Hypertension and Obesity

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ABSTRACT

Obesity is a common problem in much of the world today in that it is linked directly with several disease processes, notably, hypertension. It is becoming clear that the adipocyte is not merely an inert organ for storage of energy but that it also secretes a host of factors that interact with each other and may result in elevated blood pressure. Of particular importance is the putative role of leptin in the causation of hypertension via an activation of the sympathetic nervous system and a direct effect on the kidneys, resulting in increased sodium reabsorption leading to hypertension. Obesity per se may have structural effects on the kidneys that may perpetuate hypertension, leading to an increased incidence of end-stage renal disease that results in further hypertension. Adipose tissue may elaborate angiotensin from its own local renin-angiotensin system. The distribution of body fat is considered important in the genesis of the obesity-hypertension syndrome, with a predominantly central distribution being particularly ominous. Weight loss is the cornerstone in the management of the obesity-hypertension syndrome. It may be achieved with diet, exercise, medications, and a combination of these measures. Anti-obesity medications that are currently undergoing clinical trials may play a promising role in the management of obesity and may also result in lowering of blood pressure. Antihypertensives are considered important components in the holistic approach to the management of this complex problem.

I. Introduction

Obesity is rapidly turning into an “epidemic” afflicting much of the industrialized world, resulting in a prohibitive health and economic burden on society (Mark et al., 1999a; Hall et al., 2001,2002; Sowers, 2001). A predominantly “central” or “visceral” obesity pattern triggers a myriad of cardiovascular, renal, metabolic, prothrombotic, and inflammatory responses that are essentially mal-adaptive, some of which constitute the “cardio-metabolic syndrome” (to be defined). These responses, individually and interdependently, lead to a substantial increase in cardiovascular disease (CVD) morbidity and mortality, including
hypertension, coronary heart disease (CHD), congestive heart failure (CHF), sudden cardiac death (SCD), stroke, and end-stage renal disease (ESRD) (Gar- rison et al., 1987; Mark et al., 1999a; Zhang and Reisin, 2000; Hall et al., 2001, 2002; Sowers, 2001). This review will highlight the causative role that adipose tissue may play in the genesis of hypertension, or what recently has been referred to as “obesity hypertension.” Epidemiological studies have revealed a strong relation between obesity and hypertension. Data from the National Health and Nutrition Examination Survey (NHANES) (Figure 1) show a remarkable and linear relationship between rise in body mass index (BMI) and systolic, diastolic, and pulse pressures in the American population. In regression models corrected for age-related rise in blood pressure, a BMI gain of 1.7 kg/m² in men and 1.25 kg/m² in women or an increase in waist circumference of 4.5 cm for men and 2.5 cm for women corresponds to an increase in systolic blood pressure of 1 mmHg (Kissebah and Krakower, 1994). Obesity by itself possibly accounts for 78% and 65% of essential hypertension in men and women, respectively, according to data from the Framingham Cohort (Kannel et al., 1993). Animal experiments and human studies have confirmed this causation and given insight into the mechanisms involved (Reisen et al., 1978; Alexander et al., 1979; Reaven, 1993; Carrol

FIG. 1. Line graph shows age-adjusted systolic blood pressure (SBP) and diastolic blood pressure (DBP) from the National Health and Nutrition Examination Surveys (NHANES) II and III by NHANES III quintile of body mass index. [Source: Centers for Disease Control and Prevention, National Centers for Health Statistics.]
Hyperinsulinemia, hyperleptinemia, hypercortisolemia, renal dysfunction, altered vascular structure and function, enhanced sympathetic and renin-angiotensin system activity, and blunted natriuretic peptide activity stand out as major contributory mechanisms to “obesity hypertension” (Tuck et al., 1981; Rocchini et al., 1989a; Hall et al., 2001, 2002; Kissebah and Krakower, 1994; Cignolini et al., 1995; Mark et al., 1999a; Mansuo et al., 2000; Zhang and Reisin, 2000; Engeli and Sharma, 2001, 2002).

II. Epidemiology

The prevalence of obesity is rapidly increasing in developing as well as industrialized countries (Mark et al., 1999a; Hall et al., 2001, 2002; Sowers, 2001). Up to 61% of Americans are either overweight or obese, according to data from the 1999 census. Economic costs attributable to obesity in the United States in 2000 were estimated at $117 billion (Garrison et al., 1987; Flegal et al., 1998; Zhang and Reisin, 2000; Sowers, 2001). Increasing obesity is common to all developed societies, particularly among children. The Nurses’ Health Study involving 80,000 women revealed that a 5-kg weight gain after age 18 was associated with a 60% higher relative risk of developing hypertension (Huang et al., 1998), compared to those women who gained 2 kg or less. Those who gained 10 kg or more increased their risk by 2.2-fold. Similar increases have been observed in other populations (Wilsgaard et al., 2000) and in children (He et al., 2000).

Cardio-metabolic syndrome prevalence has been estimated at 22% of the U.S. population. It increases with age and varies according to ethnicity. Mexican-Americans have the highest age-adjusted prevalence (31.9%) (Sowers, 2001). Among African-Americans and Mexican-Americans, the prevalence is nearly twice as high in women than in men (57% and 26% higher prevalence, respectively) (Kissebah and Krakower, 1994; Cignolini et al., 1995; Hall et al., 2001, 2002).

III. Definitions

A. BODY MASS INDEX

Overweight is defined as a BMI > 25. (BMI is body weight in kilograms divided by the height in meters, squared, expressed as wt (in kg)/height (m²).) Obesity is defined as a BMI > 30; morbid obesity is a BMI > 35 (Sowers, 2001).
B. CENTRAL OBESITY

The distribution of weight gain is of crucial importance. A predominantly "central" pattern of weight gain, as measured by a waist-to-hip ratio, is considered more ominous from cardiovascular and glycemic standpoints because it confers a far higher risk than that expected by BMI measurements. Central obesity is often referred to as abdominal, upper-body, male-type, android, or visceral obesity vs. female-type or gynoid obesity, where there is preferential fat accumulation in the gluteal and femoral distribution (Kissebah and Krakower, 1994; Hall, 1997; Hall et al., 2001,2002; Rocchini et al., 2002). Abdominal obesity is diagnosed clinically by a waist-to-hip ratio that is > 0.95 in men and > 0.85 in women. Although clinical measures are considered acceptable in the diagnosis of true central obesity, better imaging techniques such as dual-energy X-ray absorptiometry (DEXA) or an abdominal computed tomography (CT) scan probably are required for accurate description. The pattern of obesity is important. For example, athletes such as football players often have BMIs higher than 35, making them morbidly obese by definition. A closer look may reveal a total body fat lower than 8%, quite different than the figures for those who are truly obese. Therefore, obesity defined solely by BMI may be an imperfect approximation. Clinicians must always be aware of this possible fallacy, further emphasizing the importance of the pattern of fat distribution.

C. CARDIO-METABOLIC SYNDROME

The presence of an interesting constellation of findings variously referred to as the cardio-metabolic syndrome, the metabolic syndrome, the deadly quartet, insulin resistance syndrome, and syndrome X is now an established predictor for premature and often severe CVD.

