

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Metabolic Syndrome

Armando Miguel de Jesus Sousa de Araújo Ribeiro

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 Armando 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 and 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 an 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- κ B) 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 pro-fibrotic 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-1 α (hypoxia-inducible factor 1 α), 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-1 β , 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-1 α) determines the transcriptional activity of HIF-1, and its increase occurs in response to hypoxia. The β (HIF-1 β) subunit is constitutively expressed and may also be referred to as an aryl hydrocarbon receptor nuclear translocator (tRNA) [78]. Under normoxia conditions, HIF-1 α 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-1 α 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-1 α [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.

Author details

Armindo Miguel de Jesus Sousa de Araújo Ribeiro^{1,2}

1 Unidade Local de Saúde do Litoral Alentejano, Hospital Litoral Alentejano, Santiago do Cacém, Portugal

2 Universidad de Extremadura, Badajoz, Spain

*Address all correspondence to: amsr29@gmail.com

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Ribeiro AS, Seixas R, Gálvez JM, Climent V. Cardiovascular risk factors: Is the metabolic syndrome related to aging? Epidemiology in a Portuguese population. *Diabetes and Metabolic Syndrome*. 2018;**12**(6):885-891
- [2] Ribeiro AS, Gálvez JM, Vicente C. Equality or disparity. Cardiovascular risk factors and their correlation within the metabolic syndrome. *The secret of Gods. Diabetes and Metabolic Syndrome*. 2019;**13**(2):1393-1398
- [3] Villar Álvarez F, Maiques Galán A, Brotons Cuixart C, Torcal Laguna T, Sánchez-Pinilla O, Vilaseca Canals J, et al. Grupos de expertos del PAPPS. Actividades preventivas cardiovasculares en atención primaria. *Atencion Primaria*. 2003; **32**(2):27-41
- [4] Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe-epidemiological update 2015. *European Heart Journal*. 2015;**36**:2696-2705
- [5] Cruz WS, Siguenza OA, Guamancela SF, Piedra C, Andrade GC, Valdez MT. Prevalencia del síndrome metabólico en individuos adultos de las parroquias urbanas de la ciudad de Cuenca, Ecuador. *Síndrome Cardiometabólico*. 2013;**3**:113-125
- [6] Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome. A Joint interim Statement of the International diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;**120**:1640-1645
- [7] Reaven GM. Banting lecture. Role of insulin resistance in human disease. *Diabetes*. 1988;**37**(12):1595-1607
- [8] Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;**24**(4):683-689
- [9] DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;**14**(3):173-194
- [10] Garber AJ, Handelsman Y, Einhorn D, Bergman DA, Bloomgarden ZT, Fonseca V, et al. Diagnosis and management of prediabetes in the continuum of hyperglycemia: When do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocrine Practice*. 2008;**14**(7):933-946
- [11] Robles JCL. Síndrome metabólico: Concepto y aplicación práctica. *Anales de la Facultad de Medicina*. 2013;**74**(4):315-320
- [12] Fernández-Bergés D, Cabrera de León C, Sanz H, Elosuad R, Guembef MJ, Alzamora M, et al. Síndrome metabólico en España: Prevalencia y riesgo coronario asociado a la definición armonizada y a la propuesta por la OMS. Estudio DARIOS. *Revista Española de Cardiología*. 2012;**65**:241-248
- [13] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabetic Medicine*. 1998;**15**(7):539-553

