not only disturbed energy balance but less healthy diets with higher salt intake, less fruit and vegetable intake, less low-fat dairy products and increased saturated fat intake (99,105), sedentary behaviors, and in many communities high alcohol consumption. These prohypertensive behaviors add to the effects of obesity per se. In industrialized communities, low socioeconomic status is a further factor predisposing to obesity (106), while in developing nations, rising urbanization and westernization with fast-food patterns and decreased physical activity create obesogenic environments (107)

Long-term weight gain is insidious, arising from the cumulative effect of excess intake, which may be as little as 50 to 100 kcal/d (108) In a longitudinal analysis, (105) weight gain in US adults was positively associated with small changes that included increased consumption of sugars, starches, refined grains, and processed foods as well as increased alcohol intake, time spent watching television, and decreased physical activity; weight change related inversely to consumption of fruit and vegetables, whole grains, nuts, and yogurt. These authors suggest that the small daily changes associated with weight gain could be prevented by small changes in lifestyle adhered to in the long-term. Long-term behavior change, however, will need recognition of effective strategies from population studies and clinical trials as well as the cooperation of governments and industry (109). Effects of low socioeconomic status and ethnic differences, with greater predisposition to obesity and hypertension in blacks and obesity in Hispanics, will need particular attention (106,110).

Lifestyle Changes in the Management of Obesity-Related Hypertension

Systematic reviews consistently report a decrease in SBP of about 1 mm Hg per kg of weight loss with follow-up of 2 to 3 years (111-114). There is attenuation in the longer-term, with a decrease of about 6 mm Hg in SBP per 10 kg of weight loss (112). Intervention programs appropriate for obesity-hypertension combine diet, physical activity, and behavioral modification and aim to achieve long-term change in health-related behaviors.

Choice of Weight-Reducing Diet

In the short-term, many variations on reduced-energy diets can achieve weight loss. Diets include very low calorie, balanced deficit (reduction in protein, fat, and carbohydrates), changes in a specific nutrient (low fat, low carbohydrate, low glycemic index, high protein), and those popularized through publications or commercial

weight-reduction plans (115,116). Meta-analyses and systematic reviews that compare these various dietary approaches do not favor a specific diet for weight reduction (117,118).

The DASH Diet

In management of obesity-related hypertension, a palatable diet rich in components that may lower BP and low in salt is supported by clinical trials (119). Such information has been incorporated in the Dietary Approaches to Stop Hypertension (DASH) diet (120) for management of BP, endorsed by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) (121). This approach focuses on a “prudent diet” rather than the effects of specific nutrients. Appropriate diets for the management of obesity-related hypertension are rich in potassium, calcium and magnesium, and fiber and low in salt and saturated fat. In terms of foods, these diets promote consumption of vegetables, fruits, low-fat dairy products, whole grains, nuts, poultry, and fish and discourage salt, red meats, sweet foods, and sugary drinks. Mediterranean (122) and lactoovovegetarian (123) diets are also associated with benefits in relation to CV risk, weight control, and BP, but vegetarian diets are not widely acceptable.

In US adults, long-term weight gain was related to foods that are discouraged in a prudent diet, while foods promoted in a DASH-type diet were associated with better weight control (105). It is important, then, to consider diets for weight management in obesity-hypertension in a wider context than energy restriction to ensure an adequate content of foods that may ameliorate BP (119).

Several trials have shown early but not sustained benefits of combining DASH-type diets with other modification of lifestyle (124-128). One study (129) found significant differences between white, African American, Chinese, and Hispanic groups in conforming to a DASH diet assessed in the Multi-Ethnic Study of Atherosclerosis (MESA), indicating that responses may improve if ethnicity is taken into account in delivery of lifestyle programs that include DASH guidelines.

The Arthritis, Diet, and Activity Promotion Trial (ADAPT) (130) included a 3-year follow-up evaluation of a behaviorally based, multifactorial lifestyle program compared with usual care in overweight or obese individuals being treated with not more than two antihypertensive drugs. The 4-month intervention promoted weight loss using a low-sodium DASH-style diet (131) with the inclusion of at least four fish meals weekly, moderate-intensity physical activity with increased incidental activity, not more than two standard alcoholic drinks daily, and quitting smoking. In the intervention group, weight loss and reduction in waist girth were significantly greater with the intervention after 4 months and 1 year, but decrease in BP was greater only at 4 months. Improvements in diet, notably in fat, sodium, fish, and vegetables, persisted to 1 year in the intervention group. Two years later, physical activity was greater in the intervention group and some dietary improvements were maintained, but with no significant between-group difference in weight change or BP.

