Hypertension Related to Obesity

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Obesity and hypertension are closely interrelated as abdominal obesity interferes with the endocrine and immune systems and carries a greater risk for insulin resistance, diabetes, hypertension, and cardiovascular disease. Many factors are at the interplay between obesity and hypertension. They include hemodynamic alterations, oxidative stress, renal injury, hyperinsulinemia, and insulin resistance, sleep apnea syndrome and the leptin-melanocortin pathway. Genetics, epigenetics, and mitochondrial factors also play a major role. The measurement of blood pressure in obese patients requires an adapted cuff and the search for other secondary causes is necessary at higher thresholds than the general population. Lifestyle modifications such as diet and exercise are often not enough to control obesity, and so far, bariatric surgery constitutes the most reliable method to achieve weight loss. Nonetheless, the emergence of new agents such as Semaglutide and Tirzepatide offers promising alternatives.

hypertension obesity pathogenesis

1. Introduction

The World Health Organization (WHO) refers to obesity as abnormal or excessive fat accumulation that presents a risk to health [1]. The body mass index (BMI), which is calculated using weight and height as kg/m² [2][3], is used to screen for obesity in adults, with a cut-off set at 30 kg/m² in adults by the Centers for Disease Control and Prevention (CDC) [4]. People having a BMI of 30.0 to 34.9 are considered as having obesity class I, those with a BMI of 35 to 39.9 belong to class II obesity, and those with a BMI of 40 and above are considered as class III patients or as having severe obesity, formerly known as morbid obesity [4]. However, this tool has several limitations: it does not reflect the pathogenesis of the disease, does not permit distinguishing the contribution of fat versus muscle mass, and does not indicate the extent of the impact on health [5][6]. Abdominal obesity is a better reflection of risk and is usually assessed by measuring waist circumference [7].

Obesity and hypertension are closely interrelated as abdominal obesity interferes with the endocrine and immune systems and carries a greater risk for insulin resistance, diabetes, hypertension, and cardiovascular disease [3][8][9]. Moreover, obesity is recognized as a major risk factor for hypertension in both adults and children, regardless of race, ethnicity, and sex [10][11]. Two landmark studies that investigated this association are the Nurse's Health Study and the Framingham Heart Study [12][13]. The Nurse's Health Study is a prospective cohort study of 83,882 adult women who were followed up for 16 years. The results showed that: (a) increased BMI was associated with the development of hypertension, (b) the relative risks for hypertension were 1.7 and 5.2 in women who gained 5–10 kg and >25 kg, respectively, and (c) 40% of the new-onset hypertension cases were attributed to overweight and obesity [12].

2. Pathogenesis of Hypertension Associated with Obesity

The factors behind obesity-induced hypertension are multiple and often take effect simultaneously. They include: hemodynamic alterations with changes in the generation of endothelium-derived constricting as well as relaxing factors, disruption of molecular signaling, increased oxidative stress, renal injury, hyperinsulinemia and insulin resistance, sleep apnea syndrome, and the leptin-melanocortin pathway [14][15]. Cardiovascular and hemodynamic alterations differ according to the distribution of obesity as patients with peripheral obesity have higher cardiac output (CO) and lower systemic vascular resistance (SVR), while patients with central obesity have lower CO and higher SVR [16].

At the cellular level, adipose tissue contributes to endothelial dysfunction by secreting multiple hormones and paracrine signals known as adipokines. These molecules play an important physiological role in regulating vascular tone. In the case of obesity, there is excessive secretion of pro-inflammatory and vasoactive adipokines such as angiotensinogen, angiotensin II, aldosterone, and resisting, along with an increase in plasma renin activity [17][18][19].

Regarding oxidative stress, the metabolism of excess free fatty acids (FFAs) through β-oxidation and the TCA cycle produces excess reactive oxygen species (ROS) [20]. ROS generation is also increased in adipocyte cells as FFAs can stimulate NADPH oxidase, an enzyme involved in superoxide radical, nutrient-based ROS generation, and vascular injury [14]. Further oxidative stress is caused by FFAs, which are released from over-accumulated fat and can activate NADPH oxidase indirectly by stimulating the production of diacylglycerol, which activates protein kinase C, a direct activator of NADPH [21]. In turn, activation of NADPH oxidase, may contribute to the progression of hypertension through activation of the central sympathetic system [22].

