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Review

Obesity and Hypertension

Canan ERSOY[1], Alparslan ERSOY[2]

[1] Division of Endocrinology and Metabolism, Department of Internal Medicine, Uludag University Faculty of Medicine, Bursa, Turkey
[2] Division of Nephrology, Department of Internal Medicine, Uludag University Faculty of Medicine, Bursa, Turkey

Abstract

Obesity is an important public health problem with increasing frequency, leading to different comorbidities including hypertension and can cause mortality. Possible mechanisms that increase blood pressure in overweight and obese people are renal damage, activation of the renin-angiotensin-aldosterone system, insulin resistance, hyperinsulinemia, sleep apnea syndrome, leptin-melanocortin pathway and genetic predisposition. Most of these mechanisms stimulate the sympathetic nervous system. Medical nutrition therapy, lifestyle interventions, medical and/or surgical antiobesity treatment modalities contribute to the control of blood pressure via weight loss. Besides antihypertensive medications should be chosen carefully in overweight and obese patients and drug groups preventing weight loss should not be preferred if possible.

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Introduction

Obesity is a very important public health problem worldwide as well as an important cause of morbidity and mortality. Obesity substantially increases the risk of diseases such as type 2 diabetes mellitus, fatty liver disease, hypertension, dyslipidemia, atherosclerosis, coronary artery disease, myocardial infarction, stroke, dementia, osteoarthritis, obstructive sleep apnea and breast or colon cancers, thereby contribute to a decline in both quality of life and life expectancy.[1,2] Obesity may occur after genetic and environmental factors and often occurs with the influence of environmental factors. Changing lifestyle and dietary habits increase the prevalence of obesity in both childhood and adulthood. Not only weight gain but also body fat distribution is important in hemodynamic and metabolic changes seen in obesity. The risks associated with obesity are higher in patients with abdominal or central obesity. Increased body fat amount presents with increased body mass index (BMI), body weight and waist circumference that relates with insulin resistance and hypertension.[3] In NHANES (National Health and Nutrition Examination Survey) 1999–2010,

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Address for Correspondence:
Canan Ersoy,
Department of Internal Medicine, Division of Endocrinology and Metabolism, Uludag University Medical School, 16059 Gorukle, Bursa, TURKEY
E-mail: ecanan@uludag.edu.tr

35.7% of obese individuals had hypertension.[4] Besides, being obese in childhood is known to increase the risk of developing adulthood hypertension by 2.7 times.[3,5] Nurses' Health Study, which included 18-year follow-up data for 77,690 women aged 30-55 years, and Health Professionals Follow-up study, which included 10-year follow-up data for 46,060 men aged 40-75 years, indicated that the incidence of hypertension is increased as the body weight and BMI increased.[6,7] In these studies it has also been reported that the frequency of hypertension is increased even when the BMI was within the normal range but elevated from the lower limit to the upper limit of normal.[5-7]

It's known that each 10 kg increase in body weight increases systolic blood pressure (SBP) by 3 mmHg, diastolic blood pressure (DBP) by 2.3 mmHg and these elevations in blood pressure increase the risk of coronary artery disease by 12% and stroke risk by 24%.[8] Increased blood pressure in obesity is associated with high cardiac output and increased systemic vascular resistance. When the haemodynamic difference between hypertensive and normotensive obese individuals is examined, it is seen that systemic vascular resistance is relatively higher in hypertensive than in normotensive subjects.[9]

Pathogenesis

Various possible mechanisms that increase blood pressure in overweight and obese people are considered which are genetic predisposition, renal damage, insulin resistance and hyperinsulinemia, activation of the renin-angiotensin-aldosterone system, sleep apnea syndrome and leptin-melanocortin pathway. Most of these mechanisms stimulate the sympathetic nervous system, leading to increased blood pressure. The most basic difference is due to genetic predisposition.[10,11] Obesity and in particular excessive visceral fat distribution is accompanied by several alterations at hormonal, inflammatory and endothelial level. These alterations induce a stimulation of several other mechanisms that contribute to the hypertensive state. The main role in the mechanisms of obesity and obesity-related hypertension other than genetic and environmental factors is caused by the sympathetic nervous system, renal and renal functions, endothelium, adipokines and insulin resistance.[12]