Low-Salt Diets

Salt sensitivity is commonly associated with obesity (132). Salt restriction decreases the risk of hypertension with or without weight loss as well as reducing the incidence of CV events (133). In the Hypertension Prevention Trial, (134) participants with DBP 78 to 89 mm Hg

were followed for 3 years after being randomized to one of five groups: control, decreased energy intake, decreased sodium intake, decreased sodium and energy intake, or decreased sodium and increased potassium intake. BP decreased in all groups, with the greatest decrease in patients assigned to reduced energy only. The groups with reduced sodium intake had a significantly lower rate of hypertension.

In the Trials of Hypertension Prevention (TOHP) phase I study, (135) participants with high normal BP were randomized to one of four groups for 18 months: control, weight loss, sodium restriction, or stress management. In the weight reduction group, weight decreased by 3.9 kg and BP by 2.9/2.3 mm Hg. Sodium restriction resulted in a decrease in BP of 1.7/2.9 mm Hg. Seven years later, the odds ratio for hypertension among 181 participants was lower by 77% with weight loss and 35% with sodium restriction.

Phase II of TOHP examined the effects of weight loss, sodium restriction, or both on BP and the incidence of hypertension (136) (137). At 6, 18, and 36 months, weight loss favored the weight reduction intervention over usual care, although weight loss was attenuated over time, and change in BP showed a similar pattern. In the sodium reduction group, a decrease in BP was greater at each time point and also became attenuated with time, from 5.1/4.4 mm Hg at 6 months to 0.7/3.0 mm Hg at 3 years.

The Trial of Nonpharmacologic Interventions in the Elderly (TONE) study (138) investigated weight loss and salt restriction and the need for antihypertensive drugs in treated hypertensive patients during follow-up to a median of 29 months. Weight reduction, sodium restriction, and the combination of both were compared with usual care in obese participants. The relative hazard ratio was 0.60 for reduced sodium alone, 0.64 for weight loss alone, and 0.47 for the combined intervention. The within-groups rate of adverse events was similar.

Physical Activity

Aerobic exercise can reduce weight and BP, but when exercise is the only intervention, weight losses are small, with an estimated change of 1.6 kg in moderate-intensity programs continued for 6 to 12 months (124,139,140). In a meta-analysis that included assessment of ambulatory BP (141) it was reported that in studies lasting 4 to 52 weeks, with physical activity as the only intervention, aerobic exercise reduced BP by 3/2.4 mm Hg. The change affected daytime (3.3/3.5 mm Hg) but not nighttime (0.6/1.0 mm Hg) BP. The effect on BP was independent of the estimated weight loss of 1.2 kg. However, when aerobic exercise is combined with calorie restriction for weight control, the effects on ambulatory BP can be substantial (142).

A few studies (141) also examined the effects of resistance training on BP. The estimated decrease in BP (3.2/3.5 mm Hg) was similar to the effects of aerobic exercise, although not statistically significant for SBP and without statistically significant weight change. A more recent meta-analysis (143) found that resistance training of at least 4 weeks resulted in an estimated decrease of 3.9/3.9 mm Hg in normotensive or prehypertensive individuals, but a decrease of 4.1/1.5 mm Hg in hypertensive patients was not statistically significant. The place of resistance training in programs for management of hypertension is not established.

Comparison of high- and low-intensity exercise programs with 3.5- to 12-month follow-up favored the higher-intensity programs with a difference in weight loss of about 1.5 kg (144). Higher levels of activity may be difficult to maintain in the long-term (145), although (146) the maintenance of 10% weight loss for 2 years in women whose activity increased by 275 minutes per week from baseline values has been reported. Physical activity encourages maintenance of weight loss and offers additional benefits in improving CV risk factors (146).

A systematic review of longitudinal studies of sedentary behaviors in adults found insufficient evidence for an association between sedentary behaviors and measures of adiposity or CV risk factors, including self-reported hypertension (147), but there was moderate evidence for an association with type 2 diabetes and strong evidence for an association with all-cause and CVD mortality. However, longitudinal analysis of data from US adults (105) showed that an increase in time spent in watching television predicted weight gain, possibly mediated by lack of physical activity, adverse food choices, and eating snacks while watching TV. While there is some variation in the relationships identified, evidence points to the need to incorporate measures to modify sedentary behavior in lifestyle intervention programs.