- [14] Mykkanen L, Zaccaro DJ, Wagenknecht LE, Robbins DC, Gabriel M, Haffner SM. Microalbuminuria is associated with insulin resistance in nondiabetic subjects: The insulin resistance atherosclerosis study. *Diabetes*. 1998;**47**(5):793-800
- [15] Crepaldi G, Maggi S. The metabolic syndrome: A historical context. *Diabetes Voice*. 2006;**51**:8-10
- [16] Kraemer FB, Ginsberg HN, Gerald M, Reaven MD. Demonstration of the central role of insulin resistance in type 2 diabetes and cardiovascular disease. *Diabetes Care*. 2014;**37**:1178-1181
- [17] Haffner S, Taegtmeier H. Epidemic obesity and the metabolic syndrome. *Circulation*. 2003;**108**:1541-1545
- [18] Himsworth HP. Insulin deficiency and insulin inefficiency. *British Medical Journal*. 1940;**1**:719-721
- [19] Fronzo R, Tobin J, Andres R. Glucose clamp technique: A method for quantifying insulin secretion and resistance. *The American Journal of Physiology*. 1979;**237**:E214-E223
- [20] Alberti KG, Zimmet P, Shaw J. The metabolic syndrome-a new worldwide definition. *Lancet*. 2005;**366**:1059-1062
- [21] Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;**112**(17):2735-2752
- [22] Sociedade Brasileira de Cardiologia. I Diretriz brasileira de diagnóstico e tratamento da síndrome metabólica. *Arquivos Brasileiros de Cardiologia*. 2005;**84**(1):1-28
- [23] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood. Cholesterol in adults (adult treatment panel III). *JAMA*. 2001;**285**:2486-2497
- [24] The IDF worldwide definition of the metabolic syndrome. 2006. Available from: <http://www.idf.org/home/index.cfm?node=1429> [Accessed: 30 April 2007]
- [25] Woo J, Ho SC, Yu AL, Sham A. Is waist circumference a useful measure in predicting health outcomes in the elderly? *International Journal of Obesity and Related Metabolic Disorders*. 2002;**26**(10):1349-1355
- [26] Adams RJ, Appleton S, Wilson DH, Taylor AW, Dal Grande E, Chittleborough C, et al. Population comparison of two clinical approaches to the metabolic syndrome: Implications of the new International Diabetes Federation consensus definition. *Diabetes Care*. Nov 2005;**28**(11):2777-2779
- [27] Qiao Q, Laatikainen T, Zethelius B, et al. Comparison of definition of metabolic syndrome in relation to the risk of developing stroke and coronary heart disease in Finnish and Swedish cohorts. *Stroke*. 2009;**40**:337-343
- [28] The DECODE Study Group. Comparison of different definitions of the metabolic syndrome in relation to cardiovascular mortality in Europe men and women. *Diabetologia*. 2006;**49**:2837-2846
- [29] Villalobos SC, Mosquera CP, Tovar CH. Prevalencia del Síndrome metabólica en consulta de medicina interna Hospital de San José de Bogotá DC. *Repertorio de Medicina y Cirugía*. 2011;**20**:93-102
- [30] Grau M, Elosua R, León AC, Guembe MJ, Baena-Díez JM, Alonso TV.

Factores de riesgo cardiovascular en España en la primera década del siglo XXI: Análisis agrupado con datos individuales de 11 estudios de base poblacional, estudio DARIOS. *Revista Española de Cardiología*. 2011;**64**(4):295-304

[31] Elias CC, Arnold DL, Trimiño FY, Armas RA. Epidemiología y prevención del síndrome metabólico. *Revista Cubana de Higiene y Epidemiología*. 2012;**50**:250-256

[32] Ford ES, Giles WH, Dietz WH. Increasing prevalence of metabolic among US adults. Findings from the third national health and nutrition examination survey. *JAMA*. 2002;**287**(3):356-359

[33] Hu G, Qiao Q, Tuomiehto J, et al. Prevalence of metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Archives of Internal Medicine*. 2004;**164**(10):1066-1076

[34] Fiuza M, Cortez-Dias N, Martins S, et al. Síndrome metabólico em Portugal: Prevalência e implicações no risco cardiovascular- resultados do estudo VALSIM. *Revista Portuguesa de Cardiologia*. 2008;**27**(12):1495-1529