The metabolic syndrome is defined by guidelines from the National Cholesterol Education Program (Adult Treatment Panel (ATP) III). These guidelines suggest that the clinical identification of the metabolic syndrome be based upon the presence of any three of the following: 1) abdominal obesity, defined as a waist circumference in men > 102 cm (40 inches) and in women > 88 cm (35 inches) (it was noted by ATP III that some men with lower waist circumference (i.e., 94–102 cm) may develop insulin resistance due to genetic factors); 2) triglycerides ≥ 150 mg/dL (1.7 mmol/L); 3) high-density lipoprotein (HDL) cholesterol < 40 mg/dL (1 mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women; 4) blood pressure ≥130/≥85 mmHg; or 5) fasting glucose ≥ 110 mg/dL (6.1 mmol/L) (National Institutes of Health, 1998).

The World Health Organization (WHO) has proposed a different definition for the metabolic syndrome. A diagnosis of the metabolic syndrome required the presence of either hyperinsulinemia or a fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/L) and an additional two characteristics from among the following: 1)
abdominal obesity, defined as a waist-to-hip ratio > 0.90, a BMI ≥ 30 kg/m², or a waist girth ≥ 94 cm (37 inches); 2) dyslipidemia, defined as serum triglyceride ≥ 150 mg/dL (1.7 mmol/L) or HDL cholesterol < 35 mg/dL (0.9 mmol/L); or 3) blood pressure ≥ 140/90 mmHg or the administration of antihypertensive drugs.

IV. Alterations in Renal Function and Structure, Leading to Obesity-related Hypertension

A. RENAL HEMODYNAMIC CHANGES

A high-fat diet consistently results in enhanced sodium reabsorption by the kidneys (Figure 2). Interestingly, weight loss in the same individual promotes urinary sodium excretion (Figure 3), demonstrating a direct link between BMI and sodium retention (Tuck et al., 1981; Lucas et al., 1985; Reaven and Hoffman, 1987; Landsberg and Krieger, 1989; Rocchini et al., 1989a; Tuck, 1992; Reisin et al., 1993; Baron et al., 1995; Kassab et al., 1995; Hall et al., 1996, 1999a; Sugarman et al., 1997; Bloomfield et al., 2000; Stern et al., 2001; U.S. Renal Data System, 2001). Obesity is associated with activation of the renin-angiotensin system (RAS) (Tuck, 1992; Zhang and Reisin, 2000; Hall et al., 2001, 2002), increased sympathetic nervous system (SNS) activity (Landsberg and Krieger, 1989; Carroll et al., 1995; Mark et al., 1999a; Weyer et al., 2000).

2000; Abate et al., 2001; Hall et al., 2001), and hyperinsulinemia (Reaven, 1993; Weyer et al., 2000), all of which may contribute to sodium reabsorption and associated fluid retention and may therefore contribute to renal obesity hypertension (Reisen et al., 1993; Burt et al., 1995; Hall et al., 1999b; Engeli and Sharma, 2001; Stern et al., 2001). A compensatory lowered renal vascular
resistance, elevated kidney plasma flow, increased glomerular filtration rate, and the higher blood pressure associated with obesity are important in overcoming increased sodium reabsorption. Neurohumoral factors like angiotensin II (AII), sympathetic system, and cytokines — either individually or synergistically — are involved in these compensatory mechanisms. In obese hypertensives, an inappropriately small natriuretic response to a saline load at mean arterial or intraglomerular pressure is seen and is often referred to as impaired pressure natriuresis (Figure 3) (Kassab et al., 1995; Hall et al., 1996; Hall, 1997; Engeli and Sharma, 2001). These adaptive changes increase glomerular wall stress and, especially in the presence of other risk factors such as hyperlipidemia and hyperglycemia, may provoke glomerulosclerosis, proteinuria, microalbuminuria, and loss of nephron function in the “obese” kidney, even before structural microscopic changes are evident. The combination of these potentially nephrotoxic mechanisms, including hyperfiltration and hypertension, may initiate and, indeed, perpetuate renal damage. The early glomerular hyperfiltration in obesity is often as great as that observed in uncontrolled type I diabetes.

B. RENAL STRUCTURAL CHANGES

Altered intrarenal physical forces are believed to play a role in sodium retention, mainly by slowing down the tubular flow rate (Weisinger et al., 1974; Reisen et al., 1984; Wesson et al., 1985; Arnold et al., 1994; Hall, 1994; Alonso-Galicia et al., 1995; Bruzzi et al., 1997; Sugarman et al., 1997; Hall et al., 1998; Bloomfield et al., 2000; Henegar et al., 2001; Kambham et al., 2001; Okosun et al., 2001; Sundquist et al., 2001). Observations from obese animals and humans have shown an increase in renal weight attributable to endothelial cell proliferation and intrarenal lipid and hyaluronate deposition in the matrix and inner medulla. These depositions in the tightly encapsulated kidney lead to distortion of the intrarenal mechanical forces. The interstitial fluid hydrostatic pressure is elevated to 19 mmHg in obese dogs, compared to 9–10 mmHg in lean dogs. This increase in pressure and volume causes parenchymal prolapse and urine outflow obstruction, resulting in slow intrarenal flow and increased sodium reabsorption. Of particular importance is the increased sodium reabsorption in the loop of Henle, which leads to a feedback-mediated renal vascular dilation, elevation of glomular filtration rate (GFR), and stimulation of the renin-angiotensin aldosterone system (RAAS), despite volume expansion overcoming the increased tubular reabsorption and maintaining sodium balance. However, persistent glomerular hyperfiltration — in combination with glucose intolerance, hyperlipidemia, and hypertension — results ultimately in glomerulosclerosis and renal failure.

The structural changes occurring in the human kidney as a consequence of obesity have been demonstrated in a large retrospective human study that
incorporated 6800 renal biopsies. Obesity was associated with a peculiar obesity-related glomerulopathy, defined as focal segmental glomerulosclerosis associated with enlargement of the glomerulus itself. The mean BMI in these patients was 41.7 kg/m². Compared with the idiopathic variety, obesity-associated focal segmental glomerulosclerosis had lower rates of nephrotic syndrome, fewer lesions of segmental sclerosis, and a greater glomerular size. The disease course in this population was dictated largely by the presence of co-morbid conditions such as hypertension and dyslipidemia. A recent study of the German WHO MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg study population found a steady increase in the presence of microalbuminuria, an early marker of renal vascular damage with quintiles of waist-to-hip ratio. In this study, the odds ratio for the development of microalbuminuria for individuals with central obesity was not very different from that for patients with hypertension. Thus, over a span of time, obesity by itself may perpetuate hypertension by these structural damages.

The parallel increase in the prevalence of obesity and ESRD (Figure 4), in addition to the close association between obesity and type II diabetes and hypertension that are the two major risks of ESRD, has led to speculation that obesity may account for at least half of ESRD in the United States.