Alcohol

The pressor effect of alcohol has been established in clinical trials, with an estimated increase in SBP of 1 mm per 10 g of alcohol (148). Paradoxically, drinking alcohol at low to moderate levels is associated with lower risk of atherosclerotic disease (149). Alcohol provides 29 kJ/g and, although weight gain from excess intake might be expected, meta-analysis has not shown a consistent relationship between alcohol and weight gain (150). In US adults, however, increased alcohol intake was associated with greater long-term weight gain (105). Moderation of heavier daily alcohol intake to no more than one standard drink in women and two standard drinks in men appears prudent (119), with potential benefits for both weight gain and BP. In a factorial trial of independent and combined effects of alcohol moderation and weight reduction in overweight and obese hypertensive drinkers, effects on BP were additive over a 3-month period, with the combined modalities achieving a 14/9 mm Hg BP reduction compared with controls who maintained usual weight and drinking habits (151).

Smoking

Although smokers tend to have lower body weight, they may gain weight because of clustering of adverse health behaviors (152). Smoking increases BP acutely, with an associated rise in arterial stiffness that lasts longer in hypertensive men (153). There is an important window of opportunity for lifestyle programs to prevent the weight gain (and BP rise) often seen with smoking cessation (105).

Behavioral Modification Techniques

Behavioral modification techniques are considered an essential part of programs to achieve and maintain weight loss (154). Social and professional support, goal-setting, self-monitoring, stimulus control, changing the environment and problem solving, daily self-weighing, and prevention of relapse are strategies that have had some success in improving adherence to weight loss programs (154-156). In the Weight Loss Maintenance Randomized Controlled Trial (157), improvement in maintenance at 30 months was associated with

TABLE IV Antihypertensive Agents

Target: $\leq 140/90$
Renin-angiotensin-aldosterone system inhibition
Angiotensin-converting enzyme inhibitors; angiotensin receptor blockers
Diuretics
Low-dose thiazide or thiazide-like agent
Loop diuretics (if required)
Potassium-sparing agents
Avoid β -blockers except for specific cardiac indication
All agents potentiated by weight loss

monthly personal contact with the program staff and regular use of an internet-based intervention (158). Contact by telephone, including text messaging, mail, or e-mail, have been used to maintain contact with staff (155), but rapid changes in technology with availability of, for example, social networking and applications for mobile phones offer new opportunities. At this time, there is no consensus about the most effective behavioral strategies for lifestyle modification, particularly in the long-term. Trials that are in progress (154) may clarify the best options for encouraging the maintenance of lifestyle change that is so critical to weight control.

Long-Term Effects of Lifestyle Interventions on Outcomes

Although limited data are available, a few interventions and meta-analyses report long-term benefits associated with improvements in lifestyle, especially in at-risk populations. In 10- to 15-year follow-up of prehypertensive adults who took part in the TONE studies, the risk of a CV event was lower by 25% to 30% in those who had been assigned to the salt-restricted group (133). In adults at risk for diabetes, a program of diet and physical activity reduced the risk of diabetes by 58%, with size of the decrease related to the extent of change in lifestyle (159). In adults with impaired glucose tolerance, a program of diet and physical activity was more effective for the prevention of diabetes than either metformin or usual care, with respective incidence rates per 100 person-years of 4.8, 7.8, and 11 (160).

Among the more than 100,000 nonsmokers who completed the Cancer Prevention Study II (CPS-II) Nutrition Cohort lifestyle questionnaire in 1992-1993 (161), responses were scored with reference to the American Cancer Society lifestyle guidelines for weight control, physical activity, diet, and alcohol. In a 14-year follow-up, individuals with the highest scores had a significantly lower risk for mortality from all causes, CVD, and cancer than those with low scores.

Meta-analyses have shown reduced morbidity and mortality associated with lifestyle interventions used for secondary prevention (162,163). However, authors stress the need for more high-quality studies of adequate duration (162-164).