[35] Santos AC, Lopes C, Barros H. Prevalence of metabolic syndrome in the city of Porto. *Revista Portuguesa de Cardiologia*. 2004;**23**(1):45-52

[36] Haffner SM, Valdez RA, Hazuda HP, et al. Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes*. 1992;**41**(6):715-722

[37] Petersen KF, Dufour S, Savage DB, et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. *Proceedings of the National Academy of Sciences of the United States of America*. 2007;**104**:12587-12594

[38] Khan AH, Pessin JE. Insulin regulation of glucose uptake: A complex interplay of intracellular signalling pathway. *Diabetologia*. 2002;**45**:1475-1483

[39] Sesti G, Federici M, Hribal ML, Lauro D, Sbraccia P, Lauro R. Defects of the insulin receptor substrate (IRS) system in human metabolic disorders. *The FASEB Journal*. 2001;**15**:2099-2111

[40] DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. *Medical Clinics of North America*. 2004;**88**:787-835

[41] Virkamaki A, Ueki K, Kahn CR. Protein-protein interaction in insulin signaling and the molecular mechanisms of insulin resistance. *Journal of Clinical Investigation*. 1999;**103**(7):931-943

[42] Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: An update. *Hypertension*. 2001;**37**:1053-1059

[43] Ribeiro AS, Bicho MP. Insulin resistance and essential hypertension. Which mechanisms? *Revista Portuguesa de Hipertensão e Risco Cardiovascular*. 2012;**30**:12-15

[44] Inoue G, Cheatham B, Emkey R, Kahn CR. Dynamic of insulin signaling in 3T3-L1 adipocytes. Differential compartmentalization and trafficking of insulin receptor substrate (IRS)-1 and IRS-2. *Journal of Biological Chemistry*. 1998;**273**(3):11548-11555

[45] Sowers J. Insulin resistance and hypertension. *American Journal of Physiology-Heart and Circulatory Physiology*. 2004;**286**:H1597-H1602

[46] Boden G, Jadali F, White J, et al. Effects of fat on insulin-stimulated carbohydrate metabolism in normal men. *Journal of Clinical Investigation*. 1991;**88**:960-966

[47] Lann D, Laroith D. Insulin resistance as the underlying cause of

metabolic syndrome. Medical Clinics of North America. 2007;**91**:1063-1077

[48] Stump CS, Hamilton MT, Sowers JR. Effect of antihypertensive agents on the development of type 2 diabetes mellitus. Mayo Clinic Proceedings. 2006:796-806

[49] Cheng LSC, Davis RC, Raffel LJ, Xiang AH, Wang N, Quinones M. Coincident linkage of fasting plasma insulin and blood pressure to chromosome 7q in hypertensive Hispanic families. Circulation. 2001;**104**:1255-1260

[50] Putman K, Shoemaker R, Yiannikouris F, Cassis LA. The renin-angiotensin system: A target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. American Journal of Physiology. Heart and Circulatory Physiology. 2012;**302**:H1219-H1230

[51] Giani JF, Mayer MA, Munoz MC, Silberman EA, Hocht C, Taira CA, et al. Chronic infusion of angiotensin-(1-7) improves insulin resistance and hypertension induced by a high-fructose diet in rats. American Journal of Physiology. Endocrinology and Metabolism. 2009;**296**:E262-E271

[52] Habibi J, Whaley-Connel A, Hayden MR, DeMarco VG, Schneider R, Sowers SD, et al. Renin inhibition attenuates insulin resistance, oxidative stress, and pancreatic remodeling in the transgenic Ren2 rat. Endocrinology. 2008;**149**:5643-5653

[53] Marinho C, Ferreira J, Levy P, Coelho C, Gomes A, Laires MJ. Contribution of genetic polymorphisms involved in the control of blood pressure and cell growth/oxidative stress for the modulation of angiotensin converting enzyme activity. Revista Portuguesa de Cardiologia. 2011;**30**(1):18

