IN THE PAST DECADE the prevalence of overweight and obesity has increased dramatically (44, 105). Currently, 65% of United States adults are overweight and 31% of adults are obese (44) and at increased risk of several chronic diseases (37). The association between obesity and hypertension is well documented but the exact nature of this relation remains unclear. Not surprisingly, the prevalence of hypertension has also increased in the last decade and almost 29% of the population is hypertensive [defined as a blood pressure (BP) >140/90 mmHg or use of hypertensive medications] (57).

The relation between adiposity and BP appears to be linear and exists throughout the nonobese range (73) but the strength of the association of obesity with hypertension varies among different racial and ethnic groups (34, 36, 74, 113). Risk estimates from the Framingham Heart Study suggest that ~75 and 65% of the cases of hypertension in men and women, respectively, are directly attributable to overweight and obesity (46). Importantly, long-duration obesity does not appear necessary to elevate BP, as the relation between obesity and hypertension is evident in children (140). Therefore, rather than a special case, obesity hypertension should be considered the most common form of essential hypertension.

Many (34, 36, 54, 77, 137, 164) but not all (43, 142, 150) studies suggest that abdominal adiposity is more closely associated with BP and/or the presence of hypertension than total adiposity. Obese individuals with elevated intra-abdominal (visceral) fat demonstrate a clustering of coronary heart disease risk factors (i.e., the Metabolic Syndrome) (121). The risk factors comprising this “syndrome” have expanded considerably since its original characterization (33). The prevailing hypothesis has been that accumulation of visceral fat is the central feature of this syndrome (16). However, recent evidence favors a role for ectopic fat storage in the etiology of the metabolic syndrome (152). In this regard, both the accumulation of visceral fat and ectopic fat storage in a number of tissues and organs may be important in the etiology and pathophysiology of obesity hypertension.

The purpose of the present review is to provide an overview of our current understanding of the etiology, pathophysiology, and treatment of obesity hypertension. Our focus is on the state of knowledge in humans. The potential role of abdominal obesity is considered throughout our review. We refer to relevant animal literature for supportive evidence and where little or no data in humans are available.

NOT ALL OBESE INDIVIDUALS ARE HYPERTENSIVE BY CLINICAL STANDARDS

Weight gain is almost invariably associated with an increased BP. The increase in BP is closely related to the magnitude of weight gain (95), and even moderate weight gain is associated with an increased risk of developing hypertension (36, 69, 74). However, there is considerable interindividual variability in the BP response to weight gain and not all obese individuals become hypertensive, at least by the standard of 140/90 mmHg. In addition, weight loss is associated with a reduction in BP in many normotensive obese individuals (110, 144). Therefore, BP is higher in obese humans than would be achieved at a lower level of adiposity. The reasons for the interindividual variability in the BP response to weight gain remain unclear, but genetic factors may contribute. In addition,
HEMODYNOmic ALTERATIONS IN OBESITY HYPERTENSION

The results of animal studies indicate that cardiac output and blood flow to adipose tissue and several other regions (e.g., heart, kidney, muscle, gut) are increased with weight gain (58, 62). In humans, this also appears to be the case. Cardiac output is elevated at rest and parallels the increase in resting oxygen consumption, whereas systemic vascular resistance is similar or reduced in obese compared with nonobese individuals (100). Resting cardiac output may reach 10 l/min in severely obese individuals (5). The higher cardiac output at rest is the result of both a higher stroke volume and heart rate in obese humans. Stroke volume is increased as a result of an expanded blood volume and elevated ventricular filling pressure (100), whereas the higher resting heart rate is due primarily to a reduction in cardiac vagal tone (12, 75).

There is little information available on the relative distribution of blood flow in obesity hypertension in humans. However, at least part of the increase in cardiac output observed in obese individuals is due to the additional blood flow required to perfuse the excess adipose tissue mass. In fact, adipose tissue blood flow can account for as much as one-third to one-half of the entire cardiac output at rest in severely obese humans (5). The available evidence suggests that blood flow to the heart, kidneys, gut, and skeletal muscle is also elevated in humans with obesity hypertension and together with adipose tissue blood flow summate to raise cardiac output (5, 120).