Treatment of Hypertension in the Obese BP Thresholds and Targets

According to JNC 7, normal BP is considered a reading of $<120/80$ mm Hg averaged over two or more seated BP readings completed during two or more office visits (Table IV). As hypertension

progresses, the risk of death from ischemic heart disease or stroke (beginning with a normal BP of 115/75 mm Hg) doubles with each increment of 20 mm Hg in SBP or 10 mm Hg in DBP across the entire BP range from 115/75 mm Hg to 185/115 mm Hg. Individuals in the general population with a SBP of 120 to 139 mm Hg or a DBP of 80 to 89 mm Hg are considered prehypertensive and require lifestyle modification to prevent CVD. Patients with prehypertension are at twice the risk of developing hypertension as those with normal BP. Stage 1 hypertension is defined as SBP between 140 and 159 mm Hg or DBP between 90 and 99 mm Hg, and stage 2 hypertension is defined as SBP \geq 160 mm Hg or DBP \geq 100 mm Hg. To reduce the incidence of CV and renal complications, target BPs for the general population should be <140/90 mm Hg and for patients with established diabetes or chronic kidney disease <130/80 mm Hg (121), but there is limited evidence in support of this lower threshold (165).

As in individuals with diabetes and chronic kidney disease, many authorities have recommended lower target BPs for obese individuals. This recommendation is partially due to the constellation of risk factors associated with obesity and the metabolic syndrome, and is also attributed to the fact that hypertension in obese patients has proven more difficult to control than hypertension in the nonobese population. In fact, even modest weight loss increases the likelihood of achieving goal BPs (166). Although logical, there is no strong evidence to support lowering BP much beyond the defined 140/90 mm Hg threshold (165).

Antihypertensive Agents: RAAS Inhibitors

More than 100 medications are available for the direct treatment of hypertension, acting on a variety of systems throughout the body. Although there is no evidence based on longitudinal outcome studies in obese patients, recommendations for the use of specific antihypertensive agents in an obese population have emerged. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), β -blockers, calcium channel blockers (CCBs), and thiazide diuretics are all effective in lowering BP in most obese patients (167). Although lowering BP is of paramount importance, studies suggest that antagonizing the RAAS system has special significance in obese patients (168,169). As noted above, angiotensin is overexpressed in obesity, directly contributing to obesity-related hypertension, making the case to consider ACE inhibitors/ARBs as first-line agents. In comparison to ARBs or ACE inhibitors, β -blocker- and thiazide-based regimens increase insulin resistance and are associated with an increase in new cases of diabetes. In contrast, regimens based on RAAS inhibition are associated with significantly fewer cases of new diabetes (168,170,171). This is of particular importance in the obese population, a group at heightened risk for the development of type 2 diabetes (172). In addition, ACE inhibitors and ARBs have not been associated with weight gain or insulin resistance and provide renal protection in diabetes, a highly prevalent disease among obese persons. The Second Australian National Blood Pressure (ANBP2) trial (173) reported slightly better outcomes in hypertensive white men (average BMI 27.4) treated with a regimen that began with an ACE inhibitor compared with a regimen that began with a diuretic. Calcium channel blockers are also effective in the treatment of obesity-related hypertension and have not been associated with weight gain or adverse changes in lipids (174-176).

Diuretics and β -Blockers

Although thiazide diuretics are often recommended as first-line agents for the treatment of hypertension (177), their known dose-

TABLE V Bariatric Agents

Approved medications
Orlistat (Alli): causes fat malabsorption
Acarbose: causes sucrose malabsorption
Phenteramine (approved for short-term use only)
↓ Appetite
↑ Energy expenditure
Lorcaserin
↓ Appetite
Medications for diabetes that cause weight loss
Metformin (insulin sensitizer that ↓ hepatic glucose output and ↓ glucose absorption)
Incretin-based agents that ↑ insulin and ↓ glucagon secretion
GLP1 agonists: exenatide, ligurptide
DPP-4 inhibitors: sitagliptin; saxagliptin; linagliptin
Pramlintide (amylin congener)
Suppresses appetite: delays gastric emptying; increases satiety
Combination agents
Phentermine/topiramate (Qnexa, Qsymia)
Naltrexone/bupropion (investigational)

related side effects, which include dyslipidemia and insulin resistance, are undesirable in obese populations prone to the metabolic syndrome and type 2 diabetes. This causes a therapeutic dilemma since obesity-related hypertension is salt-sensitive and diuretics will be required to control BP in most cases. Many experts recommend low-dose thiazides (12.5 to 25 mg of hydrochlorothiazide or equivalent agent) along with close lipid and glucose monitoring. If greater diuretic effect is required to control BP, the use of loop diuretics and/or the addition of potassium-sparing agents such as spironolactone, eplerenone, or amiloride should be considered, given the importance of aldosterone in obesity-related hypertension.

