Metabolic syndrome: molecular basis and reasons for interaction with obesity

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Abstract

When Gerald Reaven, in late 1980's, introduced the term metabolic syndrome (MS), it soon became a theme of great scientific debate. Genetic background, onadequate diet and sedentary lifestile contribute to MS outcome, whose overall prevention is now believed to be a world wide challenge. Although MS pathogenesis is not completely clarified, its various components are thought to be associated to insulin resistence. Maybe in MS there is interation among genetic, metabolic and environmental features, including diet. Diet role on the development of MS is not yet fully established on a precise or definitive way. Food and nutrition aspects in modern life, especially associated to questionable feeding behaviors and / or sedentary lifestyle, play significant role in obesity, representing a causality chain that is easily observed but hard to intervene. So this article aims at reviewing the state-of-the-art and circumstances that characterize MS, highlighting the knowledge on molecular events (genes and proteins) that regulate adipogenesis and help understand obesity as risk factor for MS.

Key words: Metabolic Syndrome X (MS) Obesity, Genes, Regulator Adipogenesis.

Introduction

This review aims to present and discuss studies that characterize the metabolic syndrome (MS) and its relationship with obesity. We analyze works that address the physical, clinical, biochemical and genetic aspects of this syndrome and shed light on its molecular bases, which have lately been unveiled and dissected in order to better understand adipogenesis and obesity.

In adult humans, the accumulation of multiple cardiovascular risk factors had already been observed since the early 20th century.[1,2] More recently, though, similar clusters of certain cardiac factors have received renewed attention and terms such as **deadly quartet**,[3] **insulin-resistance syndrome**,[4] **Metabolic Syndrome** (MS),[5] **syndrome X**,[6] or **plurimetabolic syndrome** have been proposed to describe the connection between obesity, insulin resistance, systemic arterial hypertension (SAH), dyslipidemia, type 2 *diabetes mellitus* (T2DM), and atherosclerotic cardiovascular disease (ASCVD). Thus, we can say that the definition of this syndrome varies in terms of which indicators are present and which cut-off values are used.[2]

Recent evidence, however controversial it may be,[7] has emerged with substantial information on childhood obesity in association with insulin resistance, inflammation and other risk factors and on their collective role in the increased risk of ASCVD and T2DM. The constellation of these interrelated cardiovascular risk factors in adults came to be known as the metabolic syndrome (MS), a designation that has proven to be useful both in clinical and research settings[2] and that has recently been updated according to global consensus guidelines for its study, diagnosis and prevention.[8,9] With this in mind, MS has been characterized by the occurrence of complex disorders represented by a cluster of cardiovascular risk factors commonly associated with central adiposity and insulin resistance.[10]

Other conditions associated with MS include physical inactivity, aging, hormonal imbalance and genetic predisposition. Some people are genetically susceptible to insulin resistance. However, such factors as excess body fat and physical inactivity may favor the development of MS. Insulin resistance is very commonly associated with abdominal obesity, but the molecular bases of the biological mechanisms relating insulin resistance and metabolic risk factors are not yet fully understood and do seem to be quite complex.[11] For that matter, the recent finding[9] that the stability of MS, particularly in adolescents, is low is striking and raises questions about the usefulness of the concept of MS in a clinical context.

According to the World Health Organization (WHO),[12,13] MS is a complex metabolic disorder characterized by the association of impaired glucose tolerance / *diabetes mellitus* and/or insulin resistance, plus two or more of the following factors: SAH (values greater than 140/90mmHg); hypertriglyceridemia (plasma concentrations greater than 150mg/dl) and/or serum concentrations of high density lipoprotein (HDL-c) below 35mg/dl and 39mg/dL, in men and women,

respectively; central/abdominal obesity or adiposity (determined by a waist-to-hip ratio greater than 0.90 for males and 0.85 for females) and/or Body Mass Index (BMI[a]) greater than 30kg/m²; microalbuminuria (rate of urinary albumin excretion greater than or equal to 20µg/min or albumin-to-creatinine ratio greater than or equal to 30 mg/g).

Associations and clusterings of these factors have been known for decades, serving to clearly demonstrate that MS is a common condition, with a high prevalence worldwide and that it is still on the rise and occurring in populations of sedentary and obese individuals.[14] As a result, MS now appears as a serious public health problem, other than being a serious clinical problem.

The incidence of MS has increased at an alarming rate in recent years and it is estimated that over 50 million North-American individuals are affected by this chronic non-communicable disease (CNCD).[11] In 2001, the National Cholesterol Education Program (NCEP)[b], USA, reported that the diagnosis of MS is determined by the presence of three or more of the following conditions: abdominal obesity,[c] SAH,[d] impaired glucose tolerance,[e] hypertriglyceridemia,[f] low HDL-c concentrations.[g] For illustrative purposes, below is a list of what would be a full, typical repertoire of MS conditions.

