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The “Weight” of Obesity on Arterial Hypertension

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Abstract

The prevalence of obesity and its related diseases are increasing worldwide. This phenomenon has been observed not only in adults but also in adolescents and children. Numerous scientific studies have revealed a direct correlation between the increase in blood pressure and weight gain. In fact, visceral fat can contribute to the rise in blood pressure because it is associated with an increased production of inflammatory cytokines (such as interleukin-1- β , tumor necrosis factor- α and interleukin-6) and inflammatory factors (such as C-reactive protein), inducing endothelial dysfunction and consequently arterial hypertension (AH). Insulin resistance, which develops in obese individuals, may represent an additional risk factor in the onset of AH. Postprandial hyperglycemia is not able to inhibit lipolysis, inducing a greater release of free fatty acids causing metabolic abnormalities, oxidative stress and vascular dysfunction. In this chapter, we will examine the mechanisms that correlate obesity to hypertension, such as the involvement of the sympathetic nervous system, metabolic and renal alterations. Finally, the pharmacological and nutritional treatment of obesity-related hypertension will be described.

Keywords: obesity, metabolic syndrome, renin-angiotensin system, obesity-hypertension link, anti-obesity drugs

1. Introduction

The World Health Organization (WHO) defines obesity as the clinical condition in which a subject presents a body mass index (BMI) ≥ 30 kg/m². This condition can be further classified in three stages: stage 1 BMI 30-34.99 kg/m², stage 2 BMI 35-39.99 kg/m² and stage 3 BMI ≥ 40 kg/m² [1].

Obesity and being overweight (BMI ≥ 25 kg/m²) [2] have become in recent years a substantial health burden due to their growing prevalence.

In the USA, the prevalence of obesity in adults has increased by 39.6% from 2015 to 2016, and it is forecasted to reach the astounding number of 2.1 billion people by 2030 [3]. In China, the percentage of obese men and women in 2013 was, respectively, of 3.8 and 5.8%, while in Japan it was of 4.5 and 3.3%. In Eastern Europe during 2013, the percentage of obese adult subjects did not differ much from that in the USA: 21% of the adult population resulted obese, with equal gender distribution [2]. In Germany, a recent study has highlighted that 35.4% of the adult population was overweight and the 21.3% was obese, in Italy 34.9% was overweight and 12.3% obese [4].

All epidemiologic studies conducted till date have confirmed that the global prevalence of obesity is constantly rising [5]. Therefore, it is becoming a sanitary emergency, both in terms of human resources and economically. In fact, it is worthy to consider

that excess of adipose tissue is associated with an increase in cardiovascular (CV) risk and with the precocious insurgence of CV diseases [6]. It has been underlined that obesity is characterized by an augmented activation both the sympathetic nervous system (SNS) [7], and of renin-angiotensin-aldosterone system (RAAS), which play a fundamental role in the physiopathology of AH [8]. It is estimated that about 75% of hypertension incidence is directly correlated to the contextual presence of obesity, characterizing the form of obesity-related hypertension [9, 10].

2. Physiopathological mechanisms of obesity-related hypertension

The association between body weight and arterial pressure was made for the first time during the 1960s, in the Framingham Heart Study [11]. However, the nature of such correlation remained unknown until the latter half of the 1980s, when a series of studies highlighted the possible mechanisms, which correlated these two clinical entities [12–14]. Such studies took inspiration from the clinical observation made by Vague [15], who observed that metabolic and CV complications linked to obesity were more frequent in subjects with a phenotype of “android” obesity (most fat localized in the upper part of the body) that with those with a “gynoid” phenotype (most fat localized in the inferior part of the body). Successively, during the 1980s, other population studies have been conducted which utilized the waist/hip ratio as a quantitative index of the visceral fat, demonstrating that a higher ratio was correlated with a significant increase of CV risk [12–14]. Further studies shed light on the presence of insulin resistance in the android phenotype [16, 17]. Furthermore, the possible association between insulin resistance and the presence of AH was evaluated in both obese and non-obese subjects, constructing the basis for the comprehension of the physiopathological mechanisms of obesity-related hypertension [18, 19].

The accumulation of excess adipose tissue triggers a cascade of events, which induce a rise in blood pressure values in both children and adults [20, 21]. The physiopathological mechanism at the basis of the insurgence of hypertension is complex, and encompasses the following: activation of the SNS through the action of hyperleptinemia and hyperinsulinemia, vascular damage caused by a chronic low-grade inflammatory state, endothelial dysfunction, oxidative stress and finally vasoconstriction coupled with fluid retention modulated by the RAAS activation [22–24].