β -Blockers have been shown to cause insulin resistance and have been closely associated with weight gain and higher body weights, as well as decreased diet-induced thermogenesis, fat oxidation rate, and weekly habitual activity (178-180). The use of β -blockers should be limited to obese patients with specific CV indications such as post-myocardial infarction and HF. When β -blockers are indicated, agents with a vasodilating component such as carvedilol and nebivolol appear to have less weight gain potential and less of an impact on carbohydrate and lipid metabolism (179,181) Although appropriate in HF, the protective effect of these agents with vasodilator effects post-myocardial infarction has not been definitively established.

Medical Treatment of Obesity in Hypertensive Patients

Lifestyle management is a critical component of the treatment regimen for all obese hypertensive patients (Table V). According to National Institutes of Health guidelines, pharmacotherapy for obesity can be considered if a patient has a BMI \geq 30, or a BMI \geq 27 if weight-related comorbidities, including hypertension, type 2 diabetes, dyslipidemia, and/or obstructive sleep apnea, are present (182) Many therapeutic targets have been recently identified, on both the intake and the expenditure side of the energy balance equation,

thereby providing hope that new agents, with limited off-target effects, may become available in the future.

Inhibition of Nutrient Absorption

On the intake side, targets include nutrient absorption and appetite suppression. Orlistat induces fat malabsorption by inhibiting pancreatic lipase. Acarbose, both an intestinal alpha-glucosidase and pancreatic alpha-amylase inhibitor, blocks the enzymes required to digest complex sugars into absorbable glucose and other monosaccharides. Acarbose has limited use in the United States and Europe in the treatment of diabetes and only a small impact on weight.

Appetite Suppression

Appetite is a critical target for obesity control. Research on the regulation of appetite has identified endogenous systems that both stimulate (orexigenic) and suppress (anorexigenic) food intake, yielding a variety of attractive druggable targets (183,184). Endogenous ligands, such as leptin and serotonin (5HT), work by simultaneously inhibiting the orexigenic centers in the brain and stimulating the anorexigenic pathways. Several appetite suppressants have been associated with significant weight loss in humans but off-target effects have resulted in the withdrawal of these agents. Fenfluramine, a congener of norepinephrine and amphetamine, releases serotonin from neurons in the hypothalamus and was an effective weight loss agent when combined with phentermine (Fen-Phen), but the association with pulmonary hypertension, cardiac valvular lesions, and cardiac fibrosis resembling the fibroelastosis seen in the carcinoid syndrome led to its withdrawal from the market in 1997. Sibutramine, a centrally acting uptake inhibitor of norepinephrine and serotonin, was removed from the market in 2010 because of an increase in CV events. The endocannabinoid antagonist rimonabant, which diminished the intake of high fat and sweet foods, was withdrawn because of an increase in depressive symptoms and suicidal ideation. Accordingly, the search for more effective and safer anorexigenic agents is ongoing. The Food and Drug Administration (FDA) has recently approved lorcaserin (Belviq), a selective 5HT_{2c} receptor agonist, which promotes weight loss through satiety.

Increasing Energy Output

In addition to physical activity, stimulating energy output by increasing thermogenesis has emerged as a potential critical target of anti-obesity therapy. During therapeutic dieting, resting metabolic rate, and therefore energy expenditure, decreases significantly and antagonizes weight loss. Reversing this decrease in metabolic rate would have a substantial effect on weight loss. Recent studies utilizing Fluoro-Deoxy-Glucose positron emission tomographic scans have resuscitated brown adipose tissue (BAT) as a druggable therapeutic target for stimulating energy expenditure by increasing metabolic rate (185). BAT, via SNS activation and a β -receptor cyclase-linked mechanism, uncouples fatty acid oxidation from ATP formation generating heat rather than stored forms of energy. The demonstration of functional BAT in adult humans raises the possibility that β_3 -adrenergic agonists might stimulate energy output; however, none are currently available. Another area of interest is the possibility that white adipose tissue might be converted to BAT, thereby replacing a fuel storage organ with an energy producing one (186,187). While the feasibility of this has been suggested on the basis of animal experiments, proof of principle in humans has not yet been established. Another potential target involves interference with adipose tissue blood flow; however, these studies are in their infancy.