Arterial baroreceptors have a central role in cardiovascular homeostasis control and represent the main restraining mechanism on sympathetic tone. Both sympatho-inhibitory and sympatho-excitatory components in the control of arterial baroceptor of sympathetic nerve activity show impairment in obesity and obesity-related hypertension.[12] There are additional factors affecting the relationship between body weight and blood pressure. Insulin has vasodilatory action normally. The presence of insulin resistance contributes to increased sympathetic system activation, water and salt reabsorption from the kidneys, endothelial dysfunction and the development of hypertension by inducing muscular hypertrophy in the vessels.[8,10,11] The relationship between adiposity and blood pressure varies among individuals. Adiponectin and leptin are the most important products of adipose tissue involved in blood pressure control by regulating arterial tone. Adiponectin levels decrease in obesity and may be protective against an increase in arterial blood pressure through an endothelium-dependent mechanism.[12] Leptin is the protein that transfers the amount of stored adiposity to the brain. The ratio of leptin's concentration in serum and stored fat is 0.9. High leptin levels due to increased adiposity increase renal sympathetic tone by long-term renal sympathetic stimulation and lead to hypertension. In this situation, leptin's effects on reduction in food intake and thermogenesis are eliminated.[10] Melanocortin receptors are found in leptin and insulin responsive neurons and play a role in the regulation of energy balance and blood pressure. Increased sympathetic activity caused by hyperinsulinemia has been shown to decrease when melanocortin receptors are antagonized.[13,14] Adipose tissue produces pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6. They can induced insülin resistance and promote endothelial dysfunction.[15]

Obstructive sleep apnea is a common disorder and is linked to an epidemic of obesity. While it's prevalence in the general population is 2-5% in women and 3-7% in men, the prevalence of the disease in overweight or obese people ranges from 40% to 90%.[16,17] Possible mechanisms to increase blood pressure associated with sleep apnea can be explained by increased sympathetic system activation, increased aldosterone levels and increased endothelin levels with recurrent

hypoxic episodes.[10,17] Depending on the severity of obesity and the concomitant presence of breathing alterations, chronic intermittent hypoxia and obstructive apnea, the reflex impairment involving other reflexogenic areas such as the cardiopulmonary receptors and the chemoreceptors may participate in the occurrence of the hyperadrenergic state.[12]

Renal abnormalities

Increased renal tubular sodium reabsorption plays an important role in the onset of obesity-related hypertension by disrupting pressure-associated natriuresis. They may be related to an increment in mineralcorticoid activity. Potential mechanisms of abnormal renal function in obesity are compression of the kidneys with surrounding adipose tissue, activation of the renin-angiotensin-aldosterone system and increased activity of the sympathetic nervous system.[10,11] Visceral obesity can lead the development of kidney disease with the accumulation of extracellular matrix in the renal medulla that causes both vascular and tubular compression.[12] BMI is an independent risk factor for chronic kidney disease. Obesity related glomerulopathy is observed in patients with BMI >30 kg/m^2. The most common histological changes in renal biopsy in obesity-related glomerulopathy are glomerulomegaly and focal segmental glomerulosclerosis. The electron microscope shows changes in the podocytes in the glomeruli. Major changes in podocytes are reported as swelling and vacuolization in cells, focal fusion site expansion and decreased cell density. Although the mechanisms of these changes are not clearly defined, they are tried to be explained by hemodynamic forces such as glomerular hyperfiltration and increase in renal plasma flow and the effect of growth factors such as insulin, renin-angiotensin-aldosterone and transforming growth factor β. In patients with renal damage, hypertension, edema, nephrotic syndrome and in long-term renal failure can be seen clinically in obese people.[18]

Nowadays, chronic renal complications of obesity are called obesity-related glomerulopathy (ORG). The diagnosis of ORG is based on BMI values of ≥30 kg/m^2 and exclusion of other renal diseases both clinically and histopathologically. There is no absolute relationship between the occurrence of ORG and the severity of obesity. The initial symptom in most cases is isolated proteinuria of unknown onset with or without renal failure.15 Typical features of renal histopathology for ORG patients include glomerulomegaly and focal segmental glomerulosclerosis (FSGS).[19,20] Glomerulomegaly is probably the result of abnormalities in renal hemodynamics associated with obesity. FSGS lesions may not be present in all cases of ORG, which may be related to the degree of obesity or renal impairment.[15] Obesity related FSGS exhibits a predominance of the perihilar variant, which reflects an excessive pressure load on the vascular poles of glomeruli due to the renal hemodynamic abnormalities of obesity.[19]

