Impact of the Obesity Epidemic on Hypertension and Renal Disease

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Current Hypertension Reports 2003, **5:**386–392
Current Science Inc. ISSN 1522-6417

Excess weight gain is a major cause of increased blood pressure in most patients with essential hypertension, and also greatly increases the risk for renal disease. Obesity raises blood pressure by increasing renal tubular reabsorption, impairing pressure natriuresis, causing volume expansion due to activation of the sympathetic nervous system and renin-angiotensin system, and by physical compression of the kidneys, especially when visceral obesity is present. The mechanisms of sympathetic nervous system activation in obesity may be due, in part, to hyperleptinemia that stimulates the hypothalamic pro-opiomelanocortin pathway. With prolonged obesity, there may be a gradual loss of nephron function that worsens with time and exacerbates hypertension. Weight reduction is an essential first step in the management of obesity hypertension and renal disease. Special considerations for the obese patient, in addition to adequately controlling the blood pressure, include correction of the metabolic abnormalities and protection of the kidneys from further injury.

Introduction

The rapid rise in the prevalence of obesity and overweight in the past two decades has led to a call for action by many organizations concerned with health care [1]. Obesity is a worldwide problem that increasingly affects children as well as adults [2••,3••]. The most recent reports from the National Health and Nutrition Examination Survey (NHANES) indicate that approximately 31% of the adult population in the United States is obese with a body mass index (BMI) of more than 30 [3]. Almost two thirds of the population (64%) is overweight with a BMI of more than 25, the point at which cardiovascular risk begins to increase substantially [3•]. Perhaps even more alarming is the finding that the proportion of children and adolescents who are overweight has tripled in the past three decades [4], leading to a dramatic increase in associated medical problems such as diabetes and hypertension [2••].

Overweight and obesity increase the risk for cardiovascular disease through multiple mechanisms including hypertension, diabetes, dyslipidemia, atherosclerosis, and chronic renal disease [5,6•,7,8]. These disorders often occur together and are sometimes referred to as the "metabolic syndrome," although they are almost always initiated by excess weight gain.

The total impact of obesity and overweight on cardiovascular and renal disease has been difficult to quantify, although it is clear that excess weight gain is rapidly becoming one of the most important public health problems in the industrialized world. Population studies usually assess cardiovascular risk in terms of the manifestations of obesity, such as hyperlipidemia, diabetes, and hypertension. However, many obesity-associated disorders are interdependent, and it is therefore difficult to determine with statistical or experimental methods their separate effects on cardiovascular risk. In observational studies, disorders such as dyslipidemia, diabetes, and hypertension are usually factored out of risk analyses even though excess weight gain is the major cause of each of these disorders. Also, nonlinear synergistic relationships may exist between obesity-associated disorders and cardiovascular disease so that the total risk is greater than predicted from the individual risk factors.

The duration and type of obesity (*ie*, visceral versus subcutaneous fat) are also important considerations in assessing cardiovascular risk. For example, the risk for developing diabetes is known to increase progressively with increasing duration of obesity [8]. Likewise, visceral obesity carries a greater risk for development of hypertension and cardiovascular disease than lower body obesity [9]. Unfortunately, most population studies have not taken into account these complex aspects of obesity-associated cardiovascular disease. Therefore, well-controlled animal studies, long-term weight loss studies in humans, and longitudinal observational studies in humans are all needed for mechanistic insights and to assess the quantitative importance of the multiple risk factors induced by obesity. In this brief review, we focus mainly on animal and human studies that describe the pathophysiology and treatment of obesity-associated hypertension and renal disease.

Obesity As a Major Cause of Hypertension

The importance of excess weight gain as a cause of hypertension has been clearly demonstrated in experimental studies as well as clinical and population studies. Excess weight gain is one of the best predictors of subsequent development of hypertension [6•,9–11]. Moreover, blood pressure closely correlates with BMI and other anthropometric and biochemical indices of obesity, such as waist-to-hip ratio (an indicator of central adiposity) and plasma insulin and leptin concentrations [6•,10,11]. The association between obesity and hypertension found in population studies cannot be attributed to genetic factors because it has been observed in diverse populations throughout the world and in populations of similar origin living in different locations. Other cardiovascular risks associated with industrialization cannot fully explain this relationship as it has also been observed in multiple studies of nonindustrialized populations [12,13].