In summary, persistent obesity causes renal injury and functional nephron loss, contributing to elevated blood pressure, which in turn leads to further renal injury, thereby setting off a vicious circle of events leading to further elevated BP and renal injury. Interestingly enough, it is difficult to dissociate the cause from the effect in this circle, since the overall burden of obesity may be strongly time dependent (Figure 4).

V. Role of SNS, Biochemical, Neurochemical, and Hormonal Mediators

A. SYMPATHETIC NERVOUS SYSTEM

Several mechanisms and mediators have been postulated as causative in the genesis of adrenergic overactivity in the obese (Hall et al., 1993b; Grassi et al., 1995, 1998; Rumantir et al., 1999; Esler, 2000; Mansuo et al., 2000; Weyer et al., 2000). Notable are elevated insulin levels with insulin resistance; activation of renal afferent nerves that, in turn, are stimulated by increased intrarenal pressures, leading to the subsequent activation of renal mechanoreceptors; plasma free fatty acids (FFAs); angiotensin II; elevated leptin levels; potentiation of central chemoreceptor sensitivity; and impaired baroreflex sensitivity.

There are several reasons to believe that SNS activation may contribute significantly to the obesity-hypertension syndrome. Obese subjects have elevated sympathetic activity, measured both directly and indirectly. A diet that results in obesity has been found to increase baseline plasma norepinephrine levels, to
amplify the SNS response to stimuli such as handgrip and upright posture, and to increase catecholamine turnover in peripheral tissues. In addition to elevated renal sympathetic activity, muscle sympathetic activity is elevated in obese hypertensive subjects, when measured with microneurographic methods (Grassi et al., 1998). Weight loss, on the other hand, reduces sympathetic activity, which further supports this hypothesis. Interestingly, Pima Indians do not demonstrate a markedly increased sympathetic tone when obese and also do not get hypertensive to the same degree as other racial groups. Also, medications that abolish or diminish the central sympathetic drive cause a greater blood pressure reduc-

tion in obese as compared to lean subjects (Hildebrandt et al., 1993; Licata et al., 1994a; Wofford et al., 2001). Indeed, in dogs fed a high-calorie diet, a combined blockade of α and β receptors lowered blood pressure more significantly in obese than in lean dogs. Clonidine, which blocks central α2 receptors and thereby markedly reduces the central sympathetic drive, blunts hypertension in dogs fed a high-calorie diet. Similar results have been observed in humans. To further support the hypothesis, sympathetic denervation of the kidneys has a significant negative effect on renal sodium retention and thereby on obesity hypertension. In dogs fed a high-fat diet, renal nerves appear crucially important for sodium retention and hypertension. In dogs with denervated kidneys, sodium retention was markedly attenuated, leading to a lower blood pressure. Therefore, it appears that renal nerves play a pivotal role in salt retention, impaired pressure natriuresis, and hypertension.

B. INSULIN RESISTANCE AND HYPERINSULINEMIA

Hyperinsulinemia was considered a key factor governing obesity-induced hypertension in the recent past. It is well known that obese subjects have markedly elevated insulin levels, which are required to maintain glucose and fatty acid metabolism, and often are resistant to the actions of insulin on peripheral tissues (DeFronzo et al., 1975; Rocchini et al., 1990,1996; Hall et al., 1993b; Bjorntorp and Rosmond, 2000). This resistance to insulin is not universal to all tissues; some tissues retain their sensitivity to its effects, referred to as selective insulin resistance. Studies in the acute setting suggest that insulin may contribute to sodium retention and sympathetic activity and therefore to hypertension (Rocchini et al., 1987,1989b). However, on further investigation, elevated insulin levels in both acute and chronic settings have not been found to affect salt excretion, sympathetic activity, and blood pressure in humans and dogs (Hall et al., 1986,1995; Hildebrandt et al., 1999a). In fact, infusions to raise insulin levels to match those found in the obese actually lower blood pressure, suggesting a dominant depressor effect for insulin. Even in obese dogs resistant to the metabolic effects of insulin, infusions did not have a pressor effect. A central nervous system (CNS) infusion of insulin did not demonstrate a change in blood pressure in the dog.

In rats, however, hyperinsulinemia does elevate blood pressure. The underlying mechanisms are probably mediated by a complex interaction between insulin, the RAAS, and thromboxane (TXA2) activity. This hypothesis was further tested when blockade of RAAS or TXA2 abolished the blood pressure rise (Brands et al., 1997; Keen et al., 1997; Sechi, 1999). It therefore appears that the initial enthusiasm generated by rodent studies in hyperinsulinemia as causative for hypertension in the obese may not be extrapolated to humans.
However, some researchers believe that insulin resistance plays a part in blood pressure regulation. This association, although controversial, is based upon the following hypotheses. There is evidence that insulin-mediated vasodilatation is impaired in an insulin-resistant state, which may lead to hypertension (Laasko et al., 1990). In healthy subjects, insulin infusions stimulate endothelin-1 and nitric oxide (NO) activity (Cardillo et al., 2000). In subjects who have developed hypertension, reduced insulin-mediated vasodilatation is associated with reduced endothelial NO production. Also, insulin increases renal sodium reabsorption (Gupta et al., 1992). Obese individuals tend to have glomerular hyperfiltration and these increased filtration rates correlate well with fasting insulin levels (Ribstein et al., 1995). A class of drugs called thiazolidinediones that are insulin sensitizers has been shown to have antihypertensive properties in rats and humans. It has been demonstrated that troglitazone significantly reduced both systolic and diastolic blood pressures, as assessed by 24-hour blood pressure monitoring in normotensive, insulin-resistant human subjects associated with improved insulin sensitivity and glucose tolerance (Nolan et al., 1994).

C. RESISTIN

Resistin is a newly discovered signaling protein that probably plays an important role in the development of insulin resistance and is thought to be the missing link between obesity and diabetes. The role of resistin in hypertension is being researched. A recent study from China reported that resistin gene polymorphism is an independent factor associated with systolic and diastolic blood pressures in type 2 diabetics. Diabetics with the GG genotype were found to have a higher prevalence of hypertension in this population (Tan et al., 2003). Other reports in Caucasian and Japanese populations found no association between resistin gene polymorphism and type 2 diabetes but the single nucleotide polymorphism (SNP) in the promoter region was a significant predictor of the insulin-sensitivity index. It was therefore hypothesized that noncoding SNPs in the resistin gene might influence insulin sensitivity in interaction with obesity.