Chronic kidney disease (CKD) also plays a role in the pathogenesis of obesity and hypertension as increased visceral adiposity is associated with impaired kidney function through physical compression of the kidneys by the fat around them, activation of the renin-angiotensin pathway, as well as increased sympathetic nervous system activity. Constriction of the efferent arteriole with an increase in the intraglomerular pressure leads to nephron loss and increased renal tubular sodium reabsorption, which in turn impairs pressure natriuresis plays a crucial role in the development of increased blood pressure in obese individuals [23].

Sleep breathing disorders and sleep apnea are also extremely common in obese patients, with a prevalence of 40 to 90% [24]. Sleep apnea is a known cause of hypertension through neurohormonal dysregulation, endothelial dysfunction, inflammation, and increased levels of endothelin by repeated episodes of hypoxia [25].

3. Genetics, Epigenetics and Mitochondrial Factors Related to Obesity and Hypertension

3.1. Genetics

A major factor in the interplay between obesity and hypertension is genetic susceptibility. A recent population-based study on 30,617 twin individuals showed that being overweight or obese was associated with a 94% increased risk of hypertension (OR = 1.94, 95% CI: 1.64~2.30). After controlling for all other variables, this association was mainly explained by genetics [26]. However, there is still no consensus on which specific genes have a direct role in both obesity and hypertension. Currently, several molecular mechanisms (both genetic and epigenetic) are under investigation to elucidate the role of genetics in the pathophysiology of obesity-related hypertension. This role has been primarily investigated by identifying single nucleotide polymorphisms (SNPs) in loci associated with both diseases. Genome-wide association studies (GWAS) have identified more than 50 SNPs associated with hypertension and over 250 genes/loci involved in the pathophysiology of obesity [27].

3.2. Epigenetics

The rising rate of obesity in recent years cannot be explained by genetics alone. Epigenetic factors that alter gene expression without interfering with DNA structure play an important role in this trend. Three epigenetic modifications have been studied in relation to obesity and hypertension: (a) DNA methylation, (b) histone modification, and (c) non-coding RNA. DNA methylation is the most studied [28] and consists of the covalent binding of a methyl group to a cytosine residue in the DNA, at sites where cytosines are followed by guanines (CpG sites). This process is mediated by methyltransferases and its dysregulation (either hypermethylation or hypomethylation) can alter gene transcription and lead to several diseases [29].

In hypertension, epigenetic mechanisms also play a role through the methylation of different genes. A systematic review of the role of DNA methylation in modifying blood pressure showed that lower methylation levels of *SULF1* (sulfate endosulfatase), *EHMT2* (Euchromatic Histone Lysine Methyltransferase 2), and *SKOR2* (SKI Family Transcriptional Corepressor 2) were associated with hypertension. On the other hand, lower methylation levels of *PHGDH* (phosphoglycerate dehydrogenase), *SLC7A11* (Solute Carrier Family 7 Member 11), and *TSPAN2* (Tetraspanin 2) were correlated with higher systolic and diastolic blood pressure [30].

Another important epigenetic mechanism is histone modification. Histones are proteins wrapped around DNA that contribute to making compact chromatin. Histone modification (acetylation, deacetylation, methylation, phosphorylation, or ubiquitination) is one of the epigenetic mechanisms that emerged as a factor in obesity and energy metabolism [31]. Recent studies have also investigated the role of histone modification in obesity-related hypertension. For instance, Jung et al. found that a high-fat diet inhibits the MsrA (Methionine Sulfoxide Reductase A)/Hydrogen Sulfide (H2S) Axis, which causes oxidative stress, inflammation, hyper-contractility, and hypertension.

MicroRNAs (miRNAs) are small, single-stranded, non-coding RNA molecules that regulate post-transcriptional gene expression. They function by silencing messenger RNA (mRNA) by binding to its 3′ untranslated region [32]. MicroRNAs play an important role in both physiologic and pathologic processes. Dysregulation of mRNAs has been associated with obesity and obesity-related inflammation. In fact, the metabolic disruption in obesity is rooted in chronic low-grade inflammation through the activation of TNFα, IL-6, and CRP [33]. MicroRNAs modulate this process by controlling the post-transcriptional expression of those cytokines [34].

