Chapter

Metabolic Syndrome

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Abstract

Metabolic syndrome (MS) is recognized by a set of cardiovascular risk factors (CVRF) that usually coincide with insulin resistance and hyperglycemia. These risk factors include hyperglycemia (fasting glucose > 100 mg/dl), high blood pressure (SAD ≥ 130 mmHg and TAD ≥ 85 mmHg), triglyceride increase (≥150 mg/dl), decreased HDL levels <40 mg/dl, and central obesity (waist circumference ≥102 cm in men and ≥88 cm in women). The purpose of this chapter is to review the natural history of metabolic syndrome and epidemiology and to review risk factors for the appearance of metabolic syndrome, pathophysiology, and biochemistry among the various cardiovascular risk factors and their importance within the metabolic syndrome.

Keywords: diabetes, hypertension, dyslipidemia

1. Introduction

The purpose of this chapter is to provide a review of the pathophysiology of metabolic syndrome (MS) and the relationship between its different components. Because this is a very broad subject, not all aspects will be discussed. Throughout the chapter, a bibliographic reference is left for each topic so that this can be looked into more deeply. This is a non-systematic review of the literature through research on PubMed and Google.

At an epidemiologic study conducted by Armindo Sousa Ribeiro et al, in a Portuguese population, was found that 23.8% of the population has MS more prevalent in 24 males, no smoking, no significant alcohol consumption, sedentary life style, with a high body mass index (BMI) and its prevalence increases with age [1]. Each CVRF has different importance in the metabolic syndrome [2].

In Western societies, cardiovascular diseases (CVD) are the main cause of mortality and morbidity for both sexes. This fact entails very high social and economic costs [3].

CVDs are the biggest cause of mortality worldwide. In the 2010 Global Burden of Disease Study, CVD is estimated to cause 15.6 million deaths per year worldwide, corresponding to 29.6% of all deaths [4]. Although the tendency is to reduce the number of deaths in Europe due to CVD, this remains the main cause of death, corresponding to more than 4 million deaths per year, that is to say 45% of all deaths recorded in Europe [4]. Of the CVD, coronary heart disease remains the most important cause of death in both genders, which corresponds to 19% in the male sex and 20% in the female sex.

2. Metabolic syndrome and cardiovascular risk factors (CVRF)

2.1 Definition

There are several definitions of MS. MS groups a constellation of pathophysiological factors that increase the risk of developing diabetes mellitus (DM) type 2 and CVD [5–10]. At present, attempts have been made to unify criteria to have a consensus on its diagnosis [11].

The World Health Organization (WHO), International Diabetes Federation (IDF), National Cholesterol Education Program Adult Treatment Panel III

	ATP III	WHO	AACE	IDF
Triglycerides ≥ 150 mg / dl	X	X	X	X
HDL <40 mg / dl in men and <50 mg / dl in women	X	X	X	X
Blood pressure ≥ 130/85 mmHg	X	X	X	X
Insulin Resistance (IR)		X		
Fasting glucose ›100 mg / dl	X		X	X
Glucose 2h: 140 mg / dl			X	
Abdominal Obesity	X			X
High body mass index		X	X	
Microalbuminuria		X		
Risk factors and or diagnosis	3 plus IR	More than 2	Clinical Criteria	Abdominal Obesity

Figure 1.
Components of the metabolic syndrome considering its definition: according to the National Cholesterol Education Program Adult Treatment Panel III (ATP III), World Health Organization (WHO), American Association of Clinical Endocrinologists (AACE), and International Diabetes Federation (IDF).

(NCEP-ATP III), and the American Association of Clinical Endocrinologists (AACE) have proposed their diagnostic criteria or components of MS (**Figure 1**) [11].