D. FREE FATTY ACIDS

High FFA levels are thought to raise blood pressure by increasing sympathetic activity or enhancing the sympathetic vascular responses (Stepniakowski et al., 1995; Grekin et al., 1997). Subjects with visceral obesity deliver a FFA load to the liver that, in turn, activates hepatic afferent pathways that may lead to sympathetic activation and contribute to insulin resistance (Bergman et al., 2001). FFA levels in obese subjects are approximately 2-fold higher than in lean subjects. Also, an acute rise in FFA levels induced by intralipid infusion increases vascular reactivity to α-adrenergic agonists. They may also enhance reflex vasoconstrictor responses in the peripheral circulation. Infusions of oleic
acid into the portal of systemic circulation in rats increased their blood pressure and heart rates. These effects were abolished by adrenergic blockade. Interestingly, however, portal vein infusion caused a greater blood pressure rise than systemic infusions, emphasizing the potential role of afferent pathways in the liver. In humans, high rates of intralipid and heparin infusion caused a small (i.e., 4 mmHg) increase in mean blood pressure (Steinberg et al., 1997). On the other hand, long-term effects of FFAs on blood pressure are less clear and warrant further investigation (Hildebrandt et al., 1999b). In dogs, infusion of long-chain fatty acids had no effect on blood pressure, in contrast to rats that demonstrated a rise in blood pressure and heart rate. Neither cerebral (via vertebral artery) nor systemic infusion of long-chain fatty acids in dogs has a significant effect on arterial pressure, renal function, or hemodynamic responses. Therefore, the relationship between elevated FFA levels and hypertension currently is tenuous at best and merits further investigation.

E. LEPTIN

Leptin is a 167-amino acid peptide that has been the subject of intense research and discussion in recent years due to its possible role in the obesity-hypertension syndrome. Figure 5 schematically demonstrates the possible mechanisms via which leptin may exert its pressor effects (Zhjeng et al., 1994; Pellymounter et al., 1995; Lee et al., 1996; Haynes et al., 1997, 1998a; Casto et al., 1998; Flier, 1998; Lu et al., 1998; Onions et al., 1998; Shek et al., 1998; Hall et al., 1999b; Mark et al., 1999b; Lembo et al., 2000; Rahmouni et al., 2001; Carlyle et al., 2002). It is secreted by white adipocytes (Maffei et al., 1995; Considine, 2001). Leptin levels correlate well with the body adipose tissue stores. Levels of 5–15 μg/ml are noted in lean individuals and are typically elevated in most obese subjects (Considine et al., 1996). It crosses the blood-brain barrier to the CNS via a saturable, transport-mediated endocytosis, where it binds to its receptors (Ob-R) in the lateral and medial regions of the hypothalamus (Golden et al., 1997). The Ob-Rb is a full-length receptor with a transmembrane domain and a long intracellular carboxyl-terminal tail. The Ob-Ra, Ob-Rc, and Ob-Rd are prematurely terminated receptor proteins with short intracellular tails. The Ob-Re lacks the transmembrane domain and thus may function as a soluble receptor to bind and inactivate the circulating leptin. This binding of leptin to its receptor triggers a series of reactions and neuropeptide pathways that serve to regulate energy balance by reducing appetite and increasing energy expenditure via stimulation of the adrenergic system (McAuley et al., 1993; Thornton et al., 1994; Fan et al., 1997; Huszar et al., 1997; Haynes et al., 1999). Evidence for the fact that leptin acts as a feedback inhibitor of food intake and regulates body weight comes from genetic studies in mice and humans. Mice that lack the ability to synthesize leptin (i.e., ob/ob mice) or that have mutations of the leptin receptor...
(i.e., db/db mice) develop extreme obesity. Mutations of the leptin gene in humans result in extreme obesity but are very rare and do not contribute significantly to the obesity epidemic.

Several rodent studies have indicated that intravenous (IV) and intracerebroventricular (ICV) infusion of leptin increases sympathetic activity in kidneys, adrenals, and brown adipose tissue (BAT) after 2–3 hours of infusion (Figure 6) (Shek et al., 1999; Aizawa-Abe et al., 2000). Leptin infusion in rodents causes mild acute blood pressure elevation, whereas long-term infusions cause a more-significant and sustained rise (Haynes et al., 1998b; Mark et al., 1999b). Failure of blood pressure to rise significantly in the acute scenario may be explained by a concomitant stimulation of NO synthesis, which, in turn, coun-
teracts its pressor effects (Hirose et al., 1998; Suter et al., 1998; Frubeck, 1999; Lembo et al., 2000; Kuo et al., 2001). An alternative explanation is that leptin’s sympathetic effect on peripheral vasoconstriction is probably not potent enough to produce significant blood pressure elevation, while the main leptin pressor effect is via the SNS, causing avid renal salt retention and hence hypertension. The rise in blood pressure with leptin infusion is slow in onset and occurs despite a reduction in food intake that accompanies it that would tend to reduce blood pressure. Moreover, the hypertensive effects of leptin are amplified when NO synthesis is impaired experimentally. Conceivably, NO production in the obese is impaired due to endothelial dysfunction.

Transgenic mice that overexpress leptin have elevated blood pressure levels comparable to those produced by leptin infusions. Importantly these chronic

![Diagram](image)

**FIG. 6.** A summary of the mechanisms by which obesity may lead to excessive cardiovascular morbidity and mortality. Abbreviations: SNS, sympathetic nervous system; RAAS, renin-angiotensin aldosterone system; NAP, natriuretic peptide; HR, heart rate; PVR, peripheral vascular resistance; Na, sodium; LVH, left ventricular hypertrophy; HF, heart failure; †, increase.
blood pressure elevations are abolished completely by α and β-adrenergic blockade (Shek et al., 1999; El-Haschimi et al., 2000). Also, obese mice that are leptin deficient and obese rats with a leptin receptor mutation usually do not have elevated blood pressure, compared with lean control mice. This suggests that hyperleptinemia with normally functioning leptin receptors is crucial for leptin-induced hypertension (VanHeek et al., 1997; Ishizuka et al., 1998). The role of minor differences in the production and sensitivity to leptin towards contributing to obesity is less well understood.

Women typically have higher leptin levels than men (Flier, 1998) but these differences may not be accountable by fat mass alone. The effect of ethnicity on leptin levels is even less well understood. Blacks may have higher leptin concentrations than whites, even when adjusted for fat volume. Another important concept that has gained ground is the presence of selective leptin resistance (El-Haschimi et al., 2000). Obese humans continue to overeat, despite elevated circulating leptin levels, indicating a failure of feedback mechanisms on satiety. Yet they develop hypertension, indicating that the effect of leptin on the sympathetic system is intact. As attractive as this hypothesis may sound, it has been tested only in rodents and not in humans (VanHeek et al., 1997). The complexity of the relationship between adiposity, leptin, and long-term blood pressure control is further illustrated by the fact that lower body obesity causes greater increases in leptin than visceral obesity, even though visceral obesity is more closely associated with hypertension.

