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REVIEW ON OBESITY BASED HYPERTENSION

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ABSTRACT

Obesity is a significant public health challenge worldwide and is inextricably linked to adverse cardiovascular outcomes. The relationship between excess adiposity and increased blood pressure is well established, and it is estimated that obesity accounts for 65–78% of cases of primary hypertension. The mechanisms through which obesity causes hypertension are complex and include sympathetic nervous system overactivation, stimulation of the renin-angiotensin-aldosterone system, alterations in adipose- derived cytokines, insulin resistance, and structural and functional renal changes. Weight loss is the primary goal of treatment for obesity-related hypertension, although few individuals achieve success with nonpharmacological management alone. Specific considerations apply when selecting the most appropriate pharmacological therapy for obese hypertensive patients. Metabolic surgery has proved to be the most effective means of ensuring substantial and sustained weight loss and has also been shown to confer beneficial effects in type 2 diabetes mellitus. Increasing evidence suggests that metabolic surgery may also be an effective treatment for obesity-related hypertension, although prospective data on long-term blood pressure outcomes are awaited. This review will discuss the pathophysiological mechanisms that link obesity with hypertension and will provide an overview of treatment strategies, with a focus on metabolic surgery.

Keywords: Obesity; hypertension; bariatric surgery; metabolic surgery

I.INTRODUCTION

The global prevalence of obesity and its associated comorbidities continue to increase on a pandemic scale (1). Recent estimates from the World Health Organization (WHO) indicate that in 2016, over 1.9 billion adults were overweight and, of these, over 650 million were obese (2). Furthermore, 340 million children and adolescents aged 5–19 years and 24 million children under the age of 5 were estimated to be obese or overweight in 2016 (2). Obesity is no longer a public health issue confined to high-income countries, as the developing world is now witnessing increased obesity rates secondary to urbanization, changes in diet, and the adoption of sedentary lifestyles (3). If current trends continue, the global prevalence of obesity is projected to reach 18% in men and exceed 21% in women by 2025 (4). A growing body of evidence supports the notion that obesity is a causative factor in the development of hypertension (5-7). This review provides an overview of the known pathophysiological mechanisms that link excess adiposity with elevated blood pressure (BP) and outlines therapeutic strategies for ameliorating obesity-related hypertension, with a focus on metabolic surgery.

Definitions of obesity and its association with hypertension

Obesity is most accurately defined as the abnormal or excessive accumulation of adiposity to the extent that health may be impaired (2). However, the methods used to directly quantify body fat are cumbersome, expensive, and not routinely available in daily clinical practice (8). For this reason, the body mass index (BMI; body weight in kg divided by height in m2) is the most commonly used surrogate marker of adiposity (9). The WHO defines normal weight as BMI 18.5–24.9 kg/m2; overweight as BMI 25–29.9 kg/m2; and obesity as BMI □30 kg/m2 (10). However,

BMI does not differentiate between lean muscle and fat mass and does not provide any indication of the distribution of body fat. This is an important consideration as evidence suggests that visceral or retroperitoneal fat (i.e., centrally located body fat) is a more important than peripheral or subcutaneous fat in predicting the risk of cardiometabolic sequalae associated with obesity (11-13). Therefore, alternative anthropometric measures of adiposity such as waist circumference (WC) and waist-to-hip ratio (WHR) have also been utilized (14). Central obesity is defined as a WC of >102 cm in males and >88 cm in females, or a WHR of >1.0 in males and >0.85 in females (15). However, the drawbacks of these indices include the lack of standardized measurement protocols and reference data as well as decreased accuracy in those with severe obesity (BMI >35 kg/m2) (16). Furthermore, the cut-offs for both BMI and WC/WHR were defined based on white European populations, and it is recognized that individuals of Asian descent may have a higher percentage of body fat than individuals of white European descent for a given BMI and WC (17). This has led to the development of ethnicity- specific cut-offs for BMI, WC and WHR in non-white individuals as predictors of cardiometabolic risk (18,19).