2.1 Increased SNS activity

In the condition of obesity-related hypertension, hyperactivation of the SNS can be observed [25]. In such mechanism, total body fat distribution plays a pivotal role, as microneurography studies have demonstrated that the grade of SNS activity is greater in subjects who present visceral fat distribution [26, 27]. Moreover, it has been shown that there is a direct correlation between SNS activation and the waist/hip ratio [28].

Numerous studies have demonstrated that obesity induces the alteration of the arterial baroreceptor control of sympathetic activity, which involves inhibitory and excitatory components [25].

Commonly, with obesity, a reduction of the parasympathetic tone can be observed with an increase of sympathetic activity with a reduction of heart rate variability [29, 30]. On the contrary, with weight loss, the parasympathetic tone and the heart rate variability increase.

Obesity is also associated to tissue SNS activation, at the levels of the heart, kidney and musculoskeletal tissue [31, 32]. Specifically, obese subjects present an

increase of sympathetic renal nervous tissue activity, diagnosed by an increased concentration of renal norepinephrine [33]. Moreover, obese subjects with normal blood pressure have a suppressed cardiac SNS activity, while obese subjects with AH have an increase in cardiac SNS activity [33]. Consequently, it is hypothesized that the development of obesity-related hypertension plays a fundamental role in augmenting renal and cardiac sympathetic activity. In order to confirm such hypothesis, it is worth noting that renal denervation induces a reduction of blood pressure values and an increased sodium excretion in a canine model fed with a high fat diet [34].

Other mechanisms that would seem to be involved in the regulation of the activation of the SNS, determining other direct effects on CV homeostasis are hormonal, metabolic, inflammatory and endothelial factors. The possible relation between insulin and arterial blood pressure was initially quite controversial, however, recent studies have highlighted a possible role for such hormone in the physiopathological mechanism of obesity-related hypertension [35]. Since insulin stimulates the SNS, and obese subjects have an increase in SNS activity, it is hypothesized that the stimulation of the SNS is also mediated by insulin [36]. Such hypothesis would also explain the physiopathological mechanism at the basis of the elevated blood pressure values that are recorded in central obesity. This would also seem to be supported by some studies that have shown a concomitant reduction of arterial blood pressure and SNS activity in obese subjects who underwent insulin level reduction thanks to a low calorie diet [37]. Moreover, chronic hyperinsulinemia needs to be also correlated to an arterial dysfunction, which favors a mechanism of vasoconstriction. Insulin can exert a direct action on the kidney, by stimulating sodium reabsorption and consequently inducing sodium retention via direct interaction with renal tubules [38]. Therefore, obesity-induced hyperinsulinemia seems to contribute to the increase in arterial blood pressure values by acting on sodium retention, and the expansion of extracellular volume.

Another factor involved in SNS stimulation is leptin. This adipokine is produced by adipocytes, and its plasmatic concentration is directly correlated to the amount of fat mass of the subject [39]. Leptin induces appetite suppression and stimulates the SNS [40]. With regards to leptin concentration, gender variation has been observed: female individuals present higher hormonal levels and a greater receptor expression (ObR) compared to male subjects [41]. A possible explanation for such phenomenon has highlighted that subcutaneous adipose tissue, predominating in the female gender, produces a greater quantity of leptin compared to visceral adipose tissue [42].

Studies conducted on animal models have demonstrated that leptin infusion induces an increase in blood pressure values and SNS hyperactivation [43, 44].

From recent studies, it has emerged that leptin-mediated SNS stimulation could be seen as a mechanism to stabilize bodily weight and restore energetic equilibrium in obese patients, increasing energetic expenditure by stimulating brown fat thermogenesis [45].

2.2 Increased RAAS activity

Numerous studies have highlighted that urinary and plasmatic concentration of aldosterone is increased in obese subjects compared to normal weight subjects [46]. In particular, its plasmatic concentration results directly correlated with the quantity of visceral adipose tissue [47]. Various authors have shown how adipose tissue releases adipokines, which stimulate the adrenal glands to produce aldosterone, independently from the plasmatic activity of renin [48–50]. Therefore, RAAS activation is directly involved in the development of obesity-related hypertension. Obese subjects, especially if they present a substantial visceral fat quota, often have