Glomerular hypertrophy and glomerulomegaly in ORG may cause glomerular podocytes to enlarge their foot processes to cover the expanded glomerular surface area. Consistently, there is a relative reduction in the coating area of glomerular podocytes on the glomerular surface in patients with ORG. In the result of changes in podocyte function, loss of protein selectivity, podocyte detachment and replacement by matrix deposition may result in FSGS.[15] Obesity related FSGS can be confused with idiopathic FSGS. It is important to make a differential diagnosis. The incidence of foot process fusion between glomerular podocytes in ORG was lower than in idiopathic FSGS (40% vs. 75%).[20] In ORG, the patients are older at the time of diagnosis compared to idiopathic FSGS (mean age 43-46 vs. 32 years). Although edema and nephrotic syndrome can be seen in both situations, it is milder in ORG. Lower proteinuria, higher serum albumin and lower serum cholesterol levels are detected in ORG. ORG progresses to renal failure slower.[19,21,22] Although ORG has a better prognosis than idiopathic FSGS, it is a serious disease with long-term poor prognosis.[21,23] It is important to prevent the damage and depletion of podocytes by treatment. To achieve this, weight loss, systemic and intraglomerular hypertension control is necessary. In obese hypertensive patients, angiotensin II receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEi) are able to significantly reduce sympathetic nerve activity and adequately control blood pressure.[19,24,25] However, it has been shown in studies conducted with patients with O-FSGS that ACEi can halt the progression of renal failure

if renal function is still normal.[21]

Typical ORG lesions were seen in 41% of biopsies of obese patients with proteinuria and renal dysfunction, but the rest were additional diseases. While proteinuria was the highest in patients with idiopathic FSGS and immune complex diseases, it was subnephrotic in obesity-related FSGS and tubulointerstitial diseases. Creatinine levels were highest in tubulointerstitial diseases and progressive diabetic nephropathy.[22] Various renal pathologies such as diabetic nephropathy, hypertensive nephrosclerosis, mesangial cell proliferation and matrix expansion can be seen in patients with hypertension and obesity. Obesity may worsen proteinuria in non-glomerulonephritis, IgA nephropathy and benign nephrosclerosis. Obesity is associated with structural changes such as glomerulomegaly and glomerular basement membrane thickening similar to changes in ORG.[26] Glomerulomegaly and increased glomerular basement membrane thickness resembling early diabetic nephropathy in the absence of diabetes are observed in kidney biopsies of patients with morbid obesity even before the appearance of microalbuminuria.[27] Some obese hypertensive patients with moderate to severe vascular lesions which are accompanied by collapsed glomeruli are diagnosed with hypertensive nephrosclerosis instead of ORG.[15] Occasionally, focal lipid vacuoles appear in the cytoplasm of glomerular mesangial cells and tubular epithelial cells.[28]

Relationship between weight loss and blood pressure

Weight loss is recommended to reduce blood pressure in overweight and obese patients with hypertension because various studies have shown that weight loss diets reduce body weight and blood pressure.[3,29] In a metaanalysis, the mean SBP and DBP reductions associated with an average weight loss of 5.1 kg were 4.4 and 3.6 mmHg, respectively.[30] A recent systematic review of eight studies in hypertensive patients revealed that behavioral weight loss reduced SDP and DBP by 4.5 and 3.2 mmHg, respectively.[31] Weight loss stabilizes neurohormonal activity and causes clinically significant reductions in blood pressure.[32] Medical nutrition therapy, lifestyle changes, medical and/or surgical methods contribute to the control of weight loss and blood pressure values in obese hypertensive patients.[8]