The deleterious consequences of obesity include an increased risk of death from cardiovascular disease (CVD) (20), type 2 diabetes mellitus (T2DM) (11), cancer (20), and chronic kidney disease (12). Hypertension, defined as systolic BP 140 mmHg or diastolic BP 90 mmHg by the European Society of Cardiology/ European Society of Hypertension guidelines (24), or systolic BP 130 mmHg or diastolic BP 80 mmHg in the latest American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines (15), is a comorbid condition that is frequently seen in association with obesity (5). Hypertension is currently the leading risk factor for morbidity and mortality worldwide, resulting in 182 million disability-adjusted life years and 10.4 million deaths annually (26). The relationship between obesity and hypertension is well described in children and adults and across both sexes (5,20). For instance, in the Framingham Offspring Study, 78% of new cases of essential hypertension in men and 65% in women were attributable to excess body fat (20). Furthermore, an increase in weight by 5% was associated with a 20–30% increase in the incidence of hypertension (9). In the second Nurses' Health Study, in which 82,882 adult women were prospectively followed up for 14 years, BMI was the strongest risk factor for developing hypertension, with obese women having almost five times the incidence of hypertension compared to those with BMI <23.0 kg/m2 (3). In concordance with these observations, it has been shown that even modest reductions in weight can decrease BP in hypertensive patients. For example, in the TOHP II (Trials of Hypertension Prevention, phase II) study, in which overweight and obese adults were randomized to a weight loss intervention group versus usual care, participants who maintained a weight reduction of 4.5 kg for 30 months reduced their risk of developing hypertension by 65% (1). The relationship between central obesity measures such as WC/WHR and BP appears to be independent of BMI, and it has been suggested that using these indices in combination, rather than individually, may be a superior predictor of obesity- related cardio metabolic risk in certain populations (2,3).

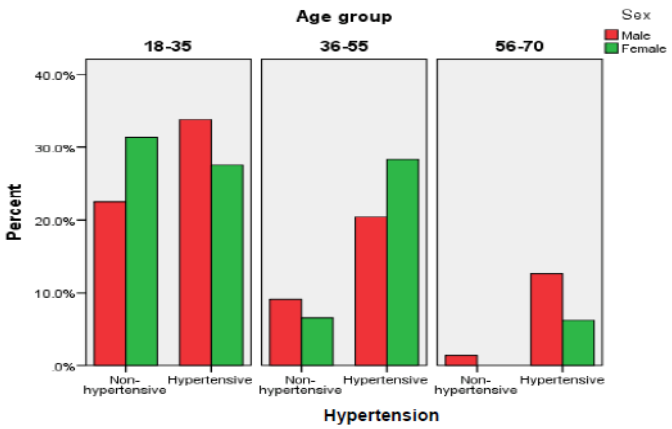

Figure 1: Bar chart showing distribution of hypertension as per gender in different age groups (in years).

II. PATIENTS AND METHODS

An epidemiological survey, to determinate the prevalence of obesity and overweight in a Spanish hypertensive population (the ESOPOH Study) and endorsed by the Spanish Society of Hypertension,was carried out in 19,039 hypertensive patients who attended primary healthcare centers throughout Spain between 1 February and 30 April 2004. In all of the cases, patients were invited to participate inthe study and gave their consent. Patients included both males and females over the age of 18 with BP readings >140/90 mmHg (>130/80 mmHg in patients with diabetes mellitus (DM) or patients who were undergoing treatment with antihypertensive drugs. Patients who showed evidence of secondary hypertension were excluded from the study, as were patients who did not want toparticipate in the study.

Data from the ESOPOH Study were collected in 1000 healthcare centers by 2000 general practitioner, and each general practitioner included the first 10 patients with hypertension who attended a their visit. An anamnesis and a physical examination were carried during the visit. Analytical data was obtained from the patients' clinical report if obtained less than 6 months prior to the study. If the clinical history was older than 6 months, we carried out a new analytical test. The type of hypertension treatment the patients were taking and the grade of BP control were noted.