increased plasmatic renin activity, together with an enhancement in angiotensin converting enzyme (ACE), a greater concentration of aldosterone, angiotensinogen and angiotensin II [51]. In obese patients, RAAS activation is determined by a number of factors, some of which are constituted by physical renal compression induced by an increment in visceral fat, SNS hyperactivation and local activation of RAAS in the adipose tissue [52]. Adipose tissue, other than containing all RAAS components, is able to produce angiotensin II [53]. Even if in obese subjects the principal bulk of angiotensinogen continues to be produced by the liver (as in healthy subjects), it has been demonstrated that in obese patients, there is an increase of angiotensinogen produced by the adipose tissue [54]. To support this finding, an interesting study conducted on adipocyte-angiotensinogen deficient mice (Agt^{ap2}) has demonstrated that a fat-rich diet induces blood pressure increase in wild type rats, but causes no pressure increase in Agt^{ap2} rats, even if both groups present an equal increase in weight and fat mass [55]. Moreover, it is worth to point out that RAAS of adipose tissue not only produces angiotensin II, through ACE enzymatic activity, but also uses a less common mechanism that relies on the enzymatic activity of cathepsins and chymases [56].

To prove the hypothesis that RAAS activity has a significant role in the pathogenesis of obesity-related hypertension; a study has been conducted on obese subjects who have undergone bariatric surgery, which demonstrated a significant reduction in RAAS activity due to considerable weight loss [57].

A fundamental role in obesity-related hypertension is also carried out by aldosterone, as obese subjects present elevated levels of this hormone [58, 59], and since weight loss is not only associated with reduced plasmatic renin activity but also with aldosterone, independently from sodium intake. As a final analysis, weight loss also induces a beneficial effect on blood pressure values [58].

Aldosterone increase has also been observed in obese adolescents [59] and obese menopausal women [60]. Moreover, one should consider that the highest levels of plasmatic renin activity, aldosterone and ACE have been highlighted in subjects with visceral obesity but not in subjects with peripheral obesity [61]. Goodfriend et al. have confirmed that in subject affected by visceral obesity, adipose tissue is involved in the excess production of aldosterone, through the action of aldosterone releasing factors [62].

2.3 Changes in kidney function and hemodynamic in obesity-related hypertension

Obese subjects present an elevated risk to develop chronic kidney disease [63]. During obesity, an expansion of extracellular volume and an increase in blood flow in many tissues that leads to increased cardiac output, can be observed [64]. The latter, increases in a consistent manner with weight gain, and part of such increase is closely correlated to the blood flow needed to supply the excess of adipose tissue. Such blood flow increase is appreciable not only at the adipose tissue level, but also in other organs and tissues such as the heart, the kidney, the gastro-intestinal apparatus and the muscle [21, 65]. Excess blood flow, which can be observed at the level of other organs, is caused by the hypertrophy that such organs undergo because of obesity; it is secondary to increased metabolic demand and to the greater work load present in this pathological condition [66]. Renally, this translates into glomerular hyperfiltration that can be encountered in the initial phases of the pathology, which will successively progress in chronic kidney disease with reduced glomerular filtration [67]. During the initial stages of obesity, there is an augmented sodium tubular reabsorption with a consequent increase in sodium retention. In order to compensate such mechanism, the kidney undergoes vasodilation with subsequent

hyperfiltration and increased filtration of water and electrolytes. However, this compensatory mechanism is incomplete and induces an extracellular volume expansion with an increase in blood pressure values. Therefore, obesity induces an increase sodium tubular reabsorption in the kidney via different mechanisms such as neural, hormonal and reno-vascular. The first involving the SNS, the second insulin and aldosterone, and the third angiotensin II [68]. During obesity, even with the expansion of extracellular volume, renin secretion by the kidneys still occurs. This is due to the action exerted by fat accumulated in the renal medulla and in the peri-renal adipose tissue [10, 69].

2.4 Inflammation and obesity-related hypertension

In obese subjects, adipose tissue dysfunction can be observed. It is characterized by a reduction in protective factor concentration such as adiponectin, nitric oxide and prostaglandins, and an increased release of pro-inflammatory adipokines such as resistin, leptin and visfatin, with subsequent development of low-grade inflammation. Cumulatively, this induces a metabolic and vascular dysfunction in the obese subjects [70, 71].

In pathologic conditions, adipocytes produce both inflammatory cytokines and extracellular matrix proteins, favoring the infiltration of immune cells in the adipose tissue and consequent inflammation [72]. In turn, the same infiltrative immune cells activate and release cytokines that can directly influence the adipocyte function or induce the secretion of pro-inflammatory adipokines. These effects are also evident at the level of the perivascular adipose tissue, particularly when adjacent to atherosclerotic or dysfunctional vessels in hypertensive subjects. In fact, in AH, perivascular adipose tissue inflammation can be observed. This kind of inflammation, is in turn involved in the dysfunction of vessels [73], favoring vasoconstriction and inhibiting endothelium-dependent vasodilation [72]. Such functional changes will have correspondent morphological changes: perivascular adipose tissue becomes pro-inflammatory, dedifferentiated and metabolically active. This tissue will produce a greater number of chemokines, such as RANTES, involved in the activation of monocyte/macrophages and CD8⁺ T cells. Moreover, an increase in sympathetic innervation can be observed at the level of the perivascular adipose tissue, which is also involved in the mechanism of obesity-related hypertension [74].