In 2009, representatives of the IDF and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)-ATP III Guidelines discussed resolving differences between definitions of MS, unifying criteria [6, 11]. The definition of MS according to the unification of criteria (harmonizing the metabolic syndrome) is used for many international works and publications and requires the presence of three of the following five criteria:

1. Elevation of fasting blood glucose (≥100 mg/dl) or receiving antidiabetic treatment with insulin or oral antidiabetics

2. Elevation of systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (PAD) ≥ 85 mmHg or receiving antihypertensive drug treatment

3. High-density lipoprotein (HDL) cholesterol values <40 mg/dl (men) or <50 mg/dl (women)

4. Triglycerides ≥150 mg/dl or under treatment with specific lipid lowering agents

5. Abdominal perimeter ≥102 cm (men) or ≥88 cm (women) [6, 12]

The concept of MS was carried out in a progressive manner. Its clinical importance is enormous due to the fact that it can identify patients with high risk of suffering some CVD and/or DM, allowing a preventive intervention [6, 13, 14].

The notion that CVRF has a tendency to aggregation allows an earlier diagnosis of MS, thus also leading to the early introduction of therapeutic, pharmacological, or non-pharmacological measures.

2.2 Historical evolution

The interest in the MS is not something recent. Its nomenclature has evolved over the years.

About 260 years ago, before the description of MS, the Italian anatomist and doctor, Morgagni, identified the association between visceral obesity, arterial hypertension (AHT), atherosclerosis, hyperuricemia, and frequent episodes of sleep apnea. In the mid-twentieth century, French physicist Vague first identified the relationship between android obesity and the increased prevalence of DM and CVD. In the 1960s Avogaro and Crepaldi attributed the name "plurimetabolic syndrome" to the simultaneous presence of obesity, AHT, and DM. They verified that all these abnormalities were frequent among the population and contributed to an increase in cardiovascular risk [15]. A decade later, Haller related this set of risk factors with atherosclerosis [15].

In 1980, Vague suggested that adipose tissue alone had little effect on the onset of DM in obese individuals. It is currently known that central or android obesity is a predisposing factor for DM and atherosclerosis and affects insulin secretion unlike gynoid obesity [15].

In 1988, Reaven described this phenomenon as syndrome X, the set of hyperglycemia and insulin resistance, obesity, dyslipidemia, and hypertension. Reaven also suggested that insulin resistance and the consequent increase in blood insulin levels were the central pathophysiological features in syndrome X which in itself was a risk factor for CVD [15, 16].

In 1991, Ferrannini and his colleagues referred to this as insulin resistance syndrome [15, 17].

In 1993, Van Gaal attributed for the first time the name MS to all comorbidities associated with visceral obesity and currently this nomenclature is being used [15].

The concept of MS has evolved significantly in the last decade, which resulted in the presentation of multiple clinical definitions by different scientific societies. In general terms as it was widely treated, MS is defined as an aggregation of several CVRF in the same individual. The nuclear elements for the classification and diagnosis of MS are basically obesity, abnormal glycemic metabolism, iatrogenic dyslipidemia, and hypertension.

The metabolic syndrome was defined by the World Health Organization (WHO) in 1998 [13, 15]. In 2001, there was a new revision of the definition through the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III), where glycemia is not considered an essential factor; in this way it only becomes one of the diagnostic components of MS [18].

With the verification of evidence of the relationship between central obesity and cardiovascular risk, there was a tendency to value this diagnostic component for MS more. Thus, in 2004, the International Diabetes Federation (IDF) created a new definition of MS, where central obesity, defined by the value of the abdominal circumference, would be essential for diagnosis [7, 19]. With the adoption of this definition, an increase in the prevalence of MS was observed in a large part of the populations studied, particularly in the elderly [20].