Orlistat (Xenical/Alli)

Orlistat is an inhibitor of gastrointestinal lipases, thereby decreasing the absorption of dietary fat. Roughly 30% of ingested lipids are not absorbed in the presence of orlistat 120 mg, resulting in a caloric deficit that has been shown to produce statistically significant weight loss. Due to its mechanism of action, orlistat induces gastrointestinal side effects if too much dietary fat is consumed. Many long-term studies have assessed the efficacy of orlistat. In one, (188) the mean placebo-corrected weight loss in the orlistat group was 2.8 kg while in combination with a hypocaloric diet and lifestyle modification. Statistically significant but small placebo-corrected reductions in BP, and LDL cholesterol were noted.

A half-dose (60 mg) formulation of orlistat is now commercially available over the counter and marketed as Alli (189). This dose has been shown to reduce absorption of ingested fat by approximately 25% as compared with roughly 30% with the 120-mg dose (190). The lower dose is only slightly less effective (191). Nearly two thirds of weight lost with this agent was maintained at the end of 2 years, and the losses remained significantly greater than with placebo. After 2 years of treatment, SBP was significantly reduced only with the higher dose (192). Orlistat, therefore, induces modest weight loss, along with improved lipid parameters, but has only minimal effects on BP.

Phentermine

Phentermine, an adrenergic agonist, is thought to promote weight loss by activation of the central nervous system and SNS, with a subsequent decrease in food intake and increased resting energy expenditure (193). Phentermine is FDA approved for the short-term treatment of obesity (up to 3 months). Given the increased release of norepinephrine promoted by phentermine, it has the potential to raise BP and heart rate (194,195). A meta-analysis (196) evaluated nine randomized controlled trials of phentermine for weight loss in obese patients. The pooled analysis showed that those treated with phentermine along with diet and lifestyle lost 3.6 kg more than patients treated with diet and lifestyle alone.

Another recent study (197) examined the impact of treatment with phentermine and a low-carbohydrate diet in obese patients. Weight loss was significantly greater in the phentermine group compared with the placebo group. Additionally, SBP and DBP decreased from baseline in both groups and heart rate did not differ.

Therapies for Comorbid Diseases

Many of the medications available to treat type 2 diabetes are associated with weight gain and increased fat deposition. For overweight and obese patients with diabetes, however, there are FDA-approved medications that have been associated with weight loss and reduced BP. The effects of these agents on weight, and especially BP, are rather modest but stand in contrast to the gain in weight frequently seen with insulin, thiazolidinediones, and insulin secretagogues.

Metformin

Metformin is an oral antihyperglycemic medication approved as first-line therapy in the management of type 2 diabetes. It has been shown to promote mild weight loss by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving

insulin sensitivity by increasing peripheral glucose uptake and utilization (198) In the Diabetes Prevention Program trial, 3234 overweight and prediabetic patients were treated with either lifestyle intervention, metformin 850 mg twice a day, or placebo and followed for an average of 2.8 years. During this time, the mean weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle-intervention groups, respectively. BP decreased in the lifestyle intervention group but not in the metformin group (160,199,200).

Incretin Therapy (GLP-1 Agonists and DPP-4 Inhibitors)

Incretins play an important role in glucose homeostasis by increasing insulin release from pancreatic β -cells and suppressing the release of glucagon from pancreatic α -cells. Glucagon-like peptide 1 (GLP-1) is a major endogenous incretin, but it is not useful therapeutically because it is rapidly metabolized by dipeptidyl peptidase-4 (DPP-4). Exenatide (Byetta) along with its extended-release form Bydureon liraglutide (Victoza) are injectable GLP-1 agonists that mimic endogenous GLP-1 but have a longer duration of action, making them suitable therapies for type 2 diabetes. GLP-1 agonists enhance glucose-dependent insulin secretion, suppress inappropriate glucagon secretion (leading to decreased hepatic glucose output and decreased insulin demand), and slow gastric emptying. In addition to improving glycemic control, these GLP-1 agonists have been shown to decrease food intake and enhance satiety, suggesting a possible role in the treatment of obesity (201) Three inhibitors of the metabolizing enzyme DPP-4 that prolong the half-life of endogenous GLP-1 are approved for use in the United States: sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Trajenta). These are given orally once per day.