VI. Role of Neuropeptide Y, Melanocortin-4 Receptors, and Other Neurochemicals

Activation of leptin receptors in the arcuate nucleus initiates a cascade of downstream events. These include inhibition of neurons containing neuropeptide Y (NPY), an orexigenic peptide, and stimulation of neurons containing pro-opiomelanocortin (POMC), the precursor of α-melanocyte-stimulating hormone (MSH), an anorexigenic peptide. NPY is a potent and effective orexigenic agent upon acute and chronic administration. Chronic ICV infusion of NPY in rats produces an obesity syndrome. It has been postulated that endogenous NPY may have an important role in basal and starvation-induced food intake. However the receptor subtype that mediates the orexigenic effects of NPY is unknown. The negative effect of leptin on NPY formation in the hypothalamus is thought to be the primary mediator causing appetite suppression. NPY injections into the thalamus reproduce all features of hypothalamic hypoactivity (e.g., obesity, excessive eating behavior, decreased BAT heat production) (Mountjoy et al., 1994; Boston et al., 1997; Huszar et al., 1997; Seeley et al., 1997; Haynes et al., 1998a; Vaisse et al., 1998; Yeo et al., 1998). The ob/ob phenotype in ob/ob mice appears to be mediated, in part, by increased NPY because ob/ob mice in which NPY
expression has been knocked out (NPY−/NPY−) are substantially less obese than ob/ob mice with normal NPY expression. However, obesity in these mice is severe, even in the absence of NPY expression, and they respond normally to the satiety effects of leptin, indicating that leptin must act on other targets to induce satiety. The administration of NPY into the vagal nucleus of tractus solitarius or caudal ventrolateral medulla causes a reduction in blood pressure (Schorr et al., 1998). Since hyperleptinemia causes a reduction in brain NPY levels, it is possible that the hypertensive effects of leptin may be mediated by a reduction in NPY levels. At present, there is little evidence regarding the putative role of reduced central levels of NPY in mediating the effects of leptin on sympathetic activity and arterial pressure.

The POMC pathway may interact with leptin to stimulate sympathetic activity and regulate energy balance. MC4-R may play an important role in feeding mechanisms. While the central administration of MC4-R agonists decreases feeding, MC4-R deletion induces obesity in rats. α-MSH, which is derived from the breakdown of POMC, may be the endogenous ligand for MC4-R. POMC expression in the arcuate nucleus may be increased by leptin, an effect that could be part of a feedback pathway for control of appetite and sympathetic activity. Increasing leptin, associated with obesity, would stimulate arcuate POMC expression and α-MSH, which would then act elsewhere in the hypothalamus on MC4-R-expressing neurons, causing decreased food intake and increased sympathetic activity. Other factors that may influence the MC4-R pathway include agouti-related peptide (AgRP), which acts as an antagonist on this receptor. Yellow agouti mice with ectopic overexpression of agouti peptide are obese and hyperleptinemic owing to antagonism of the hypothalamic melanocortin system by the excess agouti protein. Treating rodents with an MC4-R antagonist completely abolishes the increased renal sympathetic activity associated with short-term ICV leptin infusion in rats. Surprisingly, MC4-R blockade does not prevent leptin-induced stimulation of sympathetic activity in BAT. This suggests that the thermogenic effects of leptin in BAT are not mediated through MC4-R, whereas the short-term effect of leptin to enhance renal sympathetic activity appears to depend on intact MC4-R. These paradoxical effects of MC4-R blockade on BAT and renal sympathetic activity suggest that leptin may activate the SNS through complex central pathways.

The orexins and melanin-concentrating hormone (MCH), which regulate appetite and energy homeostasis, are recently discovered mediators (Sakurai, 1999; Shirasaka et al., 1999). Short-term experiments involving ICV injections of orexins increase renal sympathetic activity, heart rate, and arterial pressure in rats and thereby raise blood pressure. Control mechanisms for orexin release are opposite to those of leptin in that orexin expression usually increases with starvation and decreases with increased energy intake. Therefore, orexin levels are reduced in situations when leptin is increased (e.g., obesity) and thus
probably do not mediate the hypertensive effects of leptin. However, the importance of orexins and other neurochemical pathways in the hypothalamus in modulating the chronic effects of leptin on sympathetic activity, thermogenesis, and arterial pressure is largely unexplored.

VII. Role of Adipose Tissue and Systemic RAAS

A. SYSTEMIC RAAS

The RAAS seems to be activated in obesity, despite a state of volume expansion and sodium retention. Elevated serum aldosterone levels have been reported in the obese (Granger et al., 1994; Schorr et al., 1998; Engeli et al., 2001, 2002) and it is postulated that a yet-unidentified factor (possibly a fatty acid) derived from adipose tissue causes the release of a hepatic factor that, in turn, steps up aldosterone synthesis (Goodfriend et al., 1998, 1999). Reports in the literature suggest that a relationship between plasma angiotensin (Ang II) levels, plasma renin activity (PRA), and plasma angiotensin-converting enzyme (ACE) with BMI exists in humans (Licata et al., 1994b; Cooper et al., 1997, 1998). Sharma and colleagues reported a relationship between plasma leptin and Ang II levels and leptin and PRA. Since plasma leptin levels correlate with adipose tissue mass (Engeli et al., 2000), it is fair to speculate that adipose tissue may directly contribute to circulating Ang II. Sharma and coworkers also noted that a positive family history of hypertension predicts a relationship between plasma Ang II and blood pressure, suggesting a role for genetic factors in Ang II-related blood pressure response (Schorr et al., 1998).

The effect of weight loss on RAAS also has been investigated. On a short-term scale, Tuck and Sowers studied the effect of weight loss on RAAS and blood pressure in 25 obese patients placed on a 12-week weight-reducing diet (Tuck et al., 1981). Sodium intake was either medium or low; PRA, aldosterone, and mean arterial pressure (MAP) were significantly reduced. The reduction in PRA but not in aldosterone correlated with weight loss in both sodium-intake groups. MAP fell significantly and to the same degree in both groups, correlating with weight loss throughout the study and with PRA from weeks 4–12. These results suggest that weight loss is accompanied by reductions in PRA and aldosterone and that PRA reductions may contribute to the decline in blood pressure (Bloem et al., 1995; Umemura et al., 1997; Uckaya et al., 1999; Engeli and Sharma, 2002).

In a nutshell, despite evidence in favor of a stimulated RAAS in obesity, the role of genetic factors continues to be investigated. There is little information on the long-term effect of weight loss on the RAAS; larger studies are needed to investigate the short-term effect.
B. ADIPOSE TISSUE RAAS

It is becoming increasingly evident that adipose tissue possesses a local RAAS that plays an important role in adipose tissue function. Recent studies suggest that adipose tissue angiotensinogen mRNA expression is higher in abdominal than subcutaneous adipose tissue and therefore may be associated with increased cardiovascular risk. Fat cells possess the capability to synthesize all components of the RAAS. They apparently also express Ang II receptors, which make them a target for the paracrine-produced Ang II (Giacchetti et al., 1999). That local Ang II may be a growth factor for fat cells is suggested by experiments in angiotensinogen-knockout (KO) mice that exhibit low blood pressure, have hypotrophic fat cells with reduced fatty acid synthase activity, and demonstrate abnormal, diet-induced weight gain (Frederich et al., 1995; Engeli et al., 2000). It has been suggested from studies in these animals that adipose tissue RAAS may govern blood pressure. Massiera and coworkers expressed the angiotensinogen (AGT) gene in adipose tissue of AGT-KO mice, creating a transgenic-KO mouse model in which production of AGT is limited to adipose tissue. In these animals, systemic levels of AGT increased to 20% of wild-type levels, demonstrating that AGT produced in fat cells can enter the circulation (Massiera et al., 2001). Blood pressure and sodium homeostasis were restored in the transgenic animals, lending further credence to the theory that an increased fat cell mass may result in higher circulating AGT levels, a finding confirmed in obese individuals.