Although the precise contribution of excess weight to human essential hypertension has not been unequivocally established, risk estimates from the Framingham Heart Study suggest that approximately 78% of hypertension in men and 65% in women can be directly attributed to excess body weight [11]. There is also evidence, however, that this relationship can be modified by several factors, including the distribution of body fat, the duration of obesity, and genetic factors [12].

Clinical studies have also clearly shown the therapeutic value of weight loss for reducing blood pressure [14,15]. Although some obese persons may not be "hypertensive" (*ie*, their blood pressure may be less than 140/90 mm Hg), weight loss usually lowers blood pressure even in these "normotensive" overweight persons. This suggests that obese subjects with "normal" blood pressure are hypertensive relative to their baseline blood pressure. Also, if obesity is sustained, blood pressure may eventually rise to levels that are clearly hypertensive. Whether antihypertensive therapy, including weight loss programs or pharmacologic therapy, in these "prehypertensive" obese persons provides protection against cardiovascular and renal disease, however, remains to be determined.

Experimental studies of genetic and dietary-induced animal models of obesity have permitted mechanistic insights into the factors that link excess weight gain with hypertension. In dogs, rabbits, and rats, weight gain induced by long-term high-fat diets consistently increases arterial pressure [6•,7,16]. Moreover, the cardiovascular, renal, endocrine, and metabolic changes observed in animal models of diet-induced obesity appear to mimic very closely those found in obese humans [7,17]. Therefore, we will also discuss the results from animal experiments in the context of obesity-associated hypertension in humans.

Mechanisms of Obesity-induced Hypertension

A central feature of increased blood pressure associated with the development of obesity in animals as well as in humans is increased renal sodium reabsorption and blood volume expansion that initiate the rise in blood pressure associated with weight gain [12,17]. The increased sodium reabsorption impairs renal-pressure natriuresis so that obese subjects require higher than normal blood pressures to maintain a balance between intake and urinary output of sodium [17]. Glomerular filtration rate (GFR) is actually elevated in obesity, probably as a compensatory response to increased tubular reabsorption [17,18]. With prolonged obesity, the increases in arterial pressure, glomerular hyperfiltration, neurohumoral activation, and metabolic changes may cause renal injury and a decline in GFR, thereby causing further impairment of pressure natriuresis and more severe hypertension.

Three mechanisms appear to be especially important in mediating the increased sodium reabsorption and hypertension associated with weight gain: 1) increased sympathetic nervous system (SNS) activity; 2) activation of the renin-angiotensin system (RAS); and 3) physical compression of kidneys, especially associated with visceral obesity.

Sympathetic Nervous System Activation in Obesity Hypertension

Several observations suggest that increased SNS activity contributes to obesity hypertension [18]: 1) SNS activity, especially renal sympathetic activity, is increased in obese subjects [19,20]; 2) pharmacologic blockade of adrenergic activity lowers blood pressure to a greater extent in obese compared with lean subjects [21]; and 3) renal denervation markedly attenuates sodium retention and the development of obesity hypertension associated with a high-fat diet in experimental animals [22].

Increased SNS activity appears to be highly differentiated in obesity. For example, cardiac sympathetic activity is not substantially elevated in obese humans [19], and the high heart rate observed in obese subjects appears to be related mainly to decreased parasympathetic activity [6]. In contrast, SNS activity is usually increased in skeletal muscle and kidneys of obese compared with lean subjects [20,23].

Genetic factors may be important in modulating the sympathetic responses to excess weight gain. In Pima Indians, who have a high prevalence of obesity but a relatively low prevalence of hypertension, muscle SNS activity is lower than in whites and does not track well with adiposity [24]. In black men, however, SNS activity is higher and hypertension is more prevalent than in white men despite comparable levels of obesity [20]. In young, overweight black women, adiposity is associated with sympathetic overactivity [20]. Unfortunately, in almost all human studies muscle SNS activity has been measured rather than renal sympathetic activity, the primary pathway by which the SNS causes chronic hypertension [17]. Because there is considerable heterogeneity in the control of autonomic outflow to different organs, measurements of muscle SNS activity may not necessarily reflect renal sympathetic activity.

Factors such as differences in fat mass distribution may contribute to racial variations in sympathetic responses to increased adiposity. For reasons that are still unclear, abdominal obesity may elicit greater sympathetic activation than lower body obesity [25]. Unfortunately, a comprehensive analysis of these multiple factors that influence the relationships among obesity, SNS activity, and hypertension in diverse populations has not been conducted.