Multiple trials assessing the efficacy of exenatide have demonstrated statistically significant reductions in weight and BP (202-205) over a prolonged period but the changes in BP were small (206,207) In a comparison of therapy for type 2 diabetes (208) involving exenatide, sitagliptin, and insulin in a large retrospective study, the incretin-based treatments were associated with weight loss in comparison to small weight gains in the insulin-treated group. Weight loss was significantly associated with small reductions in both SBP and DBP in all treatment groups. Similar findings were noted with liraglutide, a long-acting once-daily GLP-1 analogue, in comparison with a sulfonyleurea or insulin.

Pramlintide

Amylin is a β -cell polypeptide co-stored with insulin and co-released with insulin in response to meals. In diabetic patients, amylin, as well as insulin secretion, is deficient. Pramlintide is a synthetic injectable congener that mimics the actions of amylin. Pramlintide promotes weight loss by a variety of effects that include slowing gastric emptying, increasing satiety, decreasing postprandial glucagon secretion, and centrally decreasing appetite and total caloric intake (209) Approved doses vary for type 1 diabetes (pramlintide dose: 30-60 μ g subcutaneously before meals) and type 2 diabetes (pramlintide dose: 60-120 μ g subcutaneously before meals). In type 1 diabetic patients, pramlintide fostered modest weight loss when added to an insulin regimen and was without effect on BP (210,211) Somewhat greater weight loss was noted in type 2 diabetic patients treated with pramlintide (212).

Studies aimed at assessing the weight loss potential of pramlintide in obese patients without type 2 diabetes demonstrated reductions in

BP that were directly associated with weight loss (213,214) In one study, (215) placebo-corrected weight loss at month 12 for the pramlintide 120 μ g three times daily group averaged 6.1 kg, with higher doses providing little additional benefit. Furthermore, the pramlintide 120 μ g three times daily group demonstrated a significant placebo-corrected 4.6-mm Hg reduction in SBP and a trend toward improvement with a placebo-corrected 2.6-mm Hg decrease in DBP.

Combination Therapies

Low-dose, controlled-release phentermine plus topiramate (Qynexa, Qysmia) has recently been approved for the treatment of obesity. Phentermine has been described above, and topiramate as monotherapy is FDA approved as an anti-epileptic and for migraine prophylaxis. In the 56-week phase 3 trial, overweight or obese adults with two or more comorbidities (including hypertension, dyslipidemia, prediabetes, diabetes, and/or abdominal obesity) were randomly assigned to one of two possible doses of Qysmia or placebo. Mean body weight decreased 1.4, 8.1, and 10.2 kg in the placebo, low-dose, and high-dose treatment groups, respectively. Moderate decreases in BP accompanied weight loss (216) This combination was recently approved by the FDA.

A sustained-release (once-daily) combination of naltrexone and bupropion (NB) is currently under investigation as a new weight loss therapy. Naltrexone is an opioid antagonist FDA approved for the treatment of opioid addiction and alcohol dependence. Bupropion is a norepinephrine and dopamine reuptake inhibitor FDA approved as an antidepressant (Wellbutrin), and to assist in smoking cessation (Zyban). NB was studied in a 56-week phase 3 trial in individuals with either uncomplicated obesity (BMI 30-45), or BMI ≥ 27 to 45 with comorbidities, including hypertension or dyslipidemia. Participants were assigned to receive two possible doses of once-daily NB or placebo. Mean weight loss was 1.3%, 5%, and 6.1% in the placebo, low-dose, and high-dose NB treatment groups, respectively. A small increase in pulse rate and a transient increase in BP was noted in the NB treatment groups (217).

Bariatric Surgery

Bariatric surgeries affect or restrict the flow of food through the gastrointestinal tract. Restrictive surgical procedures, such as laparoscopic-adjustable gastric banding (LAGB), induce earlier satiety by decreasing the volume of the stomach. The Roux-en-Y gastric bypass (RYGB) involves both restriction of the stomach and bypass of the small bowel. The sleeve gastrectomy, in which the fundus of the stomach is removed, is becoming increasingly popular. However, RYGB and LAGB remain the most broadly used surgical treatments for morbid obesity and associated conditions, including obesity-related hypertension (218).

In an extensive meta-analysis of 136 studies, Buchwald and colleagues (219) evaluated the impact of bariatric surgery on weight loss and obesity-related comorbidities including diabetes and hypertension. The mean percentage of excess weight loss ((Initial Weight - Ideal Weight)/Ideal Weight) was 61.2% for all patients. Diabetes resolved in 76.8% of patients and resolved or improved in 86.0%, whereas hypertension resolved in 61.7% of patients and resolved or improved in 78.5%.