Hypertensive subjects present at the perivascular adipose level an increment in T lymphocytes, antigen-presenting cells and factors involved in endothelial dysfunction. These factors explain the persistent relationship between hypertension and the atherosclerotic process [75]. During AH, one can observe in the perivascular adipose tissue an increase in both CD4 and CD8 and the expression of pro-inflammatory cytokines (TNF- α and INF- γ) [73, 76]. The pro-inflammatory cytokines modulate smooth muscle cell contraction, their migration and proliferation [77]. However, it is also worth considering that leptin is structurally similar to IL-6, IL-12 and IL-15 and is capable to induce leukocyte activation, chemotaxis, free radical production and the expression of endothelial adhesion molecules at the level of vascular smooth vessel cells. Moreover, pro-inflammatory cytokines (IL-17A and TNF- α) induce in the adipose tissue an increased production of leptin and resistin, which in turn cause an augmented expression of VCAM-1 and ICAM-1, causing vascular dysfunction and oxidative stress [78].

2.5 Obstructive sleep apnea

Obstructive sleep apnea (OSA) represents together with obesity, an independent risk factor for the development of AH.

The first study, which highlighted the presence of fluctuations in arterial blood pressure in course of complete or partial OSA, was conducted in 1972 [79]. OSA is characterized by a series of events that induce the collapse of the superior airways during sleep with consequent intermittent hypoxia, hypercapnia, negative intrathoracic pressure and increased activation of the SNS [80, 81]. Therefore, the intermittent hypoxia observed during OSA (which also activates the SNS) contributes to the development of obesity-related hypertension [82]. OSA-induced SNS activation is caused by a dual mechanism: on one hand from the stimulation of peripheral chemoreceptors, and on the other by the formation of ROS that contribute to systemic inflammation and endothelial dysfunction [83].

During hypoxia, it has been demonstrated that endothelin, which has a vasoconstrictor action is released [84], with the improvement of oxygenation instead, there is a decreased production of endothelin and consequent vasodilation. Phillips et al. have suggested that the cyclical alterations of endothelin production in OSA patients can contribute to the insurgence of AH [85]. Such clinical observations have been confirmed on OSA murine models [86]. Moreover, OSA patients present a higher incidence of non-dipping of nocturnal systolic pressure, indicator of an increased adrenergic tone [87].

3. Therapeutic approaches to the obesity-related hypertension

According to the 8th report of the Joint National Committee (JNC8), normal blood pressure systolic values are inferior to 130 mmHg and normal diastolic values are inferior to 80 mmHg [88].

In order to have reliable measurements, ESC/ESH recommends to perform three of them in an ambulatories setting, with intervals of 1 or 2 min between each reading. Moreover, it is advised to perform additional measurements, if the first one differ more than 10 mmHg between one another. The blood pressure value that will be given by an average of the last two readings [89].

Even if the definition and the categorization of AH have varied over time, there is a consensus that is persistent. The therapeutic target is fixed around values equal or inferior to 130/80 mmHg [89, 90].

The therapeutic approach of obesity-related hypertension is based on a pharmacological therapy (anti-hypertensive and anti-obesity pharmaceuticals) associated to a nutritional/compartamental intervention (**Figure 1**). A healthy lifestyle is a valid support to pharmacological therapy and allows the correction of certain deleterious habits such as physical activity, hypercaloric diet, sodium-rich diet and alcohol abuse.

3.1 Anti-hypertensive drugs

3.1.1 RAAS inhibitors

Numerous studies have suggested diuretics is RAAS antagonists are particularly effective in obese subjects [91, 92]. In fact, as previously described, since angiotensin is overexpressed in obesity and given its role in the development of obesity-related hypertension, ACE-inhibitors and angiotensin II receptor blockers (ARBs) are considered a valid therapeutic approach in such patients.