Additional evidence supports the role of adipose tissue in causation of hypertension. A transgenic mouse that overexpresses the cortisol-forming enzyme 11β-hydroxysteroid dehydrogenase (HSD) 1 develops obesity hypertension and all features of the metabolic syndrome (Masuzaki et al., 2001). This model was found to overexpress angiotensin in adipose tissue and elevated serum angiotensin levels. Obese hypertensive women have been found to overexpress genes encoding renin, angiotensin-converting enzyme (ACE), and Ang II type 1 receptor in subcutaneous abdominal fat cells (Gorzelniak et al., 2002). Despite the fact that expression of the AGT gene is lower in the obese, the high Ang II levels in circulation may be derived from the huge fat cell mass, resulting in hypertension. It recently has been reported that mutations in the DD phenotype of the ACE gene may be associated with obesity hypertension in Caucasian men.

VIII. Role of the Natriuretic Peptide System

The natriuretic peptide system consists of the atrial natriuretic peptide (ANP), the brain natriuretic peptide (BNP), and the C-type natriuretic peptide (CNP), each encoded by a separate gene (Rosenzweig and Seidman, 1991; Maack, 1992; Maoz et al., 1992; Nakao et al., 1992; Sarzani et al., 1993,1996;
Dessi-Fulgheri et al., 1998). They are synthesized predominantly in the heart, brain, and kidneys. They work via specific receptors, namely, NPr-A, NPr-B, and NPr-C (Nakao et al., 1992; Levin et al., 1998). The natriuretic peptides have salutary effects on plasma volume, renal sodium handling, and blood pressure and cause a reduction in sympathetic tone in the peripheral vasculature. They dampen baroreceptor function and lower the activation threshold of vagal efferents, suppressing reflex tachycardia and vasoconstriction resulting from decreased extracellular volume. Transgenic mice that overexpress the ANP gene have lower blood pressure, while animals with inactivated ANP gene are prone to develop salt-sensitive hypertension (Melo et al., 1998, 2000). Therefore, the natriuretic peptides have a protective role on the development of hypertension due to their natriuretic and vasodilator effects as well as due to their inhibitory effect on the SNS and the RAAS.

It has been noted that the NPr-C receptor is overexpressed in adipose tissue in the obese. This may adversely affect the systemic activity and actions of the natriuretic peptides, leading to sodium retention and hypertension. It has been reported that ANP plasma levels are lower in the obese hypertensive than in obese normotensive subjects (Dessi-Fulgheri et al., 1997). These obese hypertensive subjects also demonstrate a stronger response to exogenously administered ANP, as measured by blood pressure reduction, natriuresis, and increases in urine cyclic guanylate monophosphate (cGMP) excretion (Dessi-Fulgheri et al., 1999). These effects are pronounced after these subjects have been on a low-calorie diet for a span of time, rather than at baseline. The ANP response to salt load was found to be suppressed in the obese, compared to a potent ANP elevation in the lean. Concomitantly, PRA and aldosterone were suppressed in the obese when saline challenged. Obese rats that were subjected to 40% weight loss by caloric restriction demonstrated a significant increase in circulating ANP levels as well as a strong decrease in PRA (Crandall et al., 1989). A recent study reported an association between a promoter variant at position −55 in the NPr-C gene, a higher blood pressure, and lower ANP plasma levels in obese hypertensive subjects (Sarzani et al., 1999). Further studies are needed to understand the role of this finding re: its possible contribution to blood pressure elevation.

**IX. Cardiovascular System Changes**

**A. VASCULAR ADAPTATIONS**

An alteration in ions at the cellular and molecular level appears to be important in regulating vascular smooth muscle tone. These may be deregulated in the obese, resulting in abnormal vascular responsiveness (Messerli et al., 1981; Frohlich et al., 1983; Assmann and Schulte, 1998). Insulin works as a vasodilator by inhibiting voltage-gated Ca$^{2+}$ influx. It also stimulates glucose transport and
phosphorylation of glucose to glucose-6-phosphate, which further activates Ca^{2+}\text{ ATPase transcription and increases cellular Ca}^{2+}\text{ efflux. These actions result in a net decrease in intracellular Ca}^{2+}\text{ and, therefore, decreased vascular resistance. These effects are blunted in obesity due to insulin resistance, leading to increased vascular resistance (Terazi, 1983; Licata \textit{et al.}, 1990; Rocchini \textit{et al.}, 1992; Rochstroh \textit{et al.}, 1992; Schmieder and Messerli, 1993; Weir \textit{et al.}, 1998; Zemel, 1998).}

Resnick and colleagues (1997) discovered that increased abdominal visceral fat, decreased intracellular magnesium, and advanced age were closely associated with reduced aortic distensibility. In this study, magnetic resonance imaging (MRI) was utilized to evaluate the aorta of normal and hypertensive subjects.

Jacobs and Sowers studied the effect of weight reduction on peripheral vascular resistance (PVR), reflected by forearm vascular resistance and MAP in obese persons. Weight loss resulted in a clearly significant decrease in PVR and MAP (Jacobs \textit{et al.}, 1993).

B. CARDIAC ADAPTATIONS

Obesity is a major cause of type I diabetes, hypertension, and hyperlipidemia. These disorders individually and synergistically increase the cardiovascular risk, as shown in the Prospective Cardiovascular Munster (PROCAM) study (Assmann and Schulte, 1988).

Prolonged hypertension in lean subjects tends to produce a concentric left ventricular hypertrophy (LVH), whereas the predominant pattern of cardiac hypertrophy noted in obese hypertensives is eccentric. With concentric hypertrophy, cardiac dilatation is a late and terminal event (Frohlich \textit{et al.}, 1992; Simon \textit{et al.}, 1994). Heart failure is more common in the obese subject, even when corrected for the presence of hypertension (Drenick \textit{et al.}, 1980). The presence of both obesity and hypertension in a patient results in a mixed pattern of cardiac hypertrophy, caused by an elevation in both cardiac preload and afterload (Messerli \textit{et al.}, 1983). Obesity results in increased preload due to an expanded vascular volume, while the high afterload can be accounted for by the presence of hypertension and SNS activation. After adjustment for established risk factors, the risk of heart failure increases by 5% in men and 7% in women for each BMI increment of 1 (Kenchaiah \textit{et al.}, 2002). Compared with subjects having a BMI below the obese range, obese subjects have double the risk of heart failure, after adjustment for co-morbid risk factors. Autopsy data from the Mayo Clinic reveal that the average cardiac mass is 467 g in obese hypertensive subjects, compared with 367 g in obese individuals without heart disease and 272 g in nonobese hypertensive subjects (Smith and Willius, 1933). Since LVH itself is a major risk factor for sudden death and death due to progressive cardiac decompensation, it may partially explain the increased incidence of cardiovas-
cular morbidity and mortality in the obese (Lip et al., 1994). Mononuclear cell infiltration in and around the sinoatrial node, with fat deposition all along the conduction system, is present in the myocardium of obese individuals (Bharati and Lev, 1995). Lipomatous hypertrophy of the interatrial septum also has been noted in obesity (Basa et al., 1994). All these changes make the myocardium in the obese hypertensive an ideal substrate for cardiac arrhythmia and sudden death (Duflou et al., 1995).