Mechanisms of sympathetic activation in obese subjects: role of leptin and hypothalamic melanocortins

The mechanisms that activate the SNS in obesity have not been fully elucidated but several candidates have been suggested, including hyperinsulinemia, angiotensin II (Ang II), leptin, and altered baroreflex sensitivity. A detailed discussion of each of these mechanisms is beyond the scope of this article and has been previously discussed [18,19,23,26].

One of the most promising of these links between obesity and sympathetic activation is hyperleptinemia [18,27]. Leptin is a peptide that is secreted by adipocytes in proportion to the degree of adiposity. Leptin from the plasma crosses the blood-brain barrier via a saturable receptor-mediated transport system, binds to its receptor in various regions of the hypothalamus, and activates signaling pathways, especially in the arcuate nucleus, that regulate energy balance by decreasing appetite and increasing energy expenditure through sympathetic stimulation [28••]. Evidence that leptin acts as a powerful negative feedback controller of food intake and body weight comes from genetic studies of mice and humans. In either case, missense mutations of the leptin gene that prevent normal leptin synthesis result in extreme early onset obesity [28••]. Mutations of the leptin gene, however, are very rare in humans and probably do not account for a significant component of human obesity. Whether more subtle differences in leptin production or sensitivity of leptin receptors may contribute to obesity is still unclear.

There is substantial evidence in rodents that increasing plasma leptin concentrations not only activates sympathetic activity, but also increases arterial pressure [7,18,29]. Although acute leptin infusions have very little effect on blood pressure, long-term increases in plasma leptin to concentrations found in severe obesity raise blood pressure in rodents [30]. The rise in blood pressure with hyperleptinemia is slow in onset and occurs despite decreased food intake that would otherwise tend to lower blood pressure [30]. Moreover, the hypertensive effects of leptin are enhanced when nitric oxide synthesis is inhibited [31], as often occurs in obese subjects with endothelial dysfunction. The chronic effects of leptin to raise arterial pressure are completely abolished by α- and β-adrenergic blockade, indicating that they are mediated by adrenergic activation [32]. Likewise, transgenic mice that overexpress leptin also have increased blood pressure due to sympathetic activation [33]. These observations indicate that hyperleptinemia can elevate arterial pressure, at least in rodents.

An observation that points toward leptin as a potential link between obesity and hypertension is the finding that leptin-deficient obese mice and obese rats with mutations of the leptin receptor usually have little or no increase in arterial pressure compared with their lean controls [7,34]. For example, the ob/ob mouse, which has a missense mutation of the leptin gene, is extremely obese because it is unable to synthesize leptin, but actually has decreased arterial pressure compared with its lean control [34].

Whether leptin plays a major role in linking obesity with hypertension in humans has not been established, and there have been few studies in which blood pressure has been measured in obese children with leptin gene mutations. In one study by Ozata *et al*. [35], however, four young patients with homozygous missense mutations of the leptin gene were found to have early onset, morbid obesity but no indication of hypertension. Each of these children also had impaired sympathetic activity, postural hypotension, and attenuated renin-angiotensin responses to upright posture [35]. Moreover, the absence of hypertension occurred in spite of severe insulin resistance and hyperinsulinemia. These observations are consistent with those found in leptin-deficient mice and suggest that hyperleptinemia may be an important factor in linking obesity with SNS activation and hypertension in humans as well as in rodents. However, these studies do not rule out the possibility that prolonged obesity may also activate other mechanisms that raise blood pressure, such as renal injury [6•].

Leptin's stimulatory effect on SNS activity may be mediated, in part, by interaction with other hypothalamic factors, especially the pro-opiomelanocortin (POMC) pathway. Antagonism of the melanocortin 3/4 receptor (MC3/4-R) completely abolishes leptin's acute effects on renal SNS activity [36]. In addition, chronic blockade of the MC3/4-R in rats caused rapid weight gain but little or no increase in arterial pressure and a decrease in heart rate [37]. As weight gain usually raises blood pressure and heart rate, these findings are consistent with the possibility that a functional MC3/4-R is important in linking excess weight gain with increased SNS activity and hypertension. However, the importance of the POMC pathway and MC3/4-R in controlling sympathetic activity and raising blood pressure in obese humans has not been, to our knowledge, investigated.