In 2005, a new review of the criteria by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) maintained the criteria of the NCEP-ATP III [21]. The justification was the fact that in that criterion a single etiology for MS does not stand out and is of simpler application. They modified only the cutoff point of fasting blood glucose from 110 to 100 mg/dl, an adjustment promoted by the American Diabetes Association (ADA) in the diagnosis of DM. However, the first Brazilian Guideline for the Diagnosis of Treatment of MS, of 2005, uses the criteria of the NCEP-ATP III, of 2001, for diagnosis [22, 23]. In the criteria of the IDF, the component of the abdominal circumference becomes essential, using a smaller waist circumference, and categorized more people as having the MS than the ATP III definition. However, higher values of abdominal circumference in older people have been related to lower values of body mass index (BMI), in relation to younger adults [24–28].

2.3 Prevalence of metabolic syndrome

The prevalence of MS varies according to geographic area, with age, race, sex, and classification used for diagnosis [29].

The DARIOS study performs a pooled analysis of 11 studies in 24,670 Spanish individuals aged 35–74, using the criteria of the IDF/NHLBI/AHA-2009, and shows a prevalence of 32% in men and 29% in women [12, 30].

The West of Scotland Coronary Prevention Study (WOSCOPS), one of the largest in Europe, reports a general prevalence of 26.2% [31].

The Third National Health and Nutrition Examination Survey (NHANES III), in the USA showed that 7% of individuals between the ages of 20 and 29, 42% of individuals with ages between 60 and 69 years, and 44% of individuals with ages over 70 years presented MS. The overall prevalence was 23.7% in the 8814 adults who entered the study. This study showed that the incidence increased with age, mainly after 40 years, with significant variations consistent with ethnicity, being the most frequent MS in Hispanics (31.9%) compared with Caucasians (23.8%) and African-Americans (21.6%). A similar prevalence was recorded in both sexes,

although it was more prevalent in males in Caucasians and in females in African-Americans and Hispanics [32].

Based on the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study of Europe in 2004, the prevalence of MS was 15.7% in male and 14.2% in the female [33]. Epidemiological studies on MS have suggested that the prevalence of MS in Western societies is high and is increasing due to the increase in obesity, especially in younger individuals [34].

In Portugal there are few studies on the prevalence of MS. In 2004, an epidemiological study was carried out in Porto where the prevalence of MS was 23.9%, being more prevalent in females (27%) than in males (19.1%) [35].

In 2008, the first study was conducted on the prevalence of MS and its cardiovascular complications in the Portuguese adult population at the primary care level in continental Portugal, Azores, and Madeira—VALSIM study (epidemiological study of the prevalence of metabolic syndrome in the Portuguese population). In this study, 719 family doctors participated. The study was carried out between April 2006 and November 2007. A total of 16,856 individuals were evaluated between the ages of 18 and 96, with averages of 58.1 ± 15.1 years. This study showed a high prevalence of MS in adults affecting 27.5% of the population analyzed, being more prevalent in females (28.7%) compared with males (26%). This study revealed an increase in the prevalence of MS related to age, body mass index, and abdominal perimeter. This study also demonstrated the association between metabolic risk factors, including MS and the occurrence of cardiac events, stroke, and DM [34]. The prevalence of MS exhibited a regional variation, being more prevalent in Alentejo (30.99%), Madeira (29.38%), Central Region (28.79%), and North Region (28.17%) and less prevalent in Algarve (24.42%), Lisbon and Tagus Valley (25.71%), and Azores (26.05%) [34].

3. Insulin resistance and metabolic syndrome

The pathophysiology of MS is not yet fully understood, but the most accepted hypothesis is insulin resistance, so MS is also known as insulin resistance syndrome. Insulin resistance is defined as a defect in its action at the peripheral level that results in hyperinsulinemia, required to maintain normal blood glucose [36, 37]. Predisposing factors for insulin resistance are central obesity and the release of large concentrations of free fatty acids from adipose tissue. Free fatty acids in the liver will determine the increase in glycogenesis and gluconeogenesis, increased triglyceride production, and the secretion of very low-density lipoproteins (VLDL).