There is some evidence that abdominal obesity is associated with altered hemodynamic adjustments to weight gain. Specifically, individuals with an excess accumulation of abdominal fat demonstrate lower levels of cardiac output and higher peripheral resistance compared with individuals with lower body or subcutaneous obesity (72, 132). Whether these differences reflect a distinct phenotype or are simply the result of a longer duration of obesity remains unclear.

TARGET ORGAN DAMAGE IN OBESITY HYPERTENSION

Heart

Cardiac filling pressures are elevated in obese humans, due in part to an increase in ventricular stiffness in the face of an expanded blood volume (4). Diastolic dysfunction is evident early in obesity and characterized by impaired ventricular filling dynamics and relaxation. There may also be systolic dysfunction and both concentric and eccentric hypertrophy with prolonged obesity. Obesity and hypertension worsen the degree of left ventricular hypertrophy in a synergistic manner, and this translates into a greater risk of congestive heart failure (79).

The mechanisms responsible for the cardiac dysfunction and left ventricular hypertrophy are not entirely clear but many structural and functional alterations likely contribute. First, volume and pressure overload in obesity hypertension are important stimuli for left ventricular remodeling. Second, the altered β-adrenergic signaling and calcium handling observed in experimental animals (23) may contribute to the impairment in cardiac function in human obesity. Third, the arterial stiffening observed in some obese individuals (92, 127, 158) may increase aortic impedance and produce left ventricular hypertrophy and cardiac dysfunction. Finally, intramyocellular triglyceride deposition in the heart increases with experimental (28) and human (149) obesity. As such, elevated intramyocellular triglyceride may lead to ceramide-mediated apoptosis and increased deposition of fibrous tissue (152) and/or increased generation of reactive oxygen species (87) and, in turn, produce cardiac dysfunction and ventricular hypertrophy. Furthermore, experimental reductions in intramyocellular lipid can favorably affect left ventricular function and structure in obese animals (112). Whether the same occurs in obese humans is not known, although weight loss improves systolic and diastolic function and reduces left ventricular mass (3).

The severity, duration (5), and type (visceral vs. subcutaneous) (47, 107) of obesity also appear to be important determinants of the cardiac dysfunction and left ventricular hypertrophy observed in obese individuals. The degree of cardiac dysfunction and left ventricular hypertrophy appears to be more closely associated with visceral than total adiposity (99, 107, 108).

Vascularity

Endothelial dysfunction. The endothelium plays an important role in cardiovascular homeostasis by modulating vascular tone, inhibiting monocyte and platelet adhesion, and maintaining fibrinolytic balance (91, 161). In obesity, the endothelium is exposed to mechanical forces and other cardiovascular risk factors that can alter vascular structure and function (22). In experimental animals, obesity is associated with endothelial dysfunction. There is increasing evidence that obesity in humans is associated with peripheral (146) and coronary (6) endothelial dysfunction. Steinberg et al. (146) reported that the increase in forearm blood flow in response to intra-arterial methacholine infusion is smaller in obese compared with lean individuals. The severity of endothelial dysfunction appears to be more closely related to abdominal adiposity than whole body measures of adiposity (10, 117). Weight loss in combination with regular physical activity improves endothelium-dependent vasodilatation (22). However, regular physical activity also improves endothelium-dependent vasodilation without concomitant weight loss (32). Thus the independent influence of weight loss on endothelium-dependent vasodilatation remains unclear.