Obesity Activates the Renin-Angiotensin System

Although obesity is associated with marked sodium retention and extracellular fluid volume expansion, multiple components of the RAS are activated in obesity. Modest increases have been reported in obese subjects for plasma renin activity, angiotensinogen, angiotensin-converting enzyme (ACE) activity, and plasma aldosterone concentration [6•,38]. Adipose tissue has been suggested to contribute to increases in some components of the RAS [38],

especially angiotensinogen, but the functional importance of the adipose RAS compared with the renal and circulating RAS in obesity hypertension is still unclear.

An important role for Ang II in stimulating renal sodium reabsorption and mediating obesity hypertension is supported by the observation that treatment of obese dogs and humans with Ang II antagonists or ACE inhibitors blunts sodium retention and volume expansion as well as increases arterial pressure [12,39]. In the only clinical trial published thus far on the efficacy of RAS blockade in obesity, the ACE inhibitor lisinopril was shown to be effective in lowering blood pressure in obese subjects, although ACE inhibition was more effective in young and white subjects [39].

Renin-angiotensin system blockers may be especially appropriate for treating obese hypertensive patients because they do not exacerbate metabolic abnormalities and may actually improve insulin sensitivity and reduce the risk of type II diabetes [40]. Moreover, ACE inhibitors and Ang II receptor antagonists also have been shown to slow the progression of renal injury in obese hypertensive patients with type II diabetes [40]. Despite these beneficial effects of RAS blockers, there have been no long-term clinical trials that have tested the effectiveness of RAS blockers with other antihypertensive drugs in reducing morbidity and mortality in obese compared with lean hypertensive patients.

Visceral Obesity Causes Physical Compression of the Kidneys

Visceral obesity initiates several changes that lead to compression of the kidneys and increased intrarenal pressures [12]. For example, intra-abdominal pressure rises in proportion to sagittal abdominal diameter, reaching levels as high as 35 to 40 mm Hg in some subjects. In addition, retroperitoneal adipose tissue often encapsulates the kidneys and may penetrate the renal hilum into the renal medullary sinuses, causing additional compression and increased intrarenal pressures [6•,12].

Obesity also causes changes in renal medullary histology and increased extracellular matrix that could exacerbate intrarenal compression. The increased intrarenal fluid hydrostatic tissue pressure, in turn, may cause compression of the loops of Henle and vasa recta, thereby increasing tubular sodium and water reabsorption [6•,12]. Although these physical changes in the kidneys cannot account for the initial increase in arterial pressure that occurs with rapid weight gain, they may help explain why abdominal obesity is much more closely associated with hypertension than lower body obesity.

Glomerular Injury and Nephron Loss in Obesity

Several studies indicate that obese patients often develop proteinuria, frequently in the nephrotic range, that is followed by progressive loss of kidney function in a significant number of patients [41]. The most common types of renal lesions observed in renal biopsies of obese subjects are focal and segmental glomerulosclerosis and glomerulomegaly [42]. A review of 6818 biopsies indicated that the incidence of obesity-related glomerulopathy, defined as combined focal glomerulosclerosis and glomerulomegaly, rose tenfold from 1990 to 2000, coincident with the rapid increase in the prevalence of obesity during this period [42].

Animals placed on a high-fat diet for only 7 to 9 weeks demonstrate significant structural changes in the kidneys [6•,12,43]. The earliest changes observed included enlargement of Bowman's space, increased glomerular cell proliferation, increased mesangial matrix, thicker basement membranes, and increased expression of glomerular transforming growth factor-β [43]. These early changes occur with only modest hypertension, no evidence of diabetes, and only mild metabolic abnormalities, and may be the precursors of more severe renal injury as obesity is sustained [7,12,43].