Insulin is a hormone with anti-lipolytic action that is produced in pancreatic beta cells and is released into the bloodstream starting its metabolic effects after binding to its receptor. The insulin receptor is a transmembrane glycoprotein composed of four subunits linked by disulfide bridges, that is, two extracellular alpha subunits that contain the insulin binding domain and two β subunits, which contain an extracellular domain, a transmembrane domain, and a intracellular domain insulin binding to the α subunit and β subunit, and tyrosine kinase activation in the β subunit is the first stage of insulin action on glucose metabolism [38, 39]. The activation of tyrosine kinase, and phosphorylation of the β subunit of the insulin receptor, catalyzes the phosphorylation reaction of several tyrosine residues in a family of proteins called insulin receptor substrate (IRS), which include IRS-1, IRS-2, IRS-3, and IRS-4, which are the most specific in the insulin signaling cascade. Other isoforms are growth factor receptor-bound protein 2 (GRB2)-associated binding protein 1 (Gab-1), Shc, and p62 [40, 41].

Structurally, the four IRS proteins have many similarities, in particular, the phosphotyrosine-binding domain (PTB), whose function is the recognition sequence of asparagine-proline glutamic phosphotyrosine acid (NPEpY) located in the juxta membrane region of the β receptor of insulin. It is involved in the interaction of IRS proteins with the insulin receptor and with the COOH-terminal domain of the proteins, capable of binding to the SH2 domains [39]. In addition to their similarities, the four IRS proteins differ in tissue distribution [39]. The SH2 domain consists of 100 amino acids, and it is the phosphotyrosine binding site [41]. The activation of proteins that contain the SH2 domain is important for the transmission of the insulin signal and thus carry out its functions [39].

The IRS-1 gene located on chromosome 2q36–37 was the first substrate that was identified. IRS-1 is involved in many of the actions of insulin, in the activation of nitric oxide (NO) synthetase, in the activation of the activity of the iN + pump, and in vascular relaxation through activated protein kinases by mitogens (MAP kinase) [39, 42].

The IRS-2 gene is found on chromosome 13q34 [43]. The IRS-2 protein and the IRS-1 are very similar in structure and functions, and the main difference lies in the region between amino acids 591 and 789 of the IRS-2. IRS-2, unlike IRS-1, is more in the cellular cytosol [44].

IRS-3 does not appear to be expressed in human cells [39].

IRS-4 is a protein that consists of 1257 amino acids located in the cell membrane of various organs in which it is expressed. It was discovered initially in embryonic kidney cells. The IRS-4 gene is found on the X chromosome [39].

Insulin causes vascular relaxation through stimulation of NO production in the endothelial cells of blood vessels and by reducing the concentration of intracellular calcium in muscle and smooth muscle cells by decreasing sensitization of the light chains of calcium (Ca^{2+})-myosin. These effects are mediated by the activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway, as well as the stimulation of glucose transport in skeletal muscle and vascular adipose tissue [45]. In the case of insulin resistance, the increase in lipolysis produces greater amounts of fatty acids, promoting greater inhibition of the lipolytic effect of insulin, causing an increase in lipolysis [46, 47].

Insulin resistance is defined as the inability of glucose uptake by skeletal muscle and adipose tissue and the inability of the liver to inhibit gluconeogenesis in response to an increase in insulin [38, 43].

The evidence of the causal relationships between insulin resistance and hypertension is increasing [48]. There are still many uncertainties about the mechanisms that link the two conditions, but in addition to the common genetic predisposition between insulin resistance and AHT, there are several other possible mechanisms that can explain it [48, 49].

The renin-angiotensin-aldosterone system (RAAS) is a therapeutic target for AHT. Changes in the RAAS are also important in insulin resistance, and the common molecular mechanisms of insulin resistance and AHT are not well understood [50, 51].