The mechanisms responsible for endothelial dysfunction in obesity are not entirely clear. However, endothelin-mediated forearm vasoconstrictor tone is elevated and blockade of ETα receptors restores endothelium-dependent vasodilatation in obese individuals to levels observed in lean controls (97). Ascorbic acid infusion improves endothelium-dependent vasodilatation in obese but not nonobese individuals, suggesting that oxidative stress may also contribute to endothelial dysfunction in obesity (117). In addition, elevated free fatty acids and adipokines have been implicated (22). The degree to which...
obesity and hypertension have additive or synergistic effects on endothelial function remains unclear.

Arterial stiffening. Arterial compliance is defined as the ability of an artery to expand and recoil with cardiac contraction and relaxation. The elements that contribute to the stiffness of an artery include vascular smooth muscle tone and structural proteins in the vessel wall (114). Reduced arterial compliance (increased arterial stiffness) has long been regarded as an indicator of disease (114) and is associated with the development of hypertension (86) as well as other risk factors for cardiovascular diseases (11). In addition, arterial stiffness is independently associated with an increased risk of coronary events (21) and stroke (85), as well as cardiovascular, and all cause mortality (84) in individuals with essential hypertension, most of whom are obese. There is increasing evidence that obesity is associated with an increase in central arterial stiffness (29, 127, 158), and weight loss reduces arterial stiffness (14). Furthermore, arterial stiffness appears to be more closely associated with abdominal visceral fat than whole body measures of adiposity (127, 158). The mechanisms responsible for arterial stiffening in obese humans are unclear, but endothelial dysfunction, elevated advanced glycation end products, and collagen cross-linking may play a role.

Kidney

The prevalence of chronic renal disease is increasing dramatically (76). This is not surprising as two of the most common causes of chronic renal failure, diabetes and hypertension, are closely associated with obesity. Much of our understanding of the early changes in renal structure and function that accompany weight gain and obesity comes from studies in experimental animals (60, 64). Briefly, a chronic high-fat diet in dogs induces marked renal vasodilatation, glomerular hyperfiltration, increased albumin excretion, and histological changes that may precede more severe renal injury with prolonged obesity (60, 64). The histological changes include enlarged Bowman’s space, increased glomerular cell proliferation and mesangial matrix, thicker basement membranes, and enhanced expression of glomerular transforming factor-β.

In obese humans, glomerulopathy, defined as focal segmental glomerulosclerosis and glomerulomegaly, is the most common clinical sign of kidney disease (76). The results of the largest study to date suggest that the presentation of obesity-associated glomerulopathy is typically one of nephrotic range (48%) or subnephrotic range (52%) proteinuria accompanied by renal insufficiency in approximately one-half of these individuals (76). Importantly, even mild to moderate levels of obesity (class I and II) can lead to the development of glomerulopathy that is clinically and morphologically indistinguishable from that observed in severe or morbid obesity. Renal vasodilatation, glomerular hyperfiltration, and proteinuria (26) are frequently observed in obese patients and if sustained can lead to a loss of nephrons in some individuals. Other metabolic factors including hyperlipidemia and hyperglycemia may contribute to alterations in kidney structure and function in obesity. However, it is unclear whether the alterations in kidney structure and function are more severe in visceral obesity. Weight loss is associated with attenuated glomerular hyperfiltration (25) and improvements in both lipid and glucose metabolism and, if maintained, could contribute to prevention of obesity-related kidney disease.

MECHANISMS LINKING OBESITY WITH HYPERTENSION

All forms of hypertension have been linked to abnormal kidney function such that higher levels of BP are necessary to maintain normal sodium and fluid balance (55). In obesity hypertension, abnormal kidney function initially is due to increased tubular sodium reabsorption, which causes sodium retention and expansion of extracellular and blood volumes (60). The increase in sodium reabsorption results in a rightward shift in the renal pressure-natriuresis relation and BP elevation. Thus the obese individual requires higher levels of BP to maintain sodium and fluid homeostasis. There are several potential mechanisms that could mediate the sodium retention and hypertension associated with obesity, including sympathetic nervous system activation, renin-angiotensin-aldosterone system activation, and compression of the kidney.