The drugs used in the medical treatment of obesity in our country are orlistat and liraglutide. Orlistat is a gastrointestinal lipase enzyme inhibitor that prevents fat absorption and provides weight loss. Many weight loss medications, particularly sympathomimetic amines, raise blood pressure despite a decrease in weight. However, some weight loss medications such as orlistat can lower blood pressure.[33] The recommended daily dose for orlistat is 3x120 mg orally. Liraglutide is a GLP-1 analogue and shows its main effect by suppressing appetite and creating a sense of satiety. The recommended daily dose of liraglutide for antiobesity treatment is 1x3 mg/day subcutaneously, which is obtained by gradually increasing the dose in weeks. In studies evaluating the effect of orlistat related weight loss on blood pressure in obese or overweight hypertensive patients and comparing it with placebo, it was shown that both weight loss and SBP and DBP reductions were significantly higher in orlistat group.[34] Orlistat reduced SBP as compared to placebo by -2.5 mmHg and DBP by -1.9 mmHg.[35] In studies evaluating the effect of weight loss with liraglutide on blood pressure in obese patients, it has been shown that weight and blood pressure controls were better in patients receiving liraglutide combined for 12 weeks with a 1,000- to 1,200-kcal/d meal-replacement diet compared to patients receiving intensive behavioral therapy alone or with liraglutide after 52 weeks of interventions (-15.3, -14.1, -13.3 mmHg at SBPs and -3.5, -3.0 and -2.9 at DBPs, respectively).[36]

Gastric bypass, sleeve gastrectomy, gastroplasty and gastric bandage are several different methods that can be used in obesity surgery.[8,34,36,37] In a study in which surgical and medical treatments were compared in terms of long-term obesity-related comorbidities in obese patients, the rates of patients having remissions in comorbidities such as hypertension, diabetes and dyslipidemia were significantly higher and the rates of patients with newly diagnosed hypertension, diabetes and dyslipidemia were significantly lower in the surgical group compared to the medical group at the end of 6.5-year follow-up period. However, the rates of new onset depression and anxiety were significantly higher in the surgical group compared to the medical group.[37] In

some studies that compared the effects of anti-obesity treatments on blood pressure in obese patients, the weight loss ratios were significantly higher in the surgical group, while there was no significant difference between the medical and surgical groups in terms of blood pressure reduction rates.[8] The long-term effects of weight loss surgery on blood pressure over an 8-year period were examined in the SOS (Swedish Obese Subjects) study.[38] Bariatric surgery controlled hypertension by reducing blood pressure in two years compared to obese patients who had not undergo surgery. However, the weight reduction (20.1±15.7 kg, 16.3%) after bariatric surgery had a dramatic effect on the 8-year incidence of diabetes, whereas it had no effect on the 8-year incidence of hypertension.[38] Therefore, the relationship between the duration of obesity and hypertension and the effect of cardiometabolic bariatric surgery on blood pressure remains unclear. Perhaps, bariatric surgery in obese individuals may prevent the development of resistant hypertension and target organ damage.[39]

Antihypertensive drug selection in overweight and obese patients

Antihypertensive medications should be chosen carefully in overweight and obese patients and drug groups which make losing weight difficult should not be preferred if possible. Weight loss can also improve efficacy of antihypertensive medications and cardiovascular risk profile.[40] Because this axis plays a particularly prominent role in the pathophysiology of hypertension in obesity, treatment of inhibition of the renin-angiotensin-aldosterone system by ACEi or ARB should be used as the first drug for blood pressure control in these patients. These drugs are equally or more effective than other antihypertensive drugs in blood pressure control, left ventricular hypertrophy and insulin resistance reduction, kidney protection, sympathetic attenuation and baroreflex control improvement without adverse effects on weight and metabolism.[41,42] Most obese hypertensive patients require two or more antihypertensive drugs. If necessary, the combination of antihypertensive treatment with calcium channel blockers may be considered.[41]

The preferred antihypertensive drugs in overweight or obese patients should not only lower blood pressure but also maintain body weight and have no adverse effect on metabolism (eg, glycemia, insulin sensitivity and lipids). In CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan) study, the new occurrence of diabetes mellitus in candesartan (an ARB) group was significantly lower than amlodipine (a long-acting calcium channel blocker) group. This preventive effect was more marked in obese patients with a BMI of 25 kg/m^2 or greater based on the results of subanalysis.[43] Although not recommended, thiazide diuretics and beta blockers may be used in some patients. If beta blockers are mandatory, labetolol, carvedilol and nebivolol might be preferred.[8] Also beta blockers and alpha blockers can promote weight gain.[42] Although the exact mechanisms how beta blockers prevent weight loss and cause weight gain has not been demonstrated yet, decreased basal metabolic rate due to decreased sympathetic tonus and/or inhibitory effects of catecholamines on appetite are thought to be the main mechanisms. Studies have shown that beta blockers reduce total energy expenditure by 5-10%, which means 100-200 kcal less energy expenditure per day. It has also been shown that beta blockers increase insulin resistance and reduce lipolysis.[44] Diet-induced thermogenesis, fat oxidation rate and weekly activity were lower in patients receiving beta blockers than in control patients.[45] Thiazide diuretics are known to increase insulin resistance, making weight lost difficult. Some studies have shown that hypopotasemia due to diuretics increases insulin resistance by suppressing insulin secretion.[46] In a study, administration of hydrochlorothiazide in combination with a calcium channel blocker (amlodipine) or an ARB (valsartan) significantly and similarly reduced blood pressure in patient groups with obesity. However, the combination of amlodipine and hydrochlorothiazide was associated with more postprandial glucose peaks than the valsartan combination.[47]