Moreover, when comparing ACE-inhibitors and ARBs to β -blockers and thiazide diuretics, it is apparent that RAAS antagonists are seldom associated to new cases of diabetes and induce less insulin resistance [93, 94]. Furthermore, ACE-inhibitors and ARBs do not appear correlated with weight gain, and carry out a nephroprotective

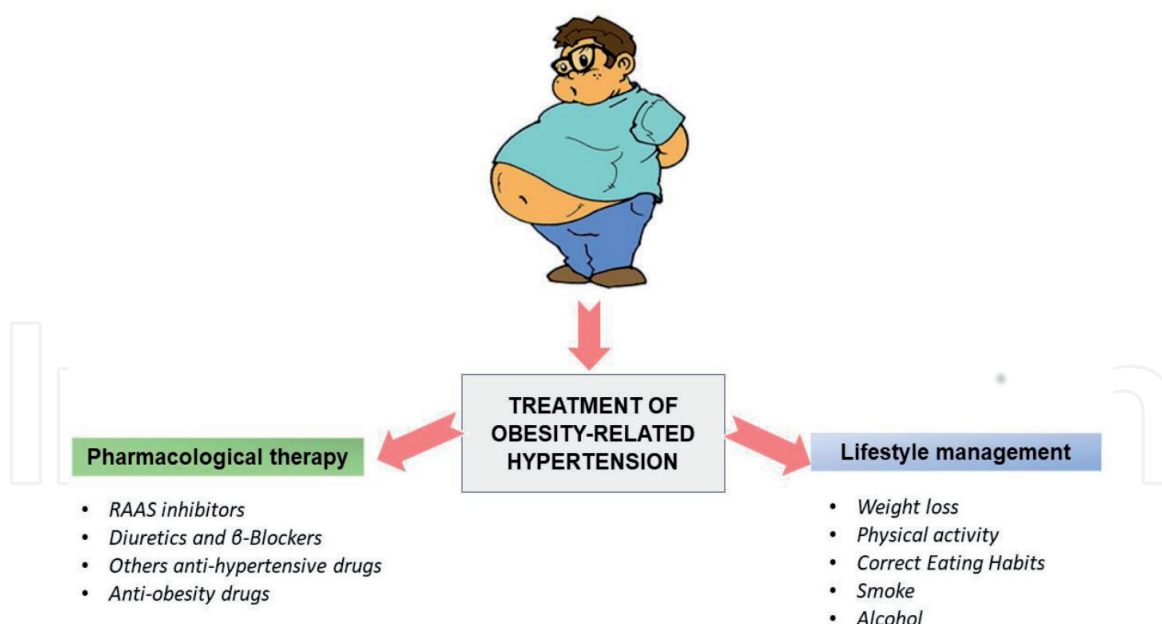


Figure 1.
Therapeutic approach of obesity-related hypertension.

action in diabetic patients, which is a frequent comorbidity in obese subjects. These pharmaceuticals also induce a 30% reduction of left ventricular hypertrophy, which has a high prevalence in subjects affected by obesity-related hypertension [95, 96].

In support of the above statements, a study conducted on 6083 hypertensive subjects (65–84 years of age) with an average BMI of 27.4 kg/m², has highlighted that starting the anti-hypertensive treatment with ACE-inhibitors will lead to a better outcome compared to an intervention with diuretics, independently of the improvement in blood pressure values [97].

3.1.2 Diuretics and β-blockers

Even if treatment with thiazide diuretics is frequently recommended in patients with AH [98], it must be kept in consideration that they present some dose-correlated collateral effects such as insulin resistance, hyperuricemia and dyslipidemia. Moreover, in obese patients who have a predisposition for type 2 diabetes mellitus and metabolic syndrome, this kind of pharmaceutical approach is harmful and should be avoided [8].

To demonstrate this, an interesting open label, randomized study conducted on CV disease free and non-diabetic, hypertensive patients had shown that the adverse metabolic effects related to the treatment with thiazide diuretics and β-blockers were more frequent in subjects with abdominal obesity. Such adverse metabolic effects manifested after only 9 weeks from the start of the treatment [99].

Therefore, according to guidelines such pharmaceuticals, should be used with caution in patients who are at risk of developing metabolic syndrome or altered fasting glucose, in order to avoid the insurgence of diabetes and other long-term complications [100, 101].

It is recommended to use a low dose of thiazides in case of need, in association with a careful monitoring of the lipid and glycemic profile. β-Blockers, in addition to inducing insulin resistance, are associated to body weight gain, because they are thought to reduce thermogenesis induced by diet and velocity of fat oxidation [102, 103]. In obese patients, the use of β-blockers should be limited to subjects with a precise CV indication (namely, cardiac insufficiency and previous myocardial infarction).