X. Proinflammatory and Prothrombotic Changes

A. ADIPOSE TISSUE IS A SOURCE OF INFLAMMATORY CYTOKINES AND HORMONES

Adipose tissue in general and central adipose tissue in particular is recognized as a rich milieu and source of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), and plasminogen activator inhibitor (PAI-1). As such, obesity has been suggested to be a low-grade inflammatory condition increasingly important in the causation and progression of hypertension and atherosclerosis (Festa et al., 2000; Das, 2001). It is thought that the central adipocyte synthesizes TNF-α, which, in turn, stimulates IL-6, considered a major regulator in the production of acute-phase reactants such as CRP, PAI-1, and fibrinogen from the hepatocyte.

It is possible that the relationship between obesity and vascular disease may depend in part on the increased production and release of these inflammatory mediators from adipose tissue. A direct cause-and-effect relationship, however, has not been clearly established. It is not known, for example, whether long-term treatment with aspirin or other nonsteroidal anti-inflammatory drugs reduces the level of inflammatory cytokines and CVD in obese patients.

B. HYPERCOAGULATION AND INCREASED RISK OF THROMBOSIS IN OBESITY

Increased risk for thrombosis may contribute to a higher incidence of heart disease and stroke in obesity. Obesity is associated with polycythemia. Epidemiologic evidence exists that hypercoagulation and impaired fibrinolysis activity are related to BMI or waist-to-hip ratio. For example, obese subjects have higher levels of factor VII antigen, fibrinogen, plasminogen, and PAI-1 activity, all of which have been suggested to increase the risk for CVD (Alessai et al., 2000; Chu et al., 2001; Rissanen et al., 2001). The increased flux of FFAs in obesity may promote thrombosis by increasing protein C, PAI-1, and/or platelet aggregation. Adipose tissue production of leptin or inflammatory mediators have been suggested as important factors causing increased thrombosis (Konstantinides et
al., 2001) but these aspects of the relationship between obesity and CVD are poorly understood and require additional study. Other mechanisms for platelet activation in the obese recently have been elucidated, at least in part. Davi and coworkers (2002) reported that a visceral or android pattern of obesity is associated with lipid peroxidation and persistent platelet activation, both of which appear partially reversible with weight loss. An association has been proposed between a circulating soluble CD40 ligand (CD40L) and platelet activation. CD40L is a trimeric, transmembrane protein of the TNF family that is inactive in resting platelets but is rapidly activated and expressed on the platelet surface when the platelet is stimulated. Therefore, increased levels of circulating CD40L represent an index of platelet activation. Desideri and Ferri (2003) addressed the relationship between central obesity and circulating levels of soluble CD40L and the effect of weight loss on this measure of platelet activation in a prospective intervention cohort study. It was found that baseline levels of circulating CD40L and 8-iso-PGF2α levels (a marker of lipid peroxidation) were significantly higher in obese vs. nonobese subjects. BMI levels correlated well with levels of CD40L and 8-iso-PGF2α. After a 16-week intervention period of caloric restriction and weight loss, levels of these markers went down, corresponding with a commensurate lowering of the BMI in the obese subjects.

XI. Management

A. PHYSICAL EXERCISE

Increased physical activity is perhaps the most-widely prescribed and the most-poorly complied with of all weight-reduction strategies. It requires considerable time, thought, and effort from the patient and the therapist. Physical activity is essential for long-term weight control. It appears to be the best predictor of maintenance of weight loss. Even in the absence of weight loss, increased physical activity is associated with other desirable outcomes, such as improved cardiovascular health and perhaps reduction in insulin resistance. Studies suggest that, in overweight and obese persons, physical activity is independently associated with the redistribution of adiposity away from the abdomen. It is important not to set inappropriately ambitious physical activity goals, since they increase the likelihood that the exercise program will be abandoned. High levels of aerobic physical activity at a fitness center are not needed to obtain health benefits. Several studies have compared the impact of lifestyle activity vs. physical exercise and demonstrated that they result in similar health benefits (e.g., control of hypertension and body fat) (Andersen et al., 1999). Based on these and other observations, it is clearly inappropriate to suggest to patients that the only acceptable physical activity included in their
weight-loss program would be vigorous in nature. Although some may choose this, those who don’t should be encouraged to start with low-impact, moderate-intensity physical activity (i.e., walking) of short duration, with a goal of accumulating at least 30 minutes of physical activity on most days of the week. A recent report suggests that physical activity participation for 60 minutes per day will impart increased benefits and is more likely to help maintain weight loss.

B. CALORIC RESTRICTION

Caloric restriction seems the most-important component of obesity management. A daily caloric reduction of 500–1000 cal produces a weight loss of 0.45–0.90 kg/week. Individually planned diets that incorporate all essential dietary components should be made available to everyone entering a weight-loss program. Many types of diets — including high-protein, low-carbohydrate, and low-fat — have been promoted. The individual macronutrient component of diet is controversial and has not been determined (Jackic et al., 2001). All low-calorie diets produce weight loss and macronutrient composition seems less important than the number of calories cut (Freedman et al., 2001).

C. BEHAVIORAL MODIFICATION

Behavioral therapy is a very important component of any weight-loss program. It helps patients develop the skills they need to identify and modify eating and activity behaviors. It also helps remodel thinking patterns that undermine weight-control measures (Wadden et al., 2000). Important components of behavioral therapy are self weight monitoring, measuring intake by keeping a food log, and physical activity. Other strategies are identification of stimuli that trigger unusual, irregular food intake or binging on food and problem solving, which identifies problems and proposes solutions. Behavioral strategies encompass the active and supportive involvement of the social and family fabric that surrounds the patient. Stress and time management are also essential to a comprehensive weight-loss program. Patients who appear depressed and have poor self-image should receive appropriate referral to psychotherapists, support groups in the community, and, if deemed necessary, a psychiatrist. Professional help from dieticians, nurse educators, and exercise physiologists should be readily available (Boutelle and Kirschenbaum, 1998).