- abdominal obesity (excessive fat accumulation in the abdomen);
- atherogenic dyslipidemia (blood fat and cholesterol disorders – hypertriglyceridemia, low HDL and high LDL levels – that cause accumulation of fatty plaques in artery walls);
- elevated blood pressure;
- insulin resistance or glucose intolerance;
- prothrombotic state (high fibrinogen or plasminogen activator inhibitor-1 levels in the bloodstream);
- proinflammatory state (elevated C-reactive protein levels in the bloodstream).

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a BMI = body mass in kilograms (Kg) divided by height in meters squared.

b NCEP, The National Cholesterol Education Program, created in 1985 by the National Heart, Lung, and Blood Institute (NHLBI) of the United States, aims at offering continuing education to professionals and the general public about the benefits of lowering cholesterol levels as a way to reduce the risks for coronary heart diseases.

c Abdominal obesity is determined by waist circumference values greater than 102 cm and 88 cm, in men and women, respectively.

d Arterial hypertension is defined by blood pressure levels equal to or greater than 130/85mmHg.

e Fasting glucose between 110 and 125mg/dl.

f Hypertriglyceridemia is determined by values equal to or greater than 150mg/dl.

g HDL-c: rates below 40mg/dl for men and 50mg/dl for women.

Representative table of the full repertoire of possible conditions, which do not always coexist all at once, in MS. Adapted from NCEP (2001)

According Lorenzo et al.,[15] the definition proposed by the NCEP detects a greater number of individuals at risk for diabetes (48.7%) than the WHO definition (41.3%), since MS is a predictor of the development of *diabetes mellitus*, regardless of other risk factors.

Although it is relatively well-studied and accepted as a major health problem, there is still controversy as to whether MS is a true syndrome[h] – i.e., whether or not it is just a mixture of unrelated phenotypes.[14] It is known that MS cannot be used as an indicator of absolute risk, given that, *per se*, it does not have many of the factors that determine absolute risk – for example, age, sex, smoking and LDL levels. Still, individuals with MS are twice as likely to develop cardiovascular disease in the next five to ten years, and five times more likely to develop T2DM. Furthermore, individuals with the triad of conditions (obesity, T2DM and inflammation) usually manifest a prothrombotic and proinflammatory state. The association of MS with cardiovascular disease increases overall mortality by about 1.5 times.

The International Diabetes Federation (IDF) has recently published its definition of metabolic syndrome in children and adolescents. This panel suggests the following criteria: (1) for children between the ages of 6-10 years old, obesity (defined as waist circumference ≥ 90th percentile), accompanied by other measurements as indicated by family history; (2) for children and adolescents aged 10-16 years, obesity (defined as waist circumference ≥ 90th percentile), followed by the adult criteria for triglycerides, HDL-C, blood pressure, and glucose; (3) for youths ≥ 16 years of age, the panel recommends using the existing IDF criteria for adults. This definition is based on waist circumference percentiles and is standard across all age groups considered.

Using the ATP III criteria defined by the NCEP and the WHO, studies were carried out in the mid-2000s, in different North-American countries, with the following results, which can be compared: in U.S. schools, with 1,513 adolescents, the prevalences of MS of 4.2% and 8.4%, respectively, were found;[16] in 965 Mexican children and adolescents, the percentages of 6.5% in children and 4.5% in adolescents were found;[17] in Canada, in the evaluation of 2,244 children and adolescents, the prevalence of MS was slightly higher (11.5%).[18]

Although the body of knowledge about the prevalence of MS in other countries and in different age groups in the population (children, adolescents and adults) is quite relevant, it is known that

h A syndrome is simply a cluster of factors that appear together more often than they would naturally occur at random, the reason for such being regarded as either uncertain or multifactorial. MS meets this criterion for inclusion as a syndrome.

the prevalence of MS in different populations is highly dependent on the criteria used for its definition and there are still no comprehensive studies, at least not with significant data, regarding this prevalence in the Brazilian population. Initial studies on the prevalence of MS differed greatly in their results due to the different criteria used and their focus on specific subgroups within the population. Moreover, it has been suggested that each population validates this definition according to local ethnic characteristics.[19]

International organizations such as the IDF (International Diabetes Federation), NHLBI (National Heart, Lung and Blood Institute, U.S.), AHA (American Heart Association), WHF (World Heart Federation), IAS (International Atherosclerosis Society), and IASO (International Association for the Study of Obesity) regularly publish consensus documents and statements on the subject[8,9,20] in order to update the scientific community on the latest relevant guidelines. The most recent document was published in 2009 in the journal *Circulation* (v. 120, p. 640-1645) and must be used as the gold standard in studies involving MS.

The most recent document[9] is considered an international guideline and represents the latest step for a unified definition of MS. In it, the consensus is that an individual must present at least three of the five clinical criteria defined as components of MS to allow for such a diagnosis. The presence of any of these criteria is not mandatory. The cut-off values for each of the criteria were well defined, except for the waist circumference, which must be assessed by each country, respecting its ethnicity, nationality and regionalization.