3.1.3 Other antihypertensive drugs

Calcium antagonists are antihypertensive drugs that induce diuresis and natriuresis, without exerting any effect on glucose and lipid metabolism.

They are constituted by two subclasses, such as non-dihydropyridines and dihydropyridines, with notably different pharmacological effects. The first are normally used for the treatment of cardiac arrhythmia and seem to have an anti-proteinuric effect, similar to that induced by ACE inhibitors [104–107], and seem to slow down the progression of diabetic nephropathy [108].

On the other hand, dihydropyridines seem to heighten albuminuria, a factor correlated to an increased CV risk [109]. Such increase seems to be caused by a dilation of the preglomerular afferent arteriole with a consequent increase of intraglomerular pressure [110].

An analysis by Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) has evaluated which type of anti-hypertensive treatment could have an impact on the CV outcome of patient based on their body surface area (evaluated thanks to their BMI). It has been highlighted that, while thiazide treatment induces minor CV protection in normal subjects compared to obese ones, patients treated with calcium antagonist (amlodipine) did not present differences in CV protection according to their BMI. Therefore, calcium antagonists appear better at exerting CV protecting action on hypertensive non-obese subjects [111].

Another clinical study has showed important differences on the CV mortality of patients treated with calcium antagonists, β -blockers or sartans, highlighting that patients treated with amlodipine were majorly protected from CV events and had a reduced risk of developing diabetes compared to those treated with β -blockers (atenolol) [112]. This study did not examine the impact induced by the body surface area on CV protection. Therefore, calcium antagonists emerge as a pharmaceutical alternative in the treatment of obesity-related hypertension with potential benefits [113], even if more clinical randomized trials are required to fully understand their beneficial effects [114, 115].

A retrospective observational study conducted in southern Italy, has examined what type of pharmaceuticals are used for the treatment of obesity-related hypertension in a clinical practice. It has highlighted that the clinicians do not differentiate between pharmaceuticals to use in relationship to the grade of obesity or the presence of metabolic syndrome. Moreover, it has been observed that antihypertensive pharmaceuticals, which cause negative effects on weight and metabolic profile, are still largely used in subjects at risk [116]. Such study underlines the necessity to conduct clinical randomized trials on a large population of patients affected by obesity-related hypertension, in order to standardize pharmacological antihypertensive therapy based on obesity severity, CV protection and limitation of metabolic complications.

3.2 Anti-obesity drugs

Lifestyle changes perform a key role in the treatment of obesity-related hypertension. According to the Obesity Education Initiative Working Group guidelines, anti-obesity drugs should represent a support strategy in the treatment of subjects with BMI ≥ 30 kg/m² without associated comorbidities, and in subjects with BMI ≥ 27 kg/m² with comorbidities [117]. Drugs used in the treatment for obesity can be divided into the following categories: (1) inhibitors of nutrient absorption (orlistat and acarbose); (2) appetite suppressors (phentermine and lorcaserin); (3) drugs used in the treatment for diabetes that determine weight loss (metformin and incretin therapy: GLP1 agonists and DPP-4 inhibitors) [8, 113].

3.2.1 Inhibitors of nutrient absorption

Orlistat is a gastrointestinal lipase inhibitor that causes a consequent reduction in absorption of dietary fat. Its use in clinical practice is limited by gastrointestinal adverse effects, which occur especially if patients have a high fat diet [118]. A study aimed at evaluating orlistat and sibutramine (serotonin and norepinephrine re-uptake inhibitor acting as an appetite suppressor, removed from the market in 2010 because of associated increased CV risk) [119] has highlighted the same level of efficacy in reducing BMI, body weight and waist circumference. Moreover, orlistat-treated subjects presented a significant reduction in blood pressure values, while they remained stable in sibutramine-treated subjects [120].

In order to reduce gastrointestinal adverse effects related to orlistat ingestion, a half dose pill (60 mg) has been produced that is still able to reduce fat absorption of 25% [121, 122].

A study has evaluated as secondary outcome, long-term effects related to orlistat treatment, demonstrating that about two-third of the weight loss was maintained over a 2 years compared to the placebo-treated group. The pharmaceutical intervention was combined during the first year with a hypocaloric diet, and during the second year with a weight maintaining diet. Moreover, patients treated with orlistat full dose (120 mg), presented after 2 years an improvement in systolic pressure values [123].