The mechanisms of obesity-induced renal injury are not fully understood but likely involve a combination of hemodynamic and metabolic abnormalities. Obesity causes marked glomerular hyperfiltration and preglomerular vasodilation that permits greater transmission of the increased arterial pressure to the glomerular capillaries [12]. These changes, along with metabolic abnormalities such as hyperglycemia and hyperlipidemia, likely exacerbate the effects of modest increases in arterial pressure to cause renal injury. A synergistic relationship may exist between the metabolic abnormalities and increased glomerular pressure in causing chronic renal vascular disease and nephron loss. Results of the Prospective Cardiovascular Munster (PROCAM) study suggest that this is the case for coronary artery disease [44]. For example, the risk for myocardial infarction was increased about twofold by hypertension and twofold by diabetes. However, when hypertension and diabetes occurred together, the risk was increased more than eightfold [44]. When hypertension, diabetes, and hyperlipidemia were all present, as occurs in most obese patients, the risk for myocardial infarction increased almost 20-fold [44]. Similar synergistic relationships between glomerular pressure and metabolic abnormalities may also exist for renal vascular disease, although there are no large-scale studies that have addressed this issue.

That obesity is also a major cause of renal disease in humans is evident from the fact that the two most important causes of end-stage renal disease (ESRD) are diabetes and hypertension, both of which are closely associated with excess weight gain. As discussed above, current evidence suggests that 65% to 75% of the risk for hypertension is due to excess weight gain, and approximately 90% of diabetics have type II diabetes, also closely associated with excess weight gain. However, the rapid and parallel increases in the prevalence of ESRD and obesity in the past two decades suggest that obesity may be a major risk for kidney disease, not only through hypertension and diabetes, but perhaps through other mechanisms as well.

Obesity also increases the risk for development of serious renal disease from other causes, such as primary immunoglobulin A nephritis or unilateral nephrectomy [41,45]. Praga *et al*. [45] reported that in patients with a BMI of more than 30 who had undergone unilateral nephrectomy, 92% developed proteinuria or renal insufficiency, whereas in patients with a BMI of less than 30 only 12% developed these disorders. These studies suggest that obesity is an additive or synergistic risk factor for other types of glomerulopathies in causing progression of nephron loss, although further investigation of this concept in much larger studies is clearly needed.

Whether weight loss can prevent or at least attenuate the progression of chronic renal disease is unknown since there have been no long-term studies on weight loss and renal function in humans. Short-term weight loss, however, usually produces a dramatic reduction in proteinuria in obese subjects. An antiproteinuric effect of weight loss is also evident in overweight subjects with nephropathies caused by factors other than obesity [41].

In experimental animals, there is little doubt that excess caloric intake causes progressive nephron loss and that caloric restriction protects against glomerular injury. Modest food restriction (8% to 18% below the usual ad lib amounts) reduces renal injury and increases life span of obese Zucker rats by approximately 30% [46]. Similar beneficial effects of food restriction have been observed in other models of obese and nonobese rodents, indicating that food restriction can largely prevent chronic renal disease in rats. Long-term weight loss studies are needed to determine whether these dramatic effects observed in rodents can also be observed in obese patients with evidence of early renal disease.

Obesity Treatment and Prevention: Current Approaches

It is clear that obesity is rapidly becoming one of the most important, as well as the most prevalent, health care problems of the modern world. It has been estimated that obesity outranks the combined effects of smoking and alcohol consumption in its deleterious effects on health and health care expenses. The number of people affected by obesity and the severity of its consequences are rapidly becoming so great that it threatens to overwhelm available medical resources. Unfortunately, few effective treatments are available to prevent or treat obesity.

For morbidly obese patients (BMI > 40 or BMI > 35 with comorbid conditions), various surgical procedures, especially gastric bypass surgery, are becoming increasingly popular and usually produce significant weight loss. However, the long-term consequences of these procedures in reversing cardiovascular and renal disease and on overall mortality are still uncertain.

Pharmacologic agents that induce satiety, increase thermogenesis, or decrease gastrointestinal fat absorption are also an option. Currently, only two drugs, sibutramine (a sympathomimetic that induces satiety and increases thermogenesis) and orlistat (which reduces fat absorption), are approved by the US Food and Drug Administration to promote weight loss. Both of these drugs have significant side effects that limit their use in many patients, and their long-term effects on morbidity and mortality are unknown [12]. Until more effective and safer pharmacologic treatments are available, voluntary weight loss is still the best option for most overweight patients. Even modest weight reductions of 5% to 10% can improve control of blood pressure as well as blood glucose and cholesterol in diabetic patients.

