

Obesity and hypertension (Review)

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Abstract. The imbalance between energy intake and expenditure is the main cause of excessive overweight and obesity. Technically, obesity is defined as the abnormal accumulation of $\geq 20\%$ of body fat, over the individual's ideal body weight. The latter constitutes the maximal healthful value for an individual that is calculated based chiefly on the height, age, build and degree of muscular development. However, obesity is diagnosed by measuring the weight in relation to the height of an individual, thereby determining or calculating the body mass index. The National Institutes of Health have defined 30 kg/m^2 as the limit over which an individual is qualified as obese. Accordingly, the prevalence of obesity in on the increase in children and adults worldwide, despite World Health Organization warnings. The growth of obesity and the scale of associated health issues induce serious consequences for individuals and governmental health systems. Excessive overweight remains among the most neglected public health issues worldwide, while obesity is associated with increasing risks of disability, illness and death. Cardiovascular diseases, the leading cause of mortality worldwide, particularly hypertension and diabetes, are the main illnesses associated with obesity. Nevertheless, the mechanisms underlying obesity-associated hypertension or other associated metabolic diseases remains to be adequately investigated. In the present review, we addressed the association between obesity and cardiovascular disease, particularly the biological mechanisms linking obesity and hypertension.

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1. Introduction

Obesity is traditionally defined as a weight $\geq 20\%$ above the ideal weight, which corresponds to the lowest death rate for individuals of a specific height, gender and age (1). More recent guidelines for obesity have introduced the use of a measurement known as body mass index (BMI), which is calculated by the individual's weight multiplied by 703 and divided by twice the height in inches. The value of BMI is now used to diagnose the stage of overweight or obesity thereby fixing at 25.9-29 the limited BMI considered as overweight, while a BMI >30 constitutes obesity (2). According to the World Health Organization (WHO), in 2005, approximately 1.6 billion adults over the age of 15 were overweight (3). At least 400 million adults were considered obese and ≥ 20 million children under the age of 5 years were overweight. The estimation for the current year (2015) is approximately 2.3 billion overweight adults and over 700 million obese ones (4). WHO defines 'globesity' as a worldwide epidemic of obesity that is currently on the increase. The situation is critical due to the fact that the diseases that can occur due to obesity are becoming increasingly prevalent, particularly cardiovascular diseases, currently the leading cause of mortality worldwide (5).

Obesity can result in serious health issues that are potentially life threatening, including hypertension, type II diabetes mellitus, increased risk for coronary disease, increased unexplained heart failure, hyperlipidemia, infertility, higher prevalence of colon, prostate, endometrial, and breast cancer (6,7). Although the relationship between obesity and hypertension is well established in children and adults (8-11), the mechanism by which obesity directly causes hypertension is under investigation (12,13). Activation of the sympathetic nervous system (SNS), the amount of intra-abdominal and intra-vascular fat, sodium retention leading to increase in renal reabsorption, and the renin-angiotensin system, are considered to have important functions in the pathogenesis of obesity-related hypertension, a chronic medical condition in which the blood pressure is persistently at or $>140/90$ mmHg but not at the normal level which is defined as $100-140$ and $60-90$ mmHg for systolic and diastolic pressure, respectively. Accordingly, obesity can be considered a complex and chronic medical condition that requires deep understanding, particularly for the mechanisms leading to hypertension to plan successful treatment strategies. The present review examines the potential mechanisms by which obesity can lead to elevated arterial blood pressure and how

management of obesity constitutes a therapeutical strategy for the treatment of hypertension.

2. Obesity and hypertension

Global causes of obesity and consequences. There is no single cause to explain all the cases of obesity worldwide. Environmental factors associated with obesity include socio-economic status, ethnicity, region of residence, season, and urban living (14). Nevertheless, obesity ultimately results from an imbalance between energy intake and energy expenditure (15). Genetic predisposition may be a determinant for weight gain; however, previous findings have shown that genetic predisposition does not automatically lead to the development of obesity, because eating habits and patterns of physical activity may play a more significant role in the amount of weight gained (16,17). In addition, a sedentary lifestyle as well as psychological factors such as depression, low esteem, or absence of night sleep can also largely contribute to weight gain (18). However, although the exact cause of weight gain remains to be clarified and likely arises from a complex combination of factors such as genetic factors that greatly affect the manner in which the body regulates the appetite, and the rate at which it turns food into energy, known as the metabolic rate (19,20), excessive weight is clearly gained by consuming an excess of calories as compared to those utilized by the body, with the excess of calories being stored as fat tissue (15).