Acarbose is an oral antidiabetic. It inhibits intestinal alpha-glucosidase and pancreatic alpha-amylase. By inhibiting these enzymes, such drug impedes the digestion and absorption of complex sugars. It has been highlighted that acarbose induces a modest reduction in body weight [124]. A study performed on 110 obese subjects with BMI between 32 and 38 kg/m², who underwent a hypocaloric diet for 10–16 weeks and substantial weight loss, has highlighted that acarbose treatment does not induce significant effects on the stabilization of weight loss [125], confirming the modest effect of the drugs in body weight reduction.

3.2.2 Appetite suppressors

Appetite control represents a cardinal step in the treatment of obesity. Studies finalized to evaluate appetite control have demonstrated the existence of an endogenous system, which is able to stimulate, through orexigenic substances, and inhibit, through anorexigenic substances, food intake [126, 127]. Leptin and serotonin are two endogenous ligands which act contemporaneously inhibiting the hypothalamic feeding center, and stimulating the satiety center [128]. An important appetite suppressor to cite is fenfluramine, which was successively removed from the market because of its severe collateral effects. It acted on serotonin release at the level of the hypothalamus and induced significant weight loss [129].

In 2012, the Food Drug Administration (FDA) has approved the use of lorcaserin for the treatment of obesity [130]. This drug is a serotonin 2C receptor agonist (5-HT_{2c}), and appears to be efficacious in co-adjuvating weight loss in obese and overweight subjects in association with a hypocaloric diet and increased physical activity [131].

Lorcaserin, being selective for 5-HT_{2c} receptors, represents a more efficacious and safe drug, compared to other non-selective serotoninergic appetite suppressor drugs because it does not induce CV collateral effects [132].

Another drug belonging to the class of the appetite suppressors is phentermine, an adrenergic agonist that, thanks to the central nervous system and SNS activation, is capable to determine reduced food intake and increase basal metabolism [133]. The FDA approves phentermine use to treat obesity for a period no greater

than 3 months. Since it causes an increase in the release of norepinephrine, it could lead to an increase in blood pressure values and cardiac frequency [134].

3.2.3 Drugs used in the treatment for diabetes that determine weight loss

Drugs used for the treatment of diabetes commonly determine weight loss and reduced fat accumulation. For overweight and obese subjects suffering of diabetes, the FDA has approved the use of hypoglycemic drugs, which are associated to weight loss and blood pressure reduction. Even if the effect is modest, it is however to be considered beneficial given the weight gain that is frequently associated with insulin and insulin secretagogue analogs.

Metformin is an oral hypoglycemic drug, used in type II diabetes treatment, that is capable of inducing modest weight loss as a consequence of a reduced hepatic production and intestinal absorption of glucose, and through the improvement of insulin sensitivity [135]. Such drug, as demonstrated by the Diabetes Prevention Program trial [136], is efficacious in reducing body weight in a follow-up period of 2.8 years in overweight diabetic subjects. However, metformin does not appear useful in reducing blood pressure, as was demonstrated in a series of clinical trials in which lifestyle modification resulted notably more efficacious in the control of blood pressure compared to this type drug [137].

Incretins are intestinal hormones secreted by enteroendocrine cells in the circulatory stream, few minutes after feeding. They regulate the quantity of post-feeding insulin secretion. There are two endogenous incretins such as glucose-dependent insulintropic peptide (GIP) and glucagon-like peptide 1 (GLP-1); both are rapidly metabolized an enzyme called dipeptidyl peptidase-4 (DPP-4). These hormones, increasing insulin release by β pancreatic cells and inhibiting glucagon release, play an important role in glucose homeostasis. GLP-1 is the most abundant, but cannot be used for therapeutic scopes given its rapid degradation by DPP-4.

In 2005, exenatide was released, an injectable GLP-1 agonist, which mimics endogenous GLP-1 but has a prolonged action. Exenatide increases glucose-dependent insulin secretion, suppresses glucagon secretion and slows down gastric filling. Therefore, it is hypothesized that exenatide could have a role in the treatment for obesity, since it induced a sense of satiety and reduced food intake.

DPP-4 inhibitors (sitagliptin, saxagliptin and linagliptin) are pharmaceuticals which increase endogenous plasmatic levels of active incretins, prolonging their action [138]. Moreover, they also reduce the degradation of many vasoactive peptides. Studies on animal models of ischemia/reperfusion have demonstrated a positive effect of DPP-4 inhibitors. Endogenous GLP-1 exerts protective effects on the myocardium and has a vasodilatory action [139]. A study that compared different pharmaceutical therapies to tackle type II diabetes mellitus, such as exenatide and sitagliptin, has demonstrated that incretin treatment was associated with superior weight loss compared to the insulin-treated group. Weight loss was associated to a statistically significant systolic and diastolic blood pressure reduction in all the treated groups [140].