Most current guidelines for achieving weight loss recommend as a first step the development of an individualized plan for the obese patient to reduce caloric intake and increase energy expenditure by behavioral modification [47]. A major obstacle, however, in successful prevention and treatment of obesity has been lack of sufficient involvement of health care professionals in helping patients develop individualized plans for weight loss. Patients whose physicians advised them to lose weight were three times more likely to attempt to lose weight as those who were not advised to lose weight [1]. Unfortunately, less than half of obese adults report being advised to lose weight by their physicians [1]. The successful management of obesity requires the same attention and planning for effective treatment as other important medical conditions such as hypertension.

Treatment of Obesity-induced Hypertension

Until effective strategies for preventing and treating obesity are developed, the cardiovascular and renal consequences of obesity must be aggressively treated. Currently, selection of specific drugs for antihypertensive therapy in obese subjects has been largely empiric or based on clinical experience and knowledge of the physiology of obesity hypertension [12,48]. This is due mainly to the fact that there have been no large clinical trials testing the effectiveness of different drugs in reducing blood pressure and preventing cardiovascular and renal disease in obese compared with lean subjects. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) includes many overweight subjects and may provide some useful information about the relative effectiveness of the four main classes of antihypertensive drugs tested: diuretics, β-adrenergic blockers, ACE inhibitors, and calcium antagonists [49].

In the meantime, physicians must rely on their understanding of the pathophysiology of obesity hypertension, their clinical experience, and individual patient characteristics in selecting the most appropriate antihypertensive regimen. The reader is referred to reviews that discuss the potential advantages and disadvantages of different antihypertensive drugs in obese patients [40,48]. However, it is important to point out that adequate blood pressure control in the obese patient may be lower than the usual 140/90 mm Hg. For many, lower levels of blood pressure

should be the goal because of the coexistence of other risk factors, such as hyperlipidemia, glucose intolerance or diabetes, and atherosclerosis.

Physicians who treat hypertension are uniquely positioned to have a major impact on the obesity epidemic. The most common reason for an overweight patient to visit a physician is for treatment of hypertension. By helping the patient lose weight, the health care provider can also manage more effectively the hypertension and prevent or slow down the development of diabetes as well as cardiovascular and renal disease.

Conclusions

There is an alarming epidemic of obesity in most industrialized countries, with its consequences of increasing diabetes mellitus, hypertension, and renal disease. Excess weight gain is the major factor responsible for increased blood pressure in most patients with essential hypertension, and also appears to be a major risk factor for ESRD. Obesity initially raises blood pressure by increasing renal tubular reabsorption, impairing pressure natriuresis, and causing volume expansion. These changes are due to activation of the SNS and RAS and to physical compression of the kidneys when marked visceral obesity is present. Blockade of the SNS and RAS are therefore effective in reducing blood pressure activation in obese subjects. With prolonged obesity, there may be a gradual loss of nephron function that not only worsens the hypertension but also makes it more difficult to control. There is also substantial evidence that obesity-induced renal injury worsens with time and can progress to ESRD in a substantial fraction of patients. Weight reduction is an essential first step in the management of obesity-associated hypertension and renal disease. Currently, however, there are few drugs available to produce significant long-term weight loss and few guidelines for treating obesity-associated hypertension. Special considerations for the obese patient, in addition to controlling the blood pressure, include correcting the metabolic abnormalities and protecting the kidneys from further injury. More emphasis should be placed on prevention of obesity and on lifestyle modifications that help patients to maintain a healthier weight.

Acknowledgment

The authors' research was supported by a grant from the National Heart, Lung and Blood Institute (P01 HL 51971).

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Hall JE, Jones DW: **What can we do about the obesity epidemic?** *Am J Hypertens* 2002, **15:**657–665.

2.•• Sorof J, Daniels S: **Obesity hypertension in children—a problem of epidemic proportions.** *Hypertension* 2002, **40:**441–447.
A thoughtful review of the cardiovascular consequences of obesity in children.

3.•• Flegal KM, Carroll MD, Ogden CL, Johnson CCL: **Prevalence and trends in obesity among US adults, 1999–2000.** *JAMA* 2002, **288:**1723–1727.
An important survey of 4115 adult men and women conducted in 1999 and 2000 as part of the NHANES documenting the rapid increase in the prevalence of obesity in adults in the United States.

4. Ogden CL, Flegal KM, Carroll MD, Johnson CL: **Prevalence and trends in overweight among US children and adolescents.** *JAMA* 2002, **288:**1728–1732.

5. Wilson PWF, D'Agostino RB, Sullivan L, *et al.*: **Overweight and obesity as determinants of cardiovascular risk—the Framingham experience.** *Arch Intern Med* 2002, **162:**1867–1872.