The RAAS thus plays an important role in MS. Angiotensinogen is a 58 kDa protein produced primarily in the liver under physiological conditions, but it can be produced in smaller amounts in adipocytes, mesangial cells, and epithelial cells of the proximal contoured tubule and in the brain (neurons and glial cells). Angiotensinogen by the action of the renin enzyme produced in the glomerular juxta cells in the kidney is subjected to cleavage in the amino-terminal acid of 10 NH2 to form angiotensin I. Angiotensin I is an inactive peptide that is hydroxylated by the enzyme angiotensin converter, forming an octapeptide designated angiotensin II [50].

The RAAS has autocrine/paracrine activity in various tissues, especially in the skeletal muscle, smooth muscle of blood vessels, kidneys, heart, and pancreas [52]. The angiotensin (AT) II receptor is a transmembrane protein that belongs to the family of receptors coupled to the G protein which is divided into type I (AT1) and type II (AT2) [40, 42, 53]. The genes encoding the AT1 receptor were cloned in 1992, and the genes encoding the AT2 receptor were cloned in 1994 [54]. The binding of angiotensin II to the AT1 receptor leads to the phosphorylation of various proteins such as IRS-1 and IRS-2, making the P110/PI3K subunit the common activation mechanism for the insulin signaling pathway. Resistance to insulin is caused by the inhibition of insulin through the inhibition of the mechanisms involved in glucose transport and vasodilation [42, 45].

Skeletal muscle is important in the development of insulin resistance, which is responsible for 75–95% glucose metabolism [55, 56]. Skeletal muscle constitutes the largest insulin-sensitive tissue in the body and is the primary site for insulin-stimulated glucose utilization [55]. Skeletal muscle resistance to insulin is fundamental to the metabolic dysregulation associated with obesity and physical inactivity and contributes to the development of the MS [55]. Potential mechanisms contributing to reduced insulin signaling and action in skeletal muscle include adipose tissue expansion and increased inflammatory adipokines, increased RAAS activity, decreases in muscle mitochondrial oxidative capacity, increased intramuscular lipid accumulation, and increased reactive oxygen species (ROS) [55].

Angiotensin II has prooxidant and pro-inflammatory effects that regulate apoptosis, inflammation, cell growth, fibrosis, and insulin sensitivity by inducing the formation of oxygen free radicals through the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [56]. ROS are formed by the electron transport chain in the mitochondria, and it increases in situations that require the oxidation of substrates such as glucose [56]. Multiple ROS activate transcription factors such as factor nuclear kappa B (NF-KB) protein-1 and hypoxia-inducible factor-1 HIF-1, which are involved in the mechanism of insulin resistance in skeletal muscle [57].

Hyperinsulinemia can alter some of the components of the RAAS such as profibrotic stimulants and pro-inflammatory actions mediated by angiotensin II and can cause cardiovascular disease development [50].

3.1 Relationship between inflammation and insulin resistance

Obesity is a worldwide epidemic that has generated many scientific publications in recent years. Thus, new paradigms were emerging, while the old challenges are still to be unraveled [58]. Obesity is a chronic disease and has become a major problem in most industrialized countries due to its increased prevalence and association with various diseases and due to its great economic impact [59]. To preserve the energy reserves of body fat during periods of negative energy balance, the body has developed various regulatory mechanisms [60]. This control is achieved by balancing the intestinal absorption of glucose, the production of glucose by the liver, and the absorption and metabolism of glucose by peripheral tissues [61]. Insulin regulates blood glucose due to its action in stimulating glucose uptake in the muscle and liver and inhibiting hepatic gluconeogenesis [61]. Despite the change in tolerance to the action of insulin initially, blood glucose is normal because pancreatic β cells have the ability to increase the ability of insulin secretion to overcome existing insulin resistance [9]. Excess nutrients induce hypertrophy of adipocytes that promote the development of various chronic morbidities such as type 2 DM and insulin resistance, glucose intolerance, and dyslipidemia with the consequent development of cardiovascular diseases [60]. There is also strong evidence to suggest that cell hypoxia may be an important factor in the pathophysiology of adipocytes and may be one of the causes of this dysfunction contributing to the metabolic alteration associated with obesity [62].