[54] Haywood Guy A, Gullestad L, Katsuya T, Hutchinson HG, Pratt RE, Horiuchi M, et al. AT1 and AT2 angiotensin receptor gene expression in human heart failure. Circulation. 1997;**95**:1201-1206

[55] Stump CS, Henriksen EJ, Wei Y, Sowers JR. The metabolic syndrome: Role of skeletal muscle metabolism. Annals of Medicine. 2006;**38**:389-402

[56] Ndisang JF, Lane N, Syed N, Jadhav A. Up-regulating the heme oxygenase system with hemin improves insulin sensitivity and glucose metabolism in adult spontaneously hypertensive rats. Endocrinology. 2010;**151**(2):549-560

[57] Wei Y, Sowers JR, Clark SE, Li W, Ferrario CM, Stump C. Angiotensin II-induced skeletal muscle insulin resistance mediated by NF- κ B activation. American Journal of Physiology-Endocrinology and Metabolism. Feb 2008;**294**(2):E345-E351

[58] Ribeiro AS, Bicho MP. Obesidade: Novos paradigmas e velhos desafios. Revista Portuguesa de Hipertensão e Fatores de Risco Cardiovasculares. 2013;**34**:20-25

[59] American Gastroenterological Association Clinical Practice Committee. AGA technical review on obesity. Gastroenterology. 2002;**123**:882-932

[60] Kopecky J, Rossmeisl M, Flachs P, Brauner P, Sponarová J, Matejková O, et al. Energy metabolism of adipose tissue-physiological aspects and target in obesity treatment. Physiological Research. 2004;**53**:S225-S232

[61] Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature. 2001;**414**:799-806

- [62] Wood IS, Heredia FP, Wang B, Trayhurn P. Cellular hypoxia and adipose tissue dysfunction in obesity. *Proceedings of the Nutrition Society*. 2009;**68**(4):370-377
- [63] Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. *Diabetology and Metabolic Syndrome*. 2011;**3**:1-13
- [64] Nedungadi TP, Clegg DJ. Sexual dimorphism in body fat distribution and risk for cardiovascular diseases. *Journal of Cardiovascular Translational Research*. 2009;**2**:321-327
- [65] Ford eS, Li C, Zhao G, Pearson WS, Mokdad AH. Prevalence of the metabolic syndrome among U.S. adolescents using the definition from the International Diabetes Federation. *Diabetes Care*. 2008;**31**:587-589
- [66] Krishnan J, Danzer C, Simka T, Ukropec J, Walter KM, Kumpf S, et al. Dietary obesity-associated HIF1 α activation in adipocytes restricts fatty acid oxidation and energy expenditure via suppression of the Sirt2-NAD $^{+}$ system. *Genes and Development*. 2011;**26**:259-270
- [67] Ye J. Emerging role of adipose tissue hypoxia in obesity and insulin resistance. *International Journal of Obesity*. 2009;**33**(1):54-66
- [68] Ye J, Gao Z, Yin J, He H. Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *American Journal of Physiology. Endocrinology and Metabolism*. 2007;**293**:E1118-E1128
- [69] Trayhurn P, Wang B, Wood SI. Hypoxia in adipose tissue: A basis for the dysregulation of tissue function in obesity? *British Journal of Nutrition*. 2008;**100**:227-235
- [70] RajalaMW, Scheerer PE. Minireview: The adipocyte-at the crossroads of energy homeostasis, inflammation, and atherosclerosis. *Endocrinology*. 2004;**144**(9):3765-2773
- [71] Trayhurn P, Wood S. Adipokines: Inflammation and the pleiotropic role of white adipose tissue. *British Journal of Nutrition*. 2004;**92**(3):347-355
- [72] Trayhurn P, Beattie JH. Physiological role of adipose tissue: White adipose tissue as an endocrine and secretory organ. *Proceedings of the Nutrition Society*. 2001;**60**:329-339
- [73] Zhang YY, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homolog. *Nature*. 1994;**372**:425-432
- [74] Jansson PA. ENdothelial dysfunction in insulin resistance and type 2 diabetes. *Journal of Internal Medicine*. 2007;**262**:173-183
- [75] Fantin VR, Sparling JD, Slot JW, Keller SR, Lienhard GE, Lavan B. Characterization of insulin receptor substrate 4 in human embryologic kidney 293 cells. *The Journal of Biological Chemistry*. 1998;**273**:10726-10732
- [76] Jiang C, Qu A, Matsubara T, Chanturiya T, Jou W, Gavrilova O, et al. Disruption of hypoxia-inducible factor 1 in adipocytes improves insulin sensitivity and decreases adiposity in high-fat diet-fed mice. *Diabetes*. 2011;**60**:2484-2495
- [77] Huang LE, Arany Z, Livingston DM, Bunn HF. Activation of hypoxia-inducible transcription factor depends primarily upon redox-sensitive stabilization of its alpha subunit. *The Journal of Biological Chemistry*. 1996;**271**(50):32253-32259