Sympathetic Nervous System Activation

The sympathetic nervous system (SNS) plays a critical role in the regulation of cardiovascular homeostasis. The results of numerous studies in experimental animals provide persuasive evidence that activation of the SNS plays an important role in the etiology of obesity hypertension (61, 62). The results of human studies are also consistent with this concept. First, in contrast to earlier reports based primarily on plasma norepinephrine concentrations (162), the results of numerous studies now support a link between body fat levels and increased SNS activity to muscle and kidney in normotensive humans (1, 8, 48, 51, 134, 143, 155). In addition, recent studies from our laboratory suggest that the association between obesity and SNS activation depends on body fat distribution. Muscle sympathetic neural activity (MSNA) is higher in men with elevated abdominal visceral fat compared with their age- and total adiposity-matched peers with lower levels (8). In contrast, MSNA does not differ in subcutaneous obese and nonobese men with similar levels of abdominal visceral fat (7). Second, MSNA and SNS activity to the kidney is elevated in obesity hypertension (40, 48, 129). Finally, combined α- and β-adrenergic receptor blockade produces greater reductions in BP in obese compared with lean hypertensive subjects (159). Taken together, these observations are consistent with the concept that SNS activation plays an important role in the pathophysiology of obesity hypertension in humans.

There a number of proposed mechanisms linking obesity with SNS activation including baroreflex dysfunction, hypothalamic-pituitary axis dysfunction, hyperinsulinemia/insulin resistance, hyperleptinemia, and elevated circulating angiotensin II concentrations (see Fig. 1).

Baroreflex Dysfunction

The arterial baroreflex plays a critical role in the acute regulation of SNS outflow and BP. However, the role of the arterial baroreflex in the long-term regulation of SNS outflow and BP has been controversial. The results of animal studies suggest that arterial baroreflex suppression of SNS activity is a long-term compensatory response in hypertension (89). However, sympathoexcitation predominates over the inhibitory effects of the baroreflex in obesity hypertension. In humans, the
ability of (acute) pharmacologically induced increases in BP to suppress SNS activity is reduced in obese hypertensive compared with both obese normotensive and lean hypertensive subjects (50). However, the degree to which baroreflex sensitivity measured in this way reflects the long-term influence of the baroreflex on SNS outflow in obesity hypertension remains unclear. Future studies will be necessary to understand the role of the arterial baroreflex in modulating SNS activity in obesity hypertension.

Hypothalamic-Pituitary Axis Dysregulation

Alterations in hypothalamic neuroendocrine pathways may be important in the development of obesity hypertension in animal models. Bjorntorp et al. (17) hypothesized that hypertension and the metabolic syndrome have a closely related central origin resulting from parallel activation of hypothalamic-pituitary axis and the SNS (i.e., a hypothalamic arousal syndrome). Recently, Grassi et al. (51) reported greater reductions in MSNA after 1 wk of dexamethasone treatment in obese compared with nonobese individuals and concluded that hypothalamic-pituitary dysfunction may contribute to SNS activation in obesity. Although intriguing, future studies are necessary to define the role of the hypothalamic-pituitary axis in obesity hypertension.

Insulin Resistance/Hyperinsulinemia

Insulin resistance and hyperinsulinemia are central components of the metabolic syndrome (30, 78, 121) and have been implicated in the pathophysiology of obesity hypertension (83, 122). However, several key observations in both experimental animals and humans question the role hyperinsulinemia in SNS activation and elevated BP in obesity. First, BP is not elevated in dogs after chronic infusion of insulin either systemically or directly into the brain circulation (62). Raising insulin concentrations in humans increases sympathetic nervous system activity but this is not associated with a corresponding rise in BP (9). The increase in SNS activity with insulin infusion could also result from baroreflex-mediated adjustments to the systemic vasodilatation that occurs with insulin infusion. Second, the association between hyperinsulinemia and BP is inconsistent in epidemiological studies. Third, neither SNS activity nor BP is elevated in patients with insulinoma, in whom fasting insulin concentrations are four- to fivefold higher than nonobese subjects (131, 133). Finally, removal of the insulinoma in these patients does not lower SNA or BP. Therefore, hyperinsulinemia does not appear to be a major cause of obesity hypertension. However, this does not rule out the possibility that insulin resistance may contribute to hypertension through other mechanisms, such as vascular damage caused by chronic abnormalities in lipid and glucose metabolism.