Accordingly, the quantity of fat in a person's diet may have greater impact on weight than the number of calories it contains. The majority of fat calories are immediately stored in fat cells, which add to the body's weight and girth as they expand and multiply (21) while carbohydrates such as cereals, breads, fruits, and vegetable and proteins are converted to fuel almost immediately following consumption (22). In addition, fat regimens result in excessive and abnormally higher levels of cholesterol in the blood (hypercholesterolemia) (23). Depending on the balance between the fractions of saturated and unsaturated fatty acids, fat contained in the blood circulation can immediately affect certain organs such as liver and kidney, concomitantly with devastating local actions inside of the vessels through the formation of atherosclerosis (24), an infringement of medium and large arteries due to a buildup of fat inside of the arterial wall, termed visceral fat. The latter is mainly involved in metabolic syndrome (25).

Diets that are extremely rich in carbohydrates and high doses of alcohol promote the increase of another lipid component present in the blood, that of triglycerides, which constitutes an additional risk factor of the formation of atherosclerosis (24). Other factors favoring the formation of atherosclerosis include physical inactivity, smoking, stress, inflammation and certain bacteria (26). However, the fat continually accumulated in branch vessels, thus blocking the blood flow of large arteries. In agreement with these data, increased carotid intima-media thickness in obese subjects independently of blood pressure levels, even in a normotensive blood pressure range has been observed (27). This observation suggests an early course of the atherosclerotic process in obesity. Accumulation gradually increases to form a type of plaque that may continue to grow until it reaches a narrowing or stenosis of the vascular wall (28)

that can continue to increase until important obstructions of arterial lumen are induced and downstream local disorders that affect organs are generated, leading to morbidity (29,30) and even sudden death (31). Another detrimental effect of high caloric intake is the increase of norepinephrine turnover in peripheral tissues, raising the resting plasma norepinephrine concentration, which is an indirect measurement of SNS activity, and amplifying the increase of plasma norepinephrine in response to stimuli such as upright posture (32). Thus, high dietary content in fat and carbohydrate has been suggested to acutely stimulate peripheral α_1 and β -adrenergic receptors thereby leading to the elevation of sympathetic activity and hypertension (33). Similarly, upregulated hypothalamic tyrosine hydroxylase and hypothalamic adrenoceptor gene expression of the α_2B receptor have been identified, in obese hypertensive rat (34). In addition, the pharmacological blockade of adrenergic activity in experimental models markedly decreased the rise of blood pressure in dogs fed a high-fat diet (10). Similarly, in human, combined α and β adrenergic blockade significantly reduced blood pressure in obese relative to lean patients with essential hypertension (35), although elevated heart rate seems to be the effect of decreased parasympathetic activity (36).

Overweight is a condition that affects the body composition thereby damaging and modifying the aspects of organs. Major organs feeling the brunt of obesity, include heart (37), liver (38), kidney (39), lungs (40), colon (41), skin (42), vessels (43) and brain (44). Whereas the effect on each organ is associated with collateral defects that may have serious concerns regarding health, renal injury seems, however, to be the most directly dependent on body weight, as dietary fat restriction ameliorates significantly the renal histology (45). The structural changes inside of the kidney, secondary to obesity, are important as the fat deposit around the kidneys, together with increased abdominal pressure secondary to central obesity, have been suggested as an additional cause of renal sodium reabsorption disorder. Specifically, initially, obesity causes renal vasodilatation and glomerular hyperfiltration, which act as a compensatory mechanism to maintain sodium balance despite the increased tubular reabsorption that, along with increased arterial blood pressure and metabolic abnormalities as well as other factors such as inflammation, oxidative stress, and lipotoxicity, may contribute to the exacerbation of renal injury or dysfunction through a vicious cycle (46,47). These factors result in clinical evidence of the presence of proteinuria that usually precedes the glomerular filtration rate decline over several years (48,49). The involvement of insulin and angiotensin II in the development of glomerular hyperfiltration have been shown in obese animals (42) in which, leptin, a hormone produced in adipose tissue, contributes to the development of renal injury through the induction of cytokines (50). Consistently, adipose tissues, particularly those of abdominal fat may specifically exert systemic effects through the secretion of a variety of hormones and cytokines, leading to obese-associated glomerulopathy (51).

In accordance to the abovementioned data, regimens rich in fat and carbohydrate, lead to hypercholesterolemia and free-fatty acids in the blood (23) which together with free-fatty acids released from phospholipids can act directly on ion channels of cellular membranes of smooth muscle

cells and other tissues (52). They can also act as potent activators of the phosphorylation of calcium-independent isoenzyme of protein kinase C (53), a vital element in mediating signal transduction and cell regulation. The binding of free-fatty acid to NA/K-ATPase is involved in the changes of interactions between the enzyme and neighboring membrane protein to induce the formation of multiple signaling modules that results in the activation and production of the epidermal growth factor receptor that increased reactive oxygen species (54). The reduction of endothelial function is mainly the result of a decrease in nitric oxide (NO) related to an increase in oxidative stress or the result from pro-inflammatory cytokines (55). Altogether, cytokines and oxidative stress as well as the decrease of NO result in vasoconstriction and vascular resistance that are detrimental and predisposed to venous insufficiency, venous thrombosis and pulmonary embolus, cardiovascular disease and particularly to hypertension (37).