3.3. Mitochondria

Aside from genetics and epigenetics, mitochondria also play a role in the multifactorial etiology of obesity-induced hypertension. Indeed, obesity-associated oxidative and inflammatory stress has been linked to a variety of cardiovascular diseases through the development of metabolic syndrome. This pathophysiologic process involves the abnormal production of reactive oxygen species (ROS) that leads to mitochondrial dysfunction [35]. In normal cells, mitochondria are highly dynamic cytoplasmic organelles that play an essential role in cellular metabolism through four dynamic processes: (a) fusion of two mitochondria into one, (b) fission or division of mitochondria into two or more; (c) biogenesis, which is required for cell growth and adaptation, and (d) mitophagy, a specialized form of autophagy similar to cell apoptosis [36].

Mitochondrial dysfunction through disruption of those dynamic processes contributes to oxidative stress and is associated with the development of both obesity and hypertension. The equilibrium between mitochondrial fusion and fission is modulated through nutrient availability and metabolic demands [37]. Nutrient depletion triggers the “Stress-Induced Mitochondrial Hyperfusion” or SIMH response, which leads to mitochondrial fusion. SIMH is an adaptation response to stress because it leads to increased ATP production and NF-κB activation, which in turn protects against autophagy and apoptosis. SIMH is essentially mediated through fusion machinery proteins (*MFN1* [Mitofusin-1] and *OPA1* [Mitochondrial Dynamin Like GTPase]), as well as the scaffold protein stomatin-like protein 2 (SLP2) [38]. Nutrient depletion also stops mitochondrial fission through the PKA-mediated phosphorylation of DRP1 [39].

In hypertension, activation of the sympathetic nervous system is a key element in cardiac remodeling, especially in obese patients. This effect is mediated through the release of catecholamines (i.e., norepinephrine) which induce hypertrophy of the cardiac myocytes. These myocytes are abundant in mitochondria since they rely on them for a constant supply of ATP needed for the cyclic contractions of the heart. In this regard, hypertension-induced cardiac hypertrophy causes dysfunction of ATP production and the electron transport chain in the mitochondria. In addition, mitochondrial dysfunction in the cardiac myocytes of hypertensive patients is linked to disrupted dynamics of fusion and fission. For instance, the expression of *OPA1*, *MFN1*, and *MF2* was decreased in hypertensive rats, all together favoring mitochondrial fission [37].

4. Treatment of Obesity to Control Hypertension

Notably both the Dietary Approaches to Stop Hypertension (DASH) diet, which consists of plant-based food and dairy products low in fat [40], and the Mediterranean diet have been successful not only in reducing both systolic and diastolic blood pressure but also in decreasing obesity-associated inflammation and complications [41]. The green Mediterranean diet, a version of the Mediterranean diet amplified with green plant-based proteins/polyphenols such as green tea and walnuts, and restricted in red/processed meat, is particularly indicated to reduce intrahepatic fat content [42]. Another promising regimen is the Very Low-Calorie Ketogenic Diet (VLCKD). This program restricts the caloric content to only 500–800 calories per day, with significantly lower carbohydrates (<50 g/day) in meals. VLCKD showed significant but equal results not only in lowering body weight and waist

circumference but also in enhancing the participants' lipid and glucose values [43]. The greater the weight loss, the more significant the improvements in cardiovascular health and blood pressure parameters [44].

An increase in physical activity is an important adjunctive to the right diet in the process of achieving the target body weight and normalizing blood pressure. It enhances the patients' mood and strengthens their commitment to the dietary regimen [45]. Aerobic exercises have shown the best outcome in decreasing total body weight and fat percentage, whereas resistance training is the method of choice to grow lean body mass [46]. Patients that combine both regimens have lower pervasiveness of obesity [47].

Pharmacotherapy is a supplemental tool to lifestyle modifications and is being increasingly prescribed. It is advised according to the European Association for the Study of Obesity in patients whose BMI is ≥30 kg/m^2 or BMI ≥27 kg/m^2 with obesity-related comorbidity such as hypertension [48]. Physicians should use constant vigilance in assessing the patient's response to pharmacotherapy. Medications should be stopped or changed if the side effects are intolerable, or the weight loss is less than 3% in diabetics or 5% in nondiabetics [48].