In the ACCOMPLISH (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension) trial compared the effects of benazepril (an ACEi) combined with amlodipine (a long-acting calcium channel blocker) or hydrochlorothiazide in hypertensive patients.

The subgroup analysis of 2,842 diabetic patients at very high risk (previous cardiovascular or stroke events) showed that combination of benazepril with amlodipine was superior in reducing cardiovascular events when compared with hydrochlorothiazide.[48] A subanalysis of the ACCOMPLISH Study with respect to the BMI level, the cohort was divided into obese (BMI ≥30 kg/m^2, n=5709), overweight (≥25 kg/m^2 to <30, n=4157), or normal weight (<25 kg/m^2, n=1616) categories. Combination therapy with an ACEi and a calcium channel blocker prevented cardiovascular events regardless of the BMI level, whereas cardiovascular protection with an ACEi and a diuretic combination did not differ between the three BMI groups. Diuretic-based regimens can be a reasonable choice in obese patients in whom excess volume.[49]

The primary objective of antihypertensive drug therapy is to achieve the target of blood pressure control. Hypertension and obesity guidelines have not clearly defined target blood pressures in hypertensive obese patients. However, in these patients, the target blood pressure can be determined individually considering the presence of diabetes, renal or cardiovascular diseases. The ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) Study investigated the significance of strict blood pressure control in hypertensive patients with diabetes mellitus. The preventive effects of strict treatment targeting a SBP of 120 mmHg on cardiovascular disease were more marked in obese patients.[50] In patients with resistant hypertension or poorly controlled hypertension, obesity can be one of responsible factors. If a sufficient decrease in blood pressure is not achieved with ARB or ACEi, combination therapy with long-acting calcium channel blockers or thiazide diuretics (at a half of the standard dose) should be considered.[51] Hypertensive patients with obesity and chronic kidney disease have particularly increased sympathetic nervous system activity and are at high risk of refractory hypertension. Renal denervation does not appear to have a role in the management of obesity or chronic kidney disease associated hypertension.[52]

Conclusion

The 2018 ESC/ESH Guidelines state that body weight control is important to prevent obesity (BMI> 30 kg/m^2 or waist circumference >102 cm in men and >88 cm in women). A healthy BMI (approximately 20-25 kg/m^2) and waist circumference values (<94 cm in men, <80 cm in women) reduce blood pressure and cardiovascular risk.[53] Although the optimal BMI is unclear, maintenance of a healthy body weight (BMI of approximately 20-25 kg/m^2 in people <60 years of age; higher in older patients) and waist circumference (<94 cm for men and <80 cm for women) is recommended for non-hypertensive individuals to prevent hypertension, and for hypertensive patients to reduce blood pressure.[54] The Prospective Studies Collaboration concluded that mortality was lowest at a BMI of approximately 22.5-25 kg/m^2, whereas a more recent meta-analysis concluded that mortality was lowest in overweight subjects.[55-57] Although weight loss medications can be an effective adjunct to lifestyle modifications in individuals with obesity, there is limited evidence regarding their benefit with regard to blood pressure.[58] Increased weight leads to increased blood pressure via different mechanisms, and long-term hypertension and obesity may lead to renal damage. Current drugs are not successful due to adverse effects and inadequate weight loss in a significant proportion of obese patients. New compounds and new molecular targets need to be developed for the effective treatment of all obese patients in the near future.[59] As a public health problem, controlling and preventing weight gain and obesity may prevent development of related comorbidities including hypertension and renal damage in long-term.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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