- [78] He Q, Gao Z, Yin J, Zhang J, Yun Z, Ye J. Regulation of HIF-1 α activity in adipose tissue by obesity-associated factors: Adipogenesis, insulin, and hypoxia. *American Journal of Physiology. Endocrinology and Metabolism*. 2001;**300**:E877-E885
- [79] Halberg N, Khan T, Trujillo ME, Wernstedt-Asterholm I, Attie AD, Sherwani S, et al. Hypoxia-inducible factor 1 α induces fibrosis and insulin resistance in white adipose tissue. *Molecular and Cellular Biology*. 2009;**29**(16):4467-4483
- [80] Michailidou Z, Turban S, Miller E, Zou X, Schrader J, Ratcliffe P, et al. Increased angiogenesis protects against adipose hypoxia and fibrosis in metabolic disease-resistant 11 β -hydroxysteroid dehydrogenase type 1 (HSD-1)-deficient mice. *Journal of Biological Chemistry*. 3 Feb 2012;**287**(6):4188-4197
- [81] Cao Y. Adipose tissue angiogenesis as a therapeutic target for obesity and metabolic diseases. *Nature Reviews. Drug Discovery*. 2010;**9**:107-115
- [82] Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: The road map to cardiovascular diseases. *Diabetes/Metabolism Reviews*. 2006;**22**:423-436
- [83] El-Atat FA, Stas SN, Mcfarlane SI, Sowers JR. The relationship between hyperinsulinemia, hypertension and progressive renal disease. *Journal of the American Society of Nephrology*. 2004;**15**:2816-2827
- [84] Kalidas K, Wasson J, Glaser B, Meyer JM, Duprat LJ, White MF, et al. Mapping of the human insulin receptor substrate-2 gene, identification of a linked polymorphic marker and linkage analysis in families with type II diabetes: No evidence for a major susceptibility role. *Diabetologia*. 1998;**41**:1389-1391
- [85] Cantley J, Grey ST, Maxwell PH, Withers DJ. The hypoxia response pathway and B-cell function. *Diabetes, Obesity and Metabolism*. 2010;**12**(2):159-167
- [86] Huang LE, Gu J, Schau M, Bunn HF. Regulation of hypoxia-inducible factor 1 α is mediated by an O₂-dependent degradation domain via the ubiquitin-proteasome pathway. *Proceedings of the National Academy of Sciences of the United States of America*. 1998;**95**:7987-7992
- [87] Ribeiro AS, Bicho M, Mascarenhas MR. Hipertensão arterial e densitometria óssea: Que relação? *Revista Portuguesa de Hipertensão*. 2014;**43**:6-8
- [88] Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G. Mechanisms of obesity-induced hypertension. *Hypertension Research*. 2010;**33**:386-393