4. Life style management

The most common consequences related to obesity are the insurgence of essential AH, diabetes mellitus, chronic kidney disease, metabolic diseases, etc. [5, 141, 142]. Even if antihypertensive drugs are of primary importance in the treatment of AH, they should always be associated with healthy eating habits, adequate levels of physical activity and a correct lifestyle [143].

For this reason, it would be advised that hypertensive-obese patients follow nutritional counseling in order to evaluate their food habits and levels of physical activity [144]. In fact, incorrect food habits, scarce levels of physical activity and psychological factors such as depression can contribute to weight gain [145].

Nutritional intervention finalized to achieving weight loss in hypertensive-obese patients, should be personalized. Different types of diet exist, for example, strongly hypocaloric diet, balanced slightly hypocaloric diet, low-sodium diet, hypolipidic diet, hypoglucidic diet and hyperproteic diet. In whichever case, the common result should be weight loss and reduction of abdominal fat [146].

In recent years, a type of nutritional intervention that has had notable success (thanks to numerous clinical trials) is the “dietary approaches to stop hypertension” (DASH) diet. The DASH diet was formulated for the first time by the National Institute of Health (NIH) in the 1990s, and was object of many research studies [147]. It promoted the ingestion of vegetable proteins, fibers, fresh vegetables, fruits, extra-virgin olive oil and dried fruits, while suggesting a reduction in animal fats, simple sugars and processed meat. Trials have demonstrated how reduced salt consumption potentiated beneficial effects linked to DASH diet, inducing a reduction in systemic arterial pressure in all patients.

Progressive reduction in energy expenditure associated to increased caloric intake translates into weight gain, which finally amounts to obesity [120].

For this reason lifestyle, and specifically physical activity, has a role of primary importance in the maintenance of a healthy status both in primary and secondary prevention [148]. Numerous studies suggest that physical activity has a beneficial effect in subjects affected by AH, to the point of being compared to pharmaceutical intervention [149, 150]. Thanks to recent technologies, it has been possible to develop network meta-analysis (NMA) models able to compare the efficacy of physical activity and pharmacotherapy alone.

A meta-analysis by Naci and Ioannidis [150] has highlighted how physical activity alone elicits similar results to pharmacological therapy in terms of reduction of mortality in hypertensive patients. Such reduction has been studied in patients with coronary heart disease, post-infarct rehabilitation, cardiac insufficiency and in the prevention of diabetes. A recent study by Dempsey et al. [151] has compared seven continuative hours of inactivity to 3 min of light physical activity every 30 min (6 min of physical activity per hour). Such light physical activity, significantly reduced systolic and diastolic arterial blood pressure values, and reduced hematic norepinephrine values.

Thus, it is evident that physical activity plays a pivotal role in the insurgence and management of AH. The challenge for the future will be to identify, using NMAs, different types of physical activity and pharmaceuticals that can be administered in a personalized manner based on the subject’s unique characteristics.

Substantial medical literature has tried to identify the mechanisms relating body weight control and cigarette smoke [152].

Even if, an increase in body weight was highlighted following smoking cessation (due to an increase in caloric intake because of the lack of smoking), many studies have also stated that this is a transitory condition [153]. In fact, it has been demonstrated that the weight gain straight after smoking cessation, normalizes in about 6 months with the re-establishment of the normal energetic intake [154].

Alcohol consumption has been a part of food culture since antiquity. Even if there are potential beneficial effects that reside in compounds present in alcoholic beverages, like in red wine, they have a caloric intake of 7.1 kcal/g of alcohol, therefore not recommended in obese subjects [155]. For this reason, alcohol intake should be controlled and modest, and in order to attain its beneficial potential the quality should also be considered [156].

5. Conclusions

Obesity-related hypertension represents a public health problem, especially as hypertensive-obese subjects has notably enhanced and precocious CV-related morbidity and mortality compared to the general population. It is therefore useful to act as promptly as possible, by intervening with strategies to contrast the insurgence excessive weight gain, obesity and their relative comorbidities such as obesity-related hypertension. It would be optimal to carry out an educational scheme aim at adolescents, in order to educate the population to undertake a correct lifestyle, which will contrast the insurgence of problems cited above later in life. A correct lifestyle is characterized by the combination of constant levels of physical activity and a balanced diet, taking as models the DASH Diet and/or the Mediterranean one. Once a subject develops obesity and hypertension, a pharmaceutical approach (to control systemic arterial blood pressure and obesity) should be flanked to the dietary intervention.

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Conflict of interest

The authors declare no conflict of interest.

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