Pharmacological treatment has been increasingly versatile, with combinations tailored to the patients' profiles. The most promising class is the class of incretins-mimetics. Incretins such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are factors released by the gut in response to ingested nutrients and play an important role in metabolism as they regulate appetite and body weight [49]. GLP-1 receptor stimulation can decrease appetite and food intake [50][51], as well as gastrointestinal motility and gastric emptying [52][53]. These effects have led to the development of GLP-1 receptor (GLP-1R) agonists not only to treat diabetes but also to decrease adipose tissue mass and to be used for weight loss [51]. Among them, subcutaneous Semaglutide seems to be the most efficacious in reducing body weight, followed by oral Semaglutide, exenatide twice daily, and liraglutide [54]. For instance, in phase III clinical trials conducted in individuals with obesity or overweight without diabetes, Semaglutide at the dose of 2.4 mg led after 68 weeks of treatment to a decrease in body weight by −14.9% relative to −2.4% in placebo-treated controls [55]. In addition, GLP-1R agonists were found to be effective at decreasing blood pressure, with Semaglutide demonstrating again the most effectiveness [54][56][57][58]. This substantial effect on blood pressure might be attributed to the GLP-1 enhancement of natriuresis [50][59]. On the other hand, GIP receptor (GIP-R) agonists were found to be either weight neutral or to induce modest and dose-dependent weight loss in mice, and when combined with long-acting selective individual agonists for GLP-1R, to enhance body weight lowering [60][61][62][63]. Subsequently, the use of dual GLP1-R and GIP-R agonism has been studied and shown to reduce body weight by more than 20% [64][65]. A new drug with that dual agonism, Tirzepatide, was approved by the United States Food and Drug Administration (FDA) in May 2022 and was shown in a phase 3 open-label study to be superior to Semaglutide for body weight reduction [66][67].

Another anti-diabetic agent pramlintide, an amylin analog that is approved by the FDA for use in patients with diabetes who are using mealtime insulin alone, or in combination with an oral agent, such as metformin or a sulfonylurea [68], is also showing promise for weight loss and its usefulness is not limited to patients with impaired glucose metabolism [69]. Amylin is a peptide that is co-secreted with insulin and reduces food intake through central control of satiety pathways [70].

Other commonly used therapies include the combination of phentermine and Topiramate [45] and the naltrexone bupropion combination [68]. Phentermine belongs to the sympathomimetic amines family and targets norepinephrine (NE) and dopamine (DA) neurons in the brain [71], whereas topiramate is a known anticonvulsant which has been noticed initially in clinical trials to induce weight loss in trials for seizure disorders and was thereafter tried for this indication [72].

Bariatric Surgery is traditionally indicated for patients who have failed the initial interventions and have a BMI of 35 kg/m^2 or more and an obesity-related comorbidity or a BMI more than 40 kg/m^2 with or without the presence of comorbidities even if the indications have been recently evolving as people with BMI 30 to 35 with type 2 diabetes mellitus could also be considered [73].

The 2 most common procedures used currently, the sleeve gastrectomy and gastric bypass, have similar effects on weight loss and a similar safety profile through at least 5-year follow-ups [74]. Massive weight loss secondary to bariatric surgery can trigger profound sympathoinhibitory effects and is associated with a stable and significant reduction in plasma leptin levels with subsequent blood pressure reduction [75]. In a series of 45 patients, postoperative weight loss after gastric bypass surgery was associated with the resolution or improvement of diastolic hypertension in approximately 70% of cases [76]. Regarding the best technique, gastric bypass surgery seems to be superior to gastroplasty and gastric banding at achieving and sustaining lower systolic and diastolic blood pressure and has also shown a better effect on natriuresis [77].

3-Amino-1,2,4-triazole (ATZ) is a heterocyclic organic compound that inhibits *α*-oxidation, fatty acid synthesis, and lipogenesis in isolated hepatocytes [78]. ATZ also inhibits aminolevulinic acid dehydratase, a key enzyme in heme synthesis. As heme activates the transcription repressor RevErb*α*, which is essential for adipocyte differentiation, ATZ could also potentially inhibit adipogenesis via that route [79]. In a group of mice fed with a high-fat diet (HFD), the administration of ATZ over 12 weeks led to the prevention of an increase in blood pressure and lower body weight, triglycerides levels, and leptin in plasma. ATZ treatment also impeded an HFD-induced increase in adipocyte diameter and induced marked atrophy and the accumulation of macrophages in this tissue [80], therefore, showing promise as a potential agent to be used in the future in the treatment of hypertension in obesity in particular and metabolic syndrome in general.