Hyperleptinemia

Leptin, the product of the OB gene, is secreted from adipocytes in proportion to fat mass and acts on hypothalamic neuronal targets to alter energy intake and expenditure (2). Leptin also exerts influences on cardiovascular and renal function in animals that are sympathetically mediated (62, 65). Whether hyperleptinemia could be a potential mechanism contributing to SNS activation and BP elevation in obese humans is less clear. Plasma leptin concentrations are higher in hypertensive compared with normotensive humans (15) but elevated leptin concentrations do not contribute in any obvious way to the relation between visceral obesity and SNA activity or BP. Leptin expression and secretion is lower in visceral compared with subcutaneous adipocytes (130, 154) and circulating concentrations of the protein are also lower, not higher, in visceral obesity (90). In addition, plasma leptin concentrations have been associated with basal MSNA in some (106, 139) but not all studies (109). However, it is possible that the concurrent accumulation of visceral and subcutaneous fat could mask a more obvious relation. It is also conceivable that other factors may modify the impact of hyperleptinemia on BP (and SNS activity) in obese individuals. Rosmond et al. (128) recently reported that when body mass index and leptin are increased, BP elevation is observed only in carriers of most prevalent LEPR genotype at codons 109 and 223, whereas variants of this receptor seem to be protective of elevated BP. Parenthetically, this might help explain why not all obese individuals are
hypertensive, at least by the clinical threshold of 140/90 mmHg.

**Renin-Angiotensin-Aldosterone System Activation**

The results of animal studies indicate that activation of the renin-angiotensin-aldosterone system (RAAS) plays an important role in the etiology of obesity hypertension (59, 60). The results of human studies are generally consistent with this concept in that several components of RAAS are elevated in obese humans (151) despite sodium retention. In addition, plasma renin activity declines with weight loss and is correlated with the reduction in BP (53, 124, 141). Furthermore, angiotensin converting enzyme inhibition is an effective pharmacological means of lowering BP in obese hypertensive humans (126).

The results of animal studies indicate that angiotensin II can act centrally to increase SNS outflow (123). Thus it is possible that angiotensin II could increase central SNS outflow in obese humans. Indeed, infusion of angiotensin II increases MSNA (98) and angiotensin converting enzyme inhibition decreases MSNA (104) in normotensive humans. Whether angiotensin II contributes to the sympathoexcitation observed in obesity hypertension is unknown. However, the observation that angiotensin II receptor blockade reduces MSNA in obese hypertensive humans (49) is consistent with this concept.

Adipose tissue expresses many components of RAAS, and this local system has been implicated in obesity hypertension (38). Interestingly, angiotensinogen is expressed and secreted more in visceral than subcutaneous adipocytes (153). In addition, adipose tissue-specific overexpression of angiotensinogen raises BP in mice (93). There is presently no information on the potential role of other local RAAS in obesity hypertension. However, the functional importance of local (e.g., adipose tissue and vascular) RAAS requires further investigation.

**Compression of the Kidney**

As indicated above, visceral obesity has been more closely associated with hypertension than total adiposity in many but not all studies conducted to date. Intra-abdominal pressure is directly related to the degree of abdominal adiposity (148), and, thus, elevated intra-abdominal fat could act to compress the kidney, increase sodium and water retention, and elevate BP (19, 20). In addition, the ectopic deposition of fat within the rigid renal capsule could also elevate intrarenal pressure, result in sodium and water retention, and increase BP (63). Future studies are necessary to determine whether ectopic fat deposition in the kidney contributes to alterations in renal function and BP regulation in humans.