6.• Hall JE, Crook ED, Jones DW, *et al.*: **Mechanisms of obesity-associated cardiovascular and renal disease.** *Am J Med Sci* 2002, **324:**127–137.
This paper provides a comprehensive review of the pathophysiologic mechanisms by which obesity causes cardiovascular and renal disease.

7. Hall JE, Kuo JJ, Silva A, *et al.*: **Obesity, hypertension and renal disease.** *Curr Opin Nephrol Hypertens* 2003, **12:**195–200.

8. Wannamethee SG, Shaper AG: **Weight change and duration of overweight and obesity in the incidence of type 2 diabetes.** *Diabetes Care* 1999, **22:**1266–1272.

9. Sundquist J, Winkeby MA, Pudaric S: **Cardiovascular disease risk factors among older black, Mexican-American, and white women and men: an analysis of NHANES III; 1988–1994.** *J Am Geriatr Soc* 2001, **49:**109–116.

10. He Q, Ding YZ, Fong DY, Karlberg J: **Blood pressure is associated with body mass index in both normal and obese children.** *Hypertension* 2000, **36:**165–170.

11. Garrison RJ, Kannel WB, Stokes J, *et al.*: **Incidence and precursors of hypertension in young adults: The Framingham Offspring Study.** *Prev Med* 1987, **16:**235–251.

12. Hall JE, Jones DW, Henegar J, *et al.*: **Obesity hypertension, and renal disease.** In *Obesity: Mechanisms and Clinical Management.* Edited by Eckel RH. Philadelphia: Lippincott, Williams & Wilkins; 2003:273–300.

13. Cooper RS, Potimi CN, Ward R: **The puzzle of hypertension in African-Americans.** *Sci Am* 1999, **280:**56–63.

14. He J, Whelton PK, Appel LJ, *et al.*: **Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension.** *Hypertension* 2001, **35:**544–549.

15. Miller ER, Erlinger TP, Young DR, *et al.*: **Results of the diet, exercise, and weight loss intervention trial (DEW-IT).** *Hypertension* 2002, **40:**612–618.

16. Dobrian AD, Davies MJ, Schriver SD, *et al.*: **Oxidative stress in a rat model of obesity-induced hypertension.** *Hypertension* 2001, **37:**554–560.

17. Hall JE: **The kidney, hypertension, and obesity.** *Hypertension* 2003, **41:**625–633.

18. Hall JE, Hildebrandt DA, Kuo J: **Obesity hypertension: role of leptin and the sympathetic nervous system.** *Am J Hypertens* 2001, **14:**103S–115S.

19. Esler M, Rumantir M, Wiesner G, *et al.*: **Sympathetic nervous system and insulin resistance: from obesity to diabetes.** *Am J Hypertens* 2001, **14:**304S–309S.

20. Abate NI, Mansour YH, Arbique D, *et al.*: **Overweight and sympathetic activity in black Americans.** *Hypertension* 2001, **38:**379–383.

21. Wofford MR, Anderson DC, Brown CA, *et al.*: **Antihypertensive effect of alpha and beta adrenergic blockade in obese and lean hypertensive subjects.** *Am J Hypertens* 2001, **14:**694–698.

22. Kassab S, Kato T, Wilkins C, *et al.*: **Renal denervation attenuates the sodium retention and hypertension associated with obesity.** *Hypertension* 1995, **25:**893–897.

23. Grassi G, Seravalle G, Dell'Oro R, *et al.*: **Adrenergic and reflex abnormalities in obesity-related hypertension.** *Hypertension* 2000, **36:**538–542.

24. Weyer C, Pratley RE, Snitker S, *et al.*: **Ethnic differences in insulinemia and sympathetic tone as links between obesity and blood pressure.** *Hypertension* 2000, **36:**531–537.
25. Alvarez GE, Beske SD, Ballard TP, Davy KP: **Sympathetic neural activation in visceral obesity.** *Circulation* 2002, **106:**2533–2536.
26. Grassi G, Seravalle G, Dell'Oro R, *et al.*: **Participation of the hypothalamus-hypophysis axis in the sympathetic activation of human obesity.** *Hypertension* 2001, **38:**1316–1320.
27. Eikelis N, Schlaich M, Aggarwal A, *et al.*: **Interactions between leptin and the human sympathetic nervous system hypertension.** *Hypertension* 2003, **41:**1072–1079.
28.•• Jequier E: **Leptin signaling, adiposity, and energy balance.** *Ann N Y Acad Sci* 2002, **967:**379–388.