The Swedish Obese Subjects Study aimed to assess the long-term benefits of bariatric surgery. The study evaluated obese patients who underwent bariatric surgery at least 2 years (4047 patients) or 10 years (1703 patients) before data analysis as compared with contemporaneously matched, conventionally treated obese control patients. After 2 years, patients' weight had increased by 0.1% in the control group and had decreased by 23.4% in the bariatric surgery group, whereas after 10 years, weight had increased by 1.6% in the control group and decreased by 16.1% in the bariatric surgery group. At 2 years, the surgery group demonstrated significant decreases in SBP (−4.4 mm Hg) and DBP (−5.2 mm Hg) as compared with increases in SBP (+0.5 mm Hg) and DBP (+0.3 mm Hg) seen in the control group. At 10 years, SBP in the surgery group had increased 0.5 mm Hg from initial baseline, as compared with 4.4 mm Hg in the control group, while DBP remained 2.6 mm Hg below baseline, as compared with 2.0 mm Hg below baseline in the control group. Although recovery from hypertension was more common in the surgery group at both 2 years (21% control vs 34% surgery) and 10 years (11% control vs 19% surgery), no change in hypertension incidence rate was noted between groups at the 2- and 10-year analysis (220).

Subgroup analysis of patients with ischemic heart disease demonstrated both sustained weight loss (surgery: −26.3 kg after 2 years and −17.3 kg after 10 years; control: −2.3 kg after 2 years and −4.3 kg after 10 years) and decreased incidence of hypertension (surgery: −15% after 2 years and −23.1% after 10 years; control: +21.2% after 2 years and 0.0% after 10 years) (221). Thus, bariatric surgery demonstrated a beneficial effect on weight and hypertension in both the short- and long-term.

Summary and Conclusions

Obesity-related hypertension is an important public health issue. As the prevalence of obesity increases, the prevalence of hypertension with its associated CV risk will increase as well. While primary and even primordial prevention is the long-term goal for diminishing the prevalence of obesity, control of both obesity and hypertension in the population at risk is the overriding current challenge. Treating hypertension in the obese requires addressing the obesity as part of the therapeutic plan. Lifestyle management is required in every case, with a focus on weight loss and risk reduction. Some have likened the treatment of obesity with caloric restriction alone to the treatment of hypertension with sodium restriction: it works if extreme enough, but it is not a feasible long-term strategy. In most patients, additional therapies including medications, aggressive diet counseling and behavioral techniques, and sometimes bariatric surgery will be required.

Lessons From the Treatment of Hypertension

Since redundancy is the hallmark of physiological regulation, complex regulatory disturbances such as obesity and hypertension cannot usually be addressed by a single agent. In the treatment of hypertension, agents that block the RAAS, the SNS and renal sodium excretion are frequently required. The need to address multiple targets in the treatment of obesity will likely be required as well. This means agents that reduce appetite as well as agents that increase metabolism will be needed in most patients. In the treatment of hypertension, agents that operate in the periphery, outside the central nervous system, provide BP control with a minimum of off-target side

effects. In the treatment of obesity, peripherally acting agents (β_3 -agonists, for example) may be useful at increasing energy expenditure. Drugs that regulate appetite will likely involve the central nervous system. The challenge here will involve precise target localization to avoid more general and unacceptable effects on the brain.

Lifestyle Management

Preventing and managing obesity-related hypertension requires multiple, parallel efforts with involvement of government, industry, health professionals, and individual self-care. The importance of increasing physician effectiveness through advocacy has been appropriately emphasized (222): “Environmental interventions are among the most effective for improving public health. In addition to addressing lifestyle issues in the office, physicians should advocate for environmental approaches at institutional, local, state, and federal levels through speaking, writing, and collaborating with others. In the United States, the timing is right to synergize with efforts such as the White House Task Force on Childhood Obesity and the Surgeon General’s emphasis on changing the national conversation from a negative one about obesity and illness to a positive one about health and fitness.”

Although more research needs to be done to find the most effective ways of helping obese hypertensive patients to sustain lifestyle changes, the first step is for health professionals to understand the options available and to provide clear advice on achievable goals. This needs to be backed up by behavioral modification techniques to assist individuals to sustain weight control and increase fitness. The end objectives are to substantially reduce the risk of CV and obesity-related metabolic disease, to minimize the need for medications, and to render the required pharmacologic therapy more effective. ○

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