**Obstructive Sleep Apnea and Obesity Hypertension**

Obesity is an important risk factor for obstructive sleep apnea (163) but obstructive sleep apnea may be more closely associated with visceral obesity than total adiposity (156). Obstructive sleep apnea has been linked to hypertension in both clinical and epidemiological studies (118). As such, obstructive sleep apnea may be an important mechanism linking obesity and hypertension in some individuals (160). The factor(s) linking obstructive sleep apnea and hypertension is(are) unclear but might include amplifying the effects of obesity on SNS activity, RAAS activity, and/or other factors (160). Interestingly, the hypertension observed in patients with obstructive sleep apnea may be a phenotype that is resistant to pharmacological intervention (24, 88). However, the efficacy of hypertension treatment in this population is less clear. Future studies will be necessary to understand the interrelation among obesity, obstructive sleep apnea, and hypertension.

**Nonpharmacological Treatment of Obesity Hypertension**

**Weight Loss**

Weight loss is considered the most effective nonpharmacological therapy for lowering BP in obese hypertensives (45, 70, 81, 101, 138, 145, 147). There is a dose-response relation between the degree of weight loss and the reduction in BP (147) that is independent of sodium intake (42). Even modest weight loss of 5–10% of body weight is associated with clinically significant reductions in BP (111). Systolic and diastolic BP decline ~2 and ~1 mmHg, respectively, with each 1 kg reduction in body weight (144), but there is considerable variability around this mean reduction in BP with weight loss (35, 94, 96). Some obese hypertensive patients demonstrate little or no reduction in BP with weight loss, whereas others experience dramatic reductions (35, 94, 96). The factor(s) that contribute to this variability remain unclear, although smaller reductions in plasma norepinephrine concentrations have been reported in individuals demonstrating little or no reduction in BP (96).

Given the association between abdominal visceral fat and BP or the presence of hypertension in some studies, it is reasonable to hypothesize that a large reduction in this depot with weight loss would be associated with a correspondingly large reduction in BP. Unfortunately, there is limited information available that addresses this issue. Kanai et al. (77) reported that the reduction in BP with weight loss was correlated with the magnitude of reduction in abdominal visceral fat; the relation was independent of changes in body mass index. The mechanisms linking reductions in abdominal visceral fat with reductions in BP remain unclear, but a reduction in SNS activity is one possibility (8).

There is little information on the long-term benefits of weight loss in obesity hypertension and there are some inconsistencies. Many obese individuals are able to lose significant amounts of weight, but usually regain this weight over a period of ~2 to 3 yr or less. Despite weight regain in the Trials of Hypertension Prevention study, the 7-yr incidence of hypertension was significantly lower in subjects who had previously lost weight compared with the control group (147). The reason(s) for this sustained protection remains unclear. In contrast, in the Swedish Obesity Study, BP returned to presurgery levels despite a sustained 16% weight loss over 8 yr (138). Similar transient reductions in BP have been made after weight loss by caloric restriction (82). The results of one study suggested that the ability to sustain reductions in BP over a 4-yr period was directly related to the ability to maintain body weight over time (66). However, regular physical activity was included as part of the weight maintenance intervention and may exert an independent influence on BP (56). Nonetheless, the reason(s) for this apparent discrepancy among studies remains unclear. Most studies do not establish weight stability before BP measurements after weight loss and many include physical activity as...
part of the weight loss intervention. Therefore, failure to control for discrete effects of energy imbalance (39) and/or regular physical activity (66) may be important. Future long-term studies are necessary to clarify this issue as well as determine the impact of weight loss on morbidity and mortality in obese hypertensive individuals.