Obesity is defined according to the WHO, as an abnormal or excessive accumulation of fat that can cause imbalances in the health of an individual [63]. Males are more likely to accumulate intra-abdominal adipose tissue compared with females [32, 64]. On average, men have twice the amount of visceral fat than women and have a higher prevalence of metabolic diseases associated with obesity and MS [65].

Obesity is associated with a higher incidence of type 2 DM, insulin resistance, AHT, dyslipidemia, some types of cancer, and CVD [66]. Fat tissue is deposited in two main compartments, subcutaneous and central or visceral [63]. Based on this, obesity can be divided into central and peripheral obesity. Central obesity is characterized by hyperplasia and hypertrophy of adipocytes around the intra-abdominal organs and is associated with greater development of MS [65].

Adipocyte hypertrophy is the main consequence of excess nutrient intake, promoting the development of insulin resistance and glucose intolerance [63]. Triglycerides present in fatty tissue are the body's largest energy reserve, so adipose tissue is a very effective energy storage mechanism that allows survival of living beings in times of famine [59].

Recent studies have shown that hypoxia in adipose tissue can play an important role in the cellular mechanisms of chronic inflammation, macrophage infiltration, adiponectin reduction, leptin elevation, adipocyte apoptosis, and reticulum endoplasmic and mitochondrial dysfunction in white adipose tissue in obese [67].

Hypoxia inhibits pre-adipocyte differentiation and stimulates the secretion of leptin and vascular epithelial growth factor (VEGF) of mature adipocytes [68].

There are several genes that regulate the action of hypoxia, such as HIF-1α (hypoxia-inducible factor 1α), vascular endothelial growth factor VEGF, glucose transporter-1 (GLUT-1), heme oxygenase-1, and pyruvate dehydrogenase kinase 1 [67]. It was found that, under conditions of hypoxia in adipose tissue, all genes increased their expression except for VEGF messenger ribonucleic acid (mRNA) [67].

Adipose tissue is thus divided into white adipose tissue and brown adipose tissue, which have different functions. Brown adipose tissue has the function of producing heat. The understanding and vision we currently have in white adipose tissue have changed significantly in the last 15 years [69]. Currently, white adipose tissue is considered, not only as a tissue in which energy is stored in the form of triglycerides but also as the main secretory and endocrine organ of the organism [70]. White adipose tissue produces and secretes various proteins. Initially, these proteins were designated adipocytokines [71]. Currently, it is universally adopted the name of adipokines to the set of proteins synthesized and secreted by adipose tissue, since not all proteins are cytokines [71].

In addition to adipokines and fatty acids, adipose tissue produces other lipid substances such as steroid hormones, prostaglandins and prostanoids, cholesterol, and retinol (cholesterol and retinol are not synthesized by adipocytes but are stored and released from them) [71].

In 1994, Friedman and his colleagues discovered leptin, a hormone produced by white adipose tissue. Leptin, also called OB protein, is a hormone composed of 16 kDa and is produced from a protein with molecular weight of 18 kDa. It is cleaved leading to the production of leptin protein. Leptin is expressed in many tissues including the white and brown adipose tissue, stomach, placenta, mammary gland, ovarian follicles, and others [72]. It is expressed primarily in adipose tissue, but it is also expressed in smaller amounts in the brain and in the cerebrospinal fluid [70].

Leptin acts both in the central nervous system (hypothalamus) and in the peripheral organs. This discovery allowed us to realize that adipose tissue is not only a tissue in which energy storage occurs but also an endocrine organ [73].

White adipose tissue produces various adipokines, many of which are inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-β, and IL-6. The production of inflammatory interleukins increases with obesity and is involved in the development of insulin resistance and in the metabolic syndrome [62, 74]. Adipokines have various functions, in particular in the energy balance (e.g., leptin) on insulin sensitivity and glucose metabolism (e.g., adiponectin), inflammation (e.g., TNF-α), immunity (e.g., adipsin), lipid metabolism (e.g., cholesterol ester transfer protein), blood pressure control (e.g., angiotensinogen) hemostasis (e.g., plasminogen activation inhibitor-1), and angiogenesis (e.g., vascular epidermal growth factor) [62, 71].