BP was measured after 5 min of rest using a mercury sphygmomanometer or a valid semiautomatic apparatus with an adequate cuff size for the weight and diameter of the arm and the mean of two consecutive readings were taken as BP of the patient. Weight was determined using a clinical scale. Body mass index (BMI) was calculated by dividing the weight of each patient in kg by the height squared. Patients were considered overweight if BMI was greater than 25 kg/m^2, obese if BMI was >30 kg/m^2 and severe obesity (SO) was diagnosed if BMI was >40 kg/m^2. Waist circumference was measured using a metric measuring tape at the level of the belly button with the patient standing. Abdominal obesity (AO) was defined as waist circumference greater than 102 cm in men and 88 cm in women. Analytical procedures were carried out in the laboratory of each center. Classic metabolic alterations were diagnosed according to usual clinical criteria, or, if patients were undergoing pharmacological treatment: fasting blood glucose greater than or equal to 6.1 mmol/l or previous diagnosis of diabetes, total cholesterol greater than 5.18 mmol/l, high-density lipoprotein (HDL)-cholesterol less than 1.036 mmol/l in men and 1.295 mmol/l in women and fasting triglycerides >1.695 mmol/l or with lipid lowering treatment. Metabolic syndrome (MetS) was considered when three or more of the NCEP criteria were fulfilled (16).

Physical activity was assessed by a questionnaire and evaluated as sedentary without any exercise activity, moderate if the patient took up exercise three times a week between 30 and 45 min, and intense activity if the patient did exercise every day.

Table 1 | Global mortality estimates (in thousands) due ischemic heart disease and cerebrovascular disease, by sex, between 1990 and 2020

	Women			Men		
	1990	2020	% Increase	1990	2020	% Increase
Ischemic heart disease						
Developing countries	1,737	3,825	120	1,828	4,337	137
Developed countries	1,397	1,809	29	1,297	1,921	48
Cerebrovascular Disease						
Developing countries	1,499	3,100	107	1,454	3,260	124
Developed countries	867	1,113	28	539	841	56

Adapted from reference 17.

Table 2 | Age-specific prevalence of hypertension and obesity in the United States at two time periods, and percent increase over time

	Hypertension prevalence (%)			Obesity prevalence (%)		
Age (years)	1988–1991	2005–2006	Percent increase	1988–1994	2005–2008	Percent increase
18-39	5.1	7.4	45	17.2	28.7	67
40-59	27.0	32.1	19	28.0	35.5	27
>60	57.9	65.8	14	23.9	34.0	42

Based on National Health and Nutrition Examination Survey data obtained from reference 25 and the following Centers for Disease Control and Prevention web sites: www.cdc.gov/nchs/nhanes/nhanes2007-2008/nhanes07_08.htm and www.cdc.gov/nchs/nhanes/nh3data.htm.
Hypertension = systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or taking antihypertensive medication. Obesity = body mass index >30 kg/m^2.

III. 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.

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 ATPIII 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 triglycer- ide ≥ 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.MANAGEMENT

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 bestpredictor 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 tosuggest 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.

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).

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 fabricthat 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).

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 withmultiple 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 recom- mended 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 consid- ered 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 Preven- tion Evaluation (HOPE) and Captopril Prevention Project (CAPPP) trials (Hans- son *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 respon- sible for the inexorable progression to obesity-hypertension-related ESRD. Fi- nally, 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-hyperten- sion 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, pharmaceu- tical 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 bloodpressure 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 param- eters 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 comparedto baseline (McMahon *et al.*, 2000). Therefore, sibutramine cannot be recom- mended 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 signifi- cantly 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.

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).

V.CONCLUSION

Obesity-related hypertension is a multifactorial phenotype determined by the interaction of genes and environments. However, currently identified genomic factors account for only a small percent of the heritable risk of this phenotype. The association of hypertension with obesity is primarily related to visceral obesity, which in turn is associated with insulin resistance and dyslipidemia. Lifestyle and pharmacologic approaches for treating obesity-related hypertension should address overall CVD risk, not simply hypertension. More work is required to identify culturally sensitive strategies for obesity prevention and their impact not only on body weight, but also on blood pressure, the metabolic phenotypes associated with obesity, and subsequent CVD. Although several mechanisms have been identified that may account for elevated arterial pressure, currently, there is no compelling evidence to indicate that any one class of antihypertensive agents is particularly advantageous for the treatment of obesity-related hypertension.

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