**Regular Physical Activity**

The incidence of hypertension is highest in obese sedentary and lowest in lean physically active individuals (116). Physically active individuals have a lower risk of hypertension compared with their sedentary counterparts (18). Importantly, the risk of hypertension associated with weight gain also appears to be lower in physically active individuals (116). As such, regular physical activity is recommended for individuals with elevated BP (27). The results of numerous studies indicate that regular aerobic exercise lowers systolic and diastolic BP by as much as ~10 and 7 mmHg, respectively, in hypertensive individuals (56). The reduction in BP with regular physical activity appears to be independent of baseline adiposity or changes in whole body adiposity (24, 56). However, it is unknown whether reductions in abdominal adiposity could be mediating, in part, the reduction in BP observed with regular physical activity. Future studies are necessary to address this issue.

**Sodium Restriction**

Many consider obesity a sodium-sensitive form of hypertension, although there is not complete agreement on this issue. Nonetheless, sodium restriction reduces BP, albeit modestly, in obese individuals (147). However, Seals et al. (135) recently reported that moderate sodium restriction resulted in dramatic reduction in BP (~16 mmHg in systolic BP) in obese postmenopausal women. The reductions in BP with sodium restriction were approximately fourfold larger than observed with regular physical activity and at least twofold larger than previously reported with sodium restriction (52, 102). The authors suggested that the relatively large reductions in BP observed in their study might be the result of the excellent compliance of the subjects to the intervention, the female gender of the participants, and/or the level of sodium intake of the subjects at baseline. That these individuals were obese may have also contributed. Future studies will be necessary to determine whether obese hypertensive individuals demonstrate larger reductions in BP in response to sodium restriction compared with nonobese hypertensives.

**ARE THE ANTIHYPERTENSIVE EFFECTS OF DIFFERENT NONPHARMACOLOGICAL THERAPIES ADDITIVE?**

There are only a few studies that have addressed this issue. The majority of these studies suggest that regular aerobic exercise and weight loss produce similar or somewhat greater reductions in BP than either intervention alone (31, 68). However, the magnitude of reduction in BP with weight loss and regular aerobic exercise does not appear to be additive. In addition, the results of studies that combine multiple lifestyle interventions suggest that the magnitude of BP reduction is in the range of that observed with any single intervention (i.e., weight loss, sodium restriction, or exercise) (103). Regular physical activity is one of the best predictors of weight maintenance (71). Thus improved weight maintenance and subsequent BP control may be one benefit of combining certain interventions. In addition, some individuals may respond better to weight loss than regular physical activity, for example, and the benefits of these interventions extend beyond lowering BP. Although these issues require further study, they should be considered when implementing nonpharmacological therapy in obese patients.

**PHARMACOLOGICAL THERAPY OF OBESITY HYPERTENSION**

There are currently no specific recommendations for the pharmacological treatment of obesity hypertension, although some have suggested that the selection of therapy should be based on etiology of the disorder (119, 125). As such, pharmacological blockade of SNS and RAAS are logical choices for intervention. Unfortunately, there is little direct clinical evidence to justify their specific use in this patient population. As emphasized in JNC VII (27), however, good clinical judgment is paramount in the selection of hypertension therapy.

In the only multicenter trial conducted to date, similar reductions in systolic BP and diastolic BP in obese hypertensive subjects were observed after 12 wk of monotherapy with the angiotensin converting enzyme inhibitor lisinopril and the diuretic hydrochlorothiazide (HCTZ) (126). However, lisinopril was more efficacious in young, white patients, whereas the diuretic was superior in young, black patients.

Grassi et al. (49) recently compared the efficacy of candesartan (an angiotensin II receptor blocker) to HCTZ in obese hypertensive individuals. The reduction in BP after 12 wk of candesartan and HCTZ was similar. However, SNS activity (via microneurography) was reduced, and insulin sensitivity was increased after candesartan but not HCTZ. Thus angiotensin II receptor blockade may be particularly efficacious in obesity hypertension in that the benefit may extend beyond BP lowering. Parenthetically, it is not clear whether the reduction in SNS activity observed in the Grassi study contributed in a mechanistic fashion to the BP lowering effect of candesartan. However, this will be an important question to address in the future.