3.2 Relationship between hypoxia and insulin resistance

Inflammation is an important process in obesity and in type 2 DM, as it promotes insulin resistance by inhibiting the function of IRS-1 and IRS-2 in the pathway insulin signaling [61, 75].

Obesity is characterized by a state of chronic inflammation with increased inflammatory parameters, for example, haptoglobin, IL-6, C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1), and TNF-α [69]. Large concentrations of cytokines produced by adipose tissue, such as TNF-α, IL-6, and IL-1β, and low concentrations of certain adiponectins cause chronic hyperinsulinemia and insulin resistance [63].

3.3 Relationship between endothelial dysfunction and insulin resistance

During periods of positive energy balance, there is an increase in white adipose tissue in order to be able to store excess triglycerides. Consequently, adipose tissue becomes hypoxic due to the decrease in vascularization of the same [62]. The role of hypoxia in adipose tissue in obesity and insulin resistance is still unclear [76]. Regulatory responses mediated by HIF-1 depend on its degree and duration [76].

HIF-1 is a heterodimeric transcription factor induced by hypoxia and composed of two subunits, the α subunit consisting of 120 kDa and the β subunit, consisting of 91 to 94 kDa [77]. The α subunit (HIF-1α) determines the transcriptional activity of HIF-1, and its increase occurs in response to hypoxia. The β (HIF-1β) subunit is constitutively expressed and may also be referred to as an aryl hydrocarbon receptor nuclear translocator (tRNA) [78]. Under normoxia conditions, HIF-1α is hydroxylated in proline and asparaginyl residues, catalyzed by the enzyme prolylhydroxylase (PHD), which promotes binding to an ubiquitin ligase complex. This process leads to proteosomal degradation mediated by HIF-1 [76, 78]. Under conditions of hypoxia, hydroxylation and activation of HIF-1 target genes are inhibited [76].

HIF-1α activates fibrosis of adipose tissue, causing an increase in macrophage infiltration into adipose tissue that mediates a greater increase in inflammation and concomitant sensitivity decrease in insulin [79, 80].

VEGF is a target gene of HIF-1. VEGF promotes angiogenesis, a necessary process for the differentiation of adipocytes and the growth of adipose tissue [81].

4. Obesity and metabolic syndrome

The endothelium is a layer of cells that lines the inner surface of the blood vessel [82]. Endothelial dysfunction is defined as the interruption of the release of vasodilator factors such as NO and prostacyclin (PGI2) and vasoconstrictor factors such as endothelin-1 (ET-1) and angiotensin II [74]. Alterations in vascular endothelial

function at the level of adipose tissue can cause insulin resistance [81]. In insulin resistance, the release rate of free fatty acids from the adipose tissue, which contribute to diabetic dyslipidemia, increased. HDL-cholesterol decreased, increasing low-density lipoprotein (LDL) cholesterol and free fatty acids. This stimulates the inflammatory response, causing the adhesion of monocytes and lymphocytes to the endothelial cells, and increases the flow of glucose and free fatty acids to the cells, causing excessive formation of oxygen free radicals, with an increase in metabolic and hemodynamic degradation. There is an increase in free radicals and nitrites by intramitochondrial enzymatic oxy-reduction which promotes apoptosis and impaired vascular endothelial function [82]. This alteration causes insulin metabolic dysfunction, promoting greater resistance to insulin [74, 82].