D. PHARMACOTHERAPY

Because antihypertensive drug treatment in obesity hypertension is not yet based on evidence from large, randomized, controlled trials that have specifically addressed this population, it remains empirical. No definitive guidelines have been framed; therefore, only suggestions can be made based upon assumed
pathophysiologic mechanisms and clinical experience. For example, since β-blockers can result in weight gain and impair glucose tolerance, their use in uncomplicated obesity and hypertension cannot be recommended as routine first-line therapy (Sharma et al., 2001). This recommendation cannot extend across the board to patients admitted to critical care units with acute coronary syndromes where β-blockers are not only essential but also may be lifesaving. They may be used to manage patients with hypertension uncontrolled with multiple other agents. The importance of adrenergic blockade in the management of this syndrome cannot be dismissed (Wofford et al., 2001). It was shown by Masuo et al. (2001a,b) that subjects who were resistant to weight loss-induced blood pressure reductions possessed a highly active SNS and would potentially benefit from adrenergic blockade. Calcium channel blockade cannot be recommended in obese hypertensive patients, since some small studies have cast doubt on their efficacy. No definitive recommendations can be made until data from large, randomized, controlled trials are gathered (Schmieder et al., 1993; Masuo et al., 2001a,b).

ACE inhibitors and angiotensin-receptor blockers (ARBs) may be considered preferred agents for several reasons. First, they are metabolically neutral, except for the risk of hyperkalemia, which can be managed effectively with careful monitoring. Second, there is evidence from the Heart Outcomes Prevention Evaluation (HOPE) and Captopril Prevention Project (CAPPP) trials (Hansson et al., 1999; Yusuf et al., 2000) that ACE inhibitors may prevent or retard the development of type 2 diabetes. Third, this class of agents may be the most effective in preventing the onset and progression of proteinuria that are responsible for the inexorable progression to obesity-hypertension-related ESRD. Finally, this class of agents may be the most effective to prevent and manage eccentric cardiac hypertrophy and thus progression to heart failure. Low-dose ACE inhibitors may be more effective than thiazides (Reisin et al., 1997; Yusuf et al., 2000; Wofford et al., 2001). Therefore, it may be reasonable to recommend ACE inhibitors and ARBs as first-line therapy for obesity-related hypertension. Thiazide diuretics may be an effective class of agents for this group of patients, since they directly address the volume-expanded state of the obesity-hypertension syndrome (Reisen et al., 1997) and may prevent cardiac dilatation by preload reduction. Caution must be exercised with use in this class of patients, primarily for the risk of exacerbating dysglycemia and erectile dysfunction, which are quite prevalent in this population. Excessive diuresis may result in a state of volume contraction, triggering further activation of the SNS and the RAAS, resulting in avid renal salt and fluid retention, with exacerbation of hypertension. Indeed, a combination of ACE inhibitors and low-dose thiazides may be more effective than either strategy alone in this population. Having said that, it is important to note that there is little evidence to support these hypotheses.
Weight loss — achieved by exercise, behavioral modification, pharmaceutical agents, or a combination — is another important and effective means of reversing insulin resistance, elevated leptin levels, decreased cardiac output, and activated SNS (Emdin et al., 2001; Itoh et al., 2001; Nakano et al., 2001). Despite significant initial success, long-term and sustained weight loss is difficult to achieve with diet and exercise alone.

Some recently developed pharmaceutical agents (e.g., orlistat, sibutramine) have shown good promise in achieving significant and sustained weight loss in the range of 5–10%. In a recent meta-analysis that pooled data from trials using orlistat (30% of participating subjects were hypertensive), significant blood pressure reductions were noted after 1 year in subjects who lost 5% or more weight. The blood pressure reductions were on the order of 7 mmHg systolic and 5.5 mmHg diastolic, comparable to those achieved with antihypertensives used as single agents (Zavoral, 1998). Other cardiovascular risk factors improved significantly in subjects who took orlistat for more than 2 years (Rossner et al., 2000). Since orlistat has no negative effect on the cardiovascular risk profile, it can be safely recommended for treating the obese patient with hypertension.

Sibutramine, another anti-obesity medication, acts by inhibiting serotonin and norepinephrine uptake. In doing so, it enhances satiety and increases energy utilization (Hansen et al., 1999). A recent trial called STORM (Sibutramine in Obesity Reduction and Management) revealed significant and sustained weight loss comparable to that achieved with orlistat. Improvement in metabolic parameters such as blood glucose and lipid levels was also noted (Hansen et al., 2001). However, small increases in blood pressure and heart rate were noted and no net blood pressure reductions could be achieved commensurate with the degree of weight loss. In another trial with sibutramine, those who maintained weight at 1 year had no significant changes in blood pressure and heart rate, when compared to baseline (McMahon et al., 2000). Therefore, sibutramine cannot be recommended in the hypertensive-obese subject. If it must be used, careful blood pressure monitoring is warranted with use of effective antihypertensive medications.

Novel weight-loss medications have been reported recently. A randomized control trial conducted with zonisamide (an anti-epileptic agent with dose-dependent biphasic dopaminergic and serotonergic activity) resulted in significantly greater weight loss and reductions in blood pressure, compared to lifestyle intervention alone in the extended phase of the trial. The drug was found to be safe, with fair compliance (Gadde et al., 2003). Therapy with a recombinant variant of ciliary neurotrophic factor (rhvCNTF) resulted in significant weight loss. This agent that was developed for the management of amyotrophic lateral sclerosis (a type of motor neuron disease) did not prevent disease progression but resulted in weight loss. It is thought to exert its effect by binding to the CNTF receptor and activating leptin-like intracellular signaling pathways (janus kinases
and signal transducers and activators of transcription 3) in hypothalamic nuclei, thereby regulating food intake and body weight (Ettinger et al., 2003). Despite significant weight loss, no significant effect on blood pressure was noted. The drug must be administered subcutaneously. Other agents such as SR141716 (Rimonabant) are in phase 3 trials. Rimonabant acts by blocking a cannabinoid receptor in the CNS that, when activated, stimulates hunger.

E. ROLE OF BARIATRIC SURGERY

The National Institutes of Health criteria for obesity surgery eligibility are a well-informed and motivated patient with a BMI > 40 or a patient with less-severe obesity (i.e., BMI > 35) with high-risk, co-morbid conditions (e.g., type 2 diabetes, cardiopulmonary problems). Trials such as the Swedish Obesity Study (SOS) found that weight-reduction surgery in the morbidly obese with significant co-morbidities can result in improved metabolic parameters and blood pressure. Surgery is an option for patients in whom all conservative measures, including pharmaceutical agents, have failed and in those who cannot tolerate drugs due to their prohibitive side effects. These procedures entail considerable operative risk and pose ethical and scientific questions, so cannot yet be routinely recommended (Sjostrom et al., 2001; Torgerson and Sjostrom, 2001; Laimer et al., 2002; Nabro et al., 2002).

XII. Summary

This review has discussed some of the mechanisms involved in the causal relation between obesity and hypertension. Obesity causes a constellation of maladaptive disorders that individually and synergistically contribute to hypertension among other cardiovascular morbidity. Well-designed, population-based studies are needed to assess the individual contribution of each of these disorders to the development of hypertension. Control of obesity may eliminate 48% of the hypertension in whites and 28% in blacks. We hope that this chapter will help scientists formulate a thorough understanding of obesity hypertension and form the basis for more research in this field, which greatly impacts on human life.

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