There are numerous ongoing clinical trials of pharmacological treatment of hypertension. Many of these will undoubtedly include large numbers of obese patients. In addition, research focused on understanding the pathophysiology of obesity hypertension should provide new insight on potential pharmacological targets for intervention.

**LOWERING BLOOD PRESSURE WITH ANTI-OBESE DRUGS**

If obesity is an underlying cause of essential hypertension, as appears to be the case, then pharmacological treatment of obesity may be a logical approach for lowering BP in obese individuals. However, only two drugs, sibutramine and orlistat, have been approved for long-term use in weight loss and weight management. The modest efficacy of both drugs in short-term weight loss and long-term weight maintenance has been documented in randomized controlled trials but attrition rates are high (157).

Sibutramine is a central nervous system norepinephrine and serotonin reuptake inhibitor that reduces food intake. Sibutramine also stimulates the SNS and produces dose-dependent increases in BP, especially in the early treatment phase (80).
Sibutramine appears effective in producing modest weight loss and weight maintenance in obese patients. However, weight loss produced by sibutramine is not always associated with a reduction in BP, and significant hypertension may occur in some patients. Therefore, the rationale for using sibutramine for the treatment of obesity hypertension is tenuous.

Orlistat is a gastric pancreatic lipase inhibitor that inhibits the systemic absorption of dietary fat. The results of several clinical trials indicate that orlistat enhances weight loss, albeit modestly, and weight maintenance for up to 2 yr in obese individuals (115). The larger weight loss and better weight maintenance with orlistat appears to translate into greater reductions in BP and enhanced BP control in patients with hypertension (136). However, there is no evidence that orlistat lowers BP by any other means than by promoting weight loss.

The medication is considered safe and reduces other cardiovascular disease risk factors (115). Although orlistat may produce unpleasant gastrointestinal effects in many patients, it may be a viable option for treatment in some. Future large-scale randomized controlled clinical trials are necessary to determine if orlistat reduces morbidity and mortality.

PREVENTION OF OBESITY HYPERTENSION

There is no sign that the rising prevalence of obesity seen over the past two decades is dwindling. The average weight gain of the population in the United States is estimated to be ~2 lb/yr (67). As indicated earlier, weight gain is almost invariably associated with an increase in BP. Thus prevention of weight gain should be a primary therapeutic target for reducing the problem of hypertension.

Regular physical activity (71) and reduced dietary fat intake (13) reduce weight gain in normal weight subjects and weight regain after weight loss in obese individuals. Hill and colleagues (67) suggested that increasing the amount of regular physical activity and reducing energy intake by an amount equal to 100 kcal/day could prevent weight gain in most of the population. This could be achieved by relatively small lifestyle changes such as adding 15 min of walking each day and reducing portion sizes by a few bites per meal. If successful, lifestyle modification such as the one proposed may have important implications for the prevention of obesity-associated hypertension.

SUMMARY

There is a continued problem of weight gain and obesity in the United States and most industrialized countries with no clear dwindling of this trend in sight. Because obesity is a major cause of human essential hypertension, rising BP and its associated comorbidities will continue to impart their health and economic consequences. There is growing support for the concept that SNS and RAAS activation play an important role in the etiology of obesity hypertension. Visceral obesity appears to be especially important in the activation of these systems, thereby increasing the risk for the development of hypertension and its associated comorbidities. The ectopic deposition of fat may also contribute to the BP-raising effect of weight gain and the accompanying cardiac, vascular, and renal dysfunction. Treatment of obesity hypertension should begin with or include weight loss and other lifestyle modifications. Unfortunately, there is little information available on the pharmacological treatment of obesity hypertension and even less on the influence of long-term treatment of any kind on morbidity and mortality. Prevention of weight gain and its metabolic and cardiovascular sequelae should be a focus of future efforts to combat the growing epidemic of obesity hypertension.

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