An excellent and comprehensive review of the pathways of leptin signaling and their role in regulating energy balance.

29. Correia MLG, Morgan DA, Sivitz WI, *et al.*: **Leptin acts in the central nervous system to produce dose-dependent changes in arterial pressure.** *Hypertension* 2001, **37:**936–942.
30. Shek EW, Brands MW, Hall JE: **Chronic leptin infusion increases arterial pressure.** *Hypertension* 1998, **31:**409–414.
31. Kuo JJ, Jones OB, Hall JE: **Inhibition of NO synthesis enhances chronic cardiovascular and renal actions of leptin.** *Hypertension* 2001, **37:**670–676.
32. Carlyle M, Jones OB, Kuo JJ, Hall JE: **Chronic cardiovascular and renal actions of leptin-role of adrenergic activity.** *Hypertension* 2002, **39:**496–501.
33. Aizawa-Abe M, Ogawa Y, Mazuzaki H, *et al.*: **Pathophysiological role of leptin in obesity related hypertension.** *J Clin Invest* 2000, **105(9):**1243–1252.
34. Mark AL, Shaffer RA, Correia ML, *et al.*: **Contrasting blood pressure effects of obesity in leptin-deficient ob/ob mice and agouti yellow mice.** *J Hypertens* 1999, **17:**1949–1953.
35. Ozata M, Ozdemir IC, Licinio J: **Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects.** *J Clin Endocrinol Metab* 1999, **10:**3686–3695.
36. Haynes WG, Morgan DA, Djalali A, *et al.*: **Interactions between the melanocortin system and leptin in control of sympathetic nerve traffic.** *Hypertension* 1999, **33:**542–547.
37. Kuo JJ, Silva AA, Hall JE: **Hypothalamic melanocortin receptors and chronic regulation of arterial pressure and renal function.** *Hypertension* 2003, **41:**768–774.
38. Sharma AM, Janke J, Gorzelniak K, *et al.*: **Angiotensin blockade prevents type 2 diabetes by formation of fat cells.** *Hypertension* 2002, **40:**609–611.
39. Reisen E, Weir M, Falkner B, *et al.*: **Lisinopril versus hydrochlorothiazide in obese hypertensive patients: A Multicenter Placebo-Controlled Trial.** *Hypertension* 1997, **30:**140–145.
40. Zanella MT, Kohlmann Jr O, Ribeiro AB: **Treatment of Obesity Hypertension and Diabetes Syndrome.** *Hypertension* 2001, **38:**705–708.
41. Morales E, Valero MA, Leon M, *et al.*: **Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies.** *Am J Kidney Dis* 2003, **41:**319–327.
42. Kambham N, Markowitz GS, Valeri AM, *et al.*: **Obesity related glomerulopathy: an emerging epidemic.** *Kidney Int* 2001, **59:**1498–1509.
43. Henegar JR, Bigler SA, Henegar LK, *et al.*: **Functional and structural changes in the kidney in the early stages of obesity.** *J Am Soc Nephrol* 2001, **12:**1211–1217.
44. Assmann G, Schulte H: **The Prospective Cardiovascular Munster Study (PROCAM): prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary artery disease.** *Am Heart J* 1988, **1116:**1713–1724.
45. Praga M, Hernandez E, Herrero JC, *et al.*: **Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy.** *Kidney Int* 2000, **58:**2111–2118.
46. Stern JS, Gades MD, Wheeldon CM, Borchers AT: **Calorie restriction in obesity: prevention of kidney disease in rodents.** *J Nutr* 2001, **131:**913S–917S.
47. **National Institutes of Health Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. 1998. National Heart, Lung, and Blood Institute and National Institute of Diabetes and Digestive and Kidney Diseases.** http://www.nhlbi.nih.gov/guidelines/index.htm. Accessed July, 2003.
48. Sharma AM, Pischon T, Engeli S, *et al.*: **Choice of drug treatment for obesity-related hypertension: where is the evidence?** *J Hypertens* 2001, **19:**667–674.
49. Oparil S: **Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): practical implications.** *Hypertension* 2003, **41:**1006–1009.