4.1 Relationship between insulin resistance and hypertension in obesity

Obesity alone is the cause of AHT in 78% of men and 65% of women [83]. Evidence of the causal relationship between insulin resistance and AHT is increasing [40]. Under physiological circumstances, insulin and insulin growth factor-1 (IGF-1) increase vasodilation by stimulating the production of NO and reducing the concentration of intravascular calcium in vascular smooth muscle cells. It also increases the sensitization of myosin-Ca^{2+} light chains. These actions are mediated through the activation of the PI3K enzyme and the Akt protein. Vascular relaxation in response to activation of PI3K/Akt pathway is mediated by endothelial cells producing NO, which involves phosphorylation of endothelial NO synthetase [41].

Patients with AHT have an increase in fasting and postprandial insulin levels in relation to non-hypertensive patients with the same body mass index [41]. It does not occur with secondary AHT but with essential AHT. This is related in part to the action of insulin that changes at the level of muscle tissue, which is the predominant site of glucose use stimulated by insulin [40].

There is an association between blood pressure and the proportion of type II fibers in skeletal muscle, which are less sensitive to insulin than type I fibers [40]. Under normal physiological conditions, there is a relationship between glucose-mediated insulin availability and increased blood flow in response to insulin. This response decreases in obese people with insulin resistance, which suggests resistance to insulin action in reference to vascular NO production [41]. Due to the difficulty of assimilating the rapid growth of adipose tissue in a hypoxia at an early stage, conditions are created for an increase in the expression of HIF-1α [84–87].

There is evidence that insulin resistance and hyperinsulinemia predispose patients to the development of AHT due to cellular abnormalities in insulin signaling pathways and are associated with metabolic and hemodynamic alterations [84]. Metabolic abnormalities are linked to hypertension caused by pathophysiological processes that involve the sympathetic-adrenergic system, the imbalance of cell cations, the increase in inflammation, the oxidative stress, and the RAAS [40].

RAAS plays an important role in insulin resistance by being more active in visceral adipose tissue compared to peripheral adipose tissue [83]. Insulin resistance in obese individuals is also associated, in part, with an antagonism to the action of angiotensin II (AT II) [83]. This produces a decrease in NO production with an increase in vasoconstriction and a decrease in GLUT-4 in skeletal muscle. It also reduces glucose uptake and decreases vasodilation in tissues [83]. Under normal conditions, the RAAS system is a mechanism for regulating blood pressure [88]. With the increase in the activity of the RAAS, there is a greater production of ATII, which leads to stimulation of the sympathetic nervous system, insulin resistance, sodium retention, and increased intravascular volume. It also contributes to kidney disease, hypertension, insulin resistance, and left ventricular hypertrophy [83].

There is a common genetic predisposition to insulin resistance and hypertension. Genetic defects have been described in people who had insulin resistance and AHT and mutations found on chromosome 7q, where other genes important for glycemic control, blood pressure, and obesity are also found [49].

Hyperinsulinemia can directly stimulate the reabsorption of sodium and water in the kidney, which increases the volume in the extracellular space, causing AHT. Another mechanism by which insulin can cause hypertension involves stimulation of the sympathetic nervous system (SNS) by increasing the concentration of norepinephrine. This increase is directly related to the increase in pulse and blood pressure by direct effect on the reabsorption of sodium in the kidney, peripheral vasoconstriction, and increased cardiac output [9].

5. Conclusion

The correlation of CVRF with the metabolic syndrome differs from one another. The notion that CVRF has a tendency to aggregation allows an earlier diagnosis of MS, thus also leading to the early introduction of therapeutic, pharmacological, or non-pharmacological measures. The prevalence of MS increases with age and is present in people of working age, increasing the risk of cardiovascular diseases, work-related absences, and socioeconomic costs. The concept of MS was carried out in a progressive manner. Its clinical importance is enormous due to the fact that it can identify patients with high risk of suffering some CVD and/or DM, allowing a preventive intervention. This may explain the importance of understanding the pathophysiology of the MS, and the author hopes that at the end of the chapter, the reader can understand it. This chapter is the beginning of an explanation of metabolic syndrome that should be complemented by reading other articles.

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