Leptin, a hormone secreted by the adipose tissue, plays a major role in body weight homeostasis and helps reduce food intake and increase energy expenditure [81]. As congenital leptin deficiency was found to result in severe weight gain and obesity in humans [82], leptin was considered an important regulator of energy balance, and its potential role as a therapy to reduce obesity was explored. However, administering additional leptin in the context of obesity has been largely ineffective, as obese individuals have higher circulating levels of leptin along with leptin resistance [83][84].

Besides pramlintide, other amylin analogs with improved pharmacokinetics are being considered as potential therapeutic agents, and the amylin pathway is another very active area of experimental investigation. For instance, Cagrilintide, a long-acting amylin analog has made it successfully to a phase II trial [85], and concomitant treatment

with Cagrilintide and Semaglutide was well tolerated in a phase 1b trial, opening pathways to potential new combinations to be used.

Ghrelin is a peptide hormone secreted from the gastric fundus that acts on receptors in the Hypothalamus to stimulate food intake in a dose-dependent fashion [86]. Ghrelin is found in 2 forms: Acyl-Ghrelin and Desacyl-Ghrelin, however, only the acylated form (which is acylated by the Ghrelin O-Acyltransferase enzyme) binds the Ghrelin receptor, which is the growth hormone secretagogue receptor (GHSR) to exert its effect [87][88]. Conversely, the liver-expressed antimicrobial peptide 2 (LEAP2) acts as an antagonist of ghrelin by inhibiting GHSR activation [89]. Both plasma levels of ghrelin and LEAP2 are highly regulated by body weight and feeding status in opposite directions [90]. Agents that act to lower plasma ghrelin, raise plasma LEAP2, block GHSR activity, and/or raise desacyl-Ghrelin signaling could therefore be efficient to treat obesity.

A more potent derivative of BAM15 named SHC517 (N5–(2-fluorophenyl)-N6 -(3-fluorophenyl)-[1,2,5]oxadiazolo-[3,4-b]pyrazine-5,6-diamine) was also tested in a mouse model and administered as an admixture in food [91]. It increased lipid oxidation without affecting body temperature, prevented diet-induced obesity, and reversed established obesity. In addition, it improved glucose tolerance and fasting glucose levels. Importantly, the drug was not found to affect food intake or lean body mass.

Growth differentiation factor 15 (GDF15) is a stress-regulated hormone that is normally found at low levels but is increased in inflammation and chronic diseases such as cardiovascular disease and cancer [92]. GDF15 acts on the GFRAL receptor in the hindbrain and leads to a dose-dependent decrease of food intake in rodents [93][94][95]. One of the effects of GDF-15 includes triggering visceral malaise, a phenomenon like food aversion seen in sickness. Both acute and chronic GDF15 exposure are able to trigger visceral malaise, demonstrable by increased ingestion of non-nutritive food [96] (p. 15). This response may be used to decrease caloric intake in obesity and drive weight loss. Another interesting finding is related to exercise as intense physical activity can increase GDF-15 levels in both mice and humans [97][98].

Peptide Tyrosine Tyrosine (PYY) is a peptide hormone co-secreted by intestinal L cells as PYY1-36 along GLP-1 in response to nutrient intake and cleaved into its active form PYY3-36 by DPP-IV [99]. PYY3-36 acts on NPY receptor type 2, expressed centrally including limbic and cortical areas and peripherally [100]. PYY3-26 plays an important role in energy homeostasis as its administration has been shown to lead to decreased food intake in both humans and rodents and to reduce body weight in rodents [101][102]. It does so through silencing Npy neurons and, hence, indirectly activating Pomc neurons [102], but also through activation of the mesolimbic dopaminergic system as well as of GABAergic and glutamatergic neurons in cortical and subcortical regions and the brainstem [100].

5. Conclusions

Hypertension is closely linked to the prevalence, pathophysiology, and morbidity of obesity. The pathogenesis of hypertension related to obesity is multifactorial and complex. Weight loss stabilizes neurohormonal activity and causes clinically significant reductions in blood pressure. Bariatric surgery remains so far, the most reliable method

to achieve sustained weight reduction. However, new drugs such as Semaglutide and Tirzepatide are also emerging as potent, safe, and effective alternatives for weight reduction. In addition, many new investigational drugs that could potentially also alleviate the morbidity and mortality associated with obesity-induced hypertension are being developed and their role should be further defined in the future.

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