Biochemical, physiological and functional studies have suggested that the renin-angiotensin system is mainly involved in the development of hypertension through two systems including tissue and circulating (55). In agreement with this finding, adipose tissue-derived angiotensinogen, the major site in which all components of the RAS are formed, can enter the circulation. The tissue RAS was in a state of constant interaction with the blood. Angiotensinogen, angiotensin (Ang) I and AngII are locally produced and are simultaneously taken up by the cells, in which AngII receptors are overexpressed. Angiotensinogen production serves as a cause and effect of adipocyte hypertrophy and leads to elevation of blood pressure through the action of AngII, which induces systematic vasoconstriction, direct sodium and water retention and increased aldosterone production (56). Consequently, AngII determines a high salt-sensitive blood pressure condition in obesity as it is produced at high rates and is not suppressed by volume expansion. An alternative mechanism of RAS activation may be a chronic elevation of sympathetic tone, causing renal vasoconstriction and renin-dependent chronic hypertension. The arterial blood pressure controlling mechanism of diuresis and natriuresis according to the principle of infinite feedback gain seems to be raised near the higher blood pressure value in obese patients. Abnormalities in these mechanisms tend to raise blood pressure, increase sodium and water excretion through pressure natriuresis and diuresis (57), which lead to extracellular fluid volume expansion, resulting in a hypertensive adjustment of the pressure natriuresis (10,11), a resetting of the kidney fluid apparatus to a hypertensive level, consistent with the model of hypertension because of volume overload. Another significant cause of the shift of pressure natriuresis towards higher blood pressure levels in obesity is the possibility of alterations in intrarenal forces caused by histological changes in the renal medulla that may compress the loops of Henle and vasa recta (58).

Furthermore, high levels of plasma renin activity, plasma AngII and aldosterone values were observed in human obesity (59) in which a presynaptic potentiating effect was observed on the sympathetic neurotransmission in patients under sodium restriction (60), likely through hypothetical mechanisms including impaired function of baroreceptors

sensitivity and increased levels of circulating free-fatty acids, AngII, insulin and leptin (61).

Elevated levels and abnormally distributed free-fatty acids were reported in obese hypertensive in which they enhanced vascular α -adrenergic sensitivity and consequently the increase of α -adrenergic tone (62). Although the mechanisms were endogenous, the effect exerted by free-fatty remains to be investigated. At present, it has been documented that free-fatty acids inhibit Na⁺, K⁺ ATPase and the sodium pump raising vascular smooth muscle tone and resistance (54).

3. Treatment of obesity-induced hypertension

Although antihypertensive drugs, including RAS blockers, β -blockers, and diuretic drugs, particularly at high doses are eligible for obese hypertensive patients, they provide significant side effects including hyperglycemia, hyperlipidemia and hyperuricemia. Therapeutic approaches of hypertension-induced obesity required the management of the component obesity. The treatment of obesity itself requires guidelines suggesting deep lifestyle modifications aiming to reduce body weight, thereby consuming a low-caloric diet with a total of 500-1,500 or 500-1,200 calories for men or women, respectively. This may include the restriction of salt intake and lower intake of saturated fats and cholesterol with increased consumption of water, fruits, fresh and raw vegetables, fish, lean meats, whole grain, and/or moderate and constant physical activity as well as adequate night sleep (63,64). The aim of these habits and activities involve the increase and strengthening of muscular mass vs. decreasing fat mass.

4. Conclusion

Obesity is a major risk for essential hypertension, diabetes and other morbidity that contribute to the development of kidney disease because it mainly increases tubular reabsorption to impair pressure natriuresis and cause volume expansion via the activation of the SNS and the RAS. Additionally, obesity causes cardiovascular and renal diseases through several mechanisms including hypertension, hyperglycemia, inflammation, dyslipidemia and atherosclerosis, which are disorders that can coexist, particularly in the presence of excess visceral fat to cause metabolic syndrome (65) and are characterized by alteration in fat metabolism through lipid accumulation. Therefore, the habit of regular diets with content of plenty of fiber, ω -3, good vegetable and animal proteins, antioxidant, less fat and sugar, vitamins and regular exercise, are healthy practices allowing the body's nutritional signaling mechanisms to equilibrate to reference levels.

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