The role of insulin resistance as a factor able to explain all the clinical aspects remains unclear, both from a pathogenic viewpoint and as a criterion for diagnosis. The causes of MS remain linked to the social, economic and cultural context of the population, especially in what relates to physical activity and eating habits.

Obesity as a risk factor for MS

Obesity, defined as increased adipose tissue mass, is usually associated with chronic systemic inflammation and confers high risk for cancer and cardiovascular and metabolic disorders.[21] Obesity is considered a global epidemic, and the World Health Organization[22,23] describes it as multifactorial, originating either isolatedly or from the interaction of genetic, social, cultural, nutritional, metabolic and/or endocrine factors. According to Conway & René,[24] obesity is a complex disease with a multifaceted etiology and its own pathophysiology, comorbidities and disabling capabilities. In Brazil, the demographic, socioeconomic and epidemiological changes over time allowed for a transition in dietary patterns, with a gradual reduction of malnutrition and increase in obesity.[25]

Over the last decade, there has been a continuing increase in obesity and its comorbidity with MS, although, in fact, little is actually known about the rate of metabolic dysfunction in these cases.[26] Several factors have been implicated as biomarkers for MS, among which insulin, uric acid[26] and C-reactive protein (CRP), plus two other factors directly related to obesity due to their association with adipose tissue, namely adiponectin and leptin.[27,28]

Obesity has been associated with insulin resistance[29] and is considered the main risk factor for the development of prediabetes and T2DM[30,31] and also of coronary heart disease (CHD).[32] Most cases of MS occur in individuals with overweight, which, by itself, affects the sensitivity to insulin that, in turn, decreases by 40% when the subject has a body mass 35% to 40% above the desirable range.[33] The excess body fat leads to lipid accumulation in various tissues, notably adipose tissue, muscles, liver and pancreatic β-cells, which seems to induce the biochemical changes occurring in the MS.[20]

Cellular and molecular bases of adipose tissue function and dysfunction

Knowing about the molecular events that regulate the differentiation of preadipocytes and mesenchymal stem cells into adipocytes (adipogenesis) is important for understanding the genesis of obesity. Obesity results from an increase in the size and number of adipocytes, and the balance between adipogenesis and adiposity helps determine the degree of obesity of an individual.[34] In obesity, several hormones and cytokines seem to play a critical role in maintaining a high body weight.

It is known that mature adipocytes secrete adipokines[i] or adipocytokines, whose production is much higher in obesity, contributing to the onset of peripheral insulin resistance. In MS, adipose tissue has been shown to function as a paracrine and endocrine organ, secreting several adipocytokines, such as adiponectin and leptin,[28] besides the classic proinflammatory cytokines (interleukin-6 or IL-6, and tumor necrosis factor, TNF-α),[27] as well as lipokine, resistin, omentin, lipocalin and fatty acid-binding proteins (A-FABP), among others. These adipocytokines are known to interact in a quite complex manner.

Adiponectin and leptin appear to be directly associated with obesity and insulin resistance.[27,28] It should be mentioned that adiponectin and leptin appear to have opposite associations with regard

i Proinflammatory cytokines have widespread metabolic effects throughout the body, such as metabolic alterations in proteins, fats and trace elements, besides changes in hepatic protein synthesis.40 Cytokines are defined as soluble proteins, synthesized by immune cells or not, mediating intracellular communication by transmitting information to target cells via interactions with specific receptors. Many cytokines have physiological activities other than those originally discovered.41 Currently, the most accepted term to describe a protein that is secreted (and synthesized) by adipose tissue, whether or not it is a cytokine,42 is adipokine.

to MS and CHD.[35] Adipocytes and adipose tissue macrophages produce interleukin-6 (IL-6) in excess, while tumor necrosis factor-alpha (TNF-α) expression is increased in the visceral fat of obese subjects and correlates positively with the degree of obesity and plasma insulin levels.[36] IL-6 and TNF-α mediate lipolysis indirectly and increase hepatic fatty acid synthesis, therefore increasing serum levels of fatty acids and triglycerides.[37] In turn, the inflammatory cascade triggered by these cytokines is further stimulated by hyperinsulinemia.[38] IL-6 and TNF-α also act directly on the insulin receptor in order to reduce its signaling and, thus, increase insulin resistance.[39] In brief, visceral adipose tissue, increased in MS patients, disturbs adipocytokine secretion and leads to a low-grade chronic inflammatory state, through the infiltration of macrophages in the adipose tissue.[43] This inflammatory state is associated with insulin resistance and atherosclerosis.[43,44,45]

To be more specific, it follows that adiponectin has anti-atherogenic, anti-diabetic, and anti-inflammatory properties, which reduce insulin resistance, by increasing insulin sensitivity in the liver. In muscle tissue, adiponectin increases glucose utilization and fatty acid oxidation, besides also increasing endothelial nitric oxide (NO) secretion and inhibiting monocyte adhesion and smooth muscle cell proliferation of the vascular wall.[45,46,47]

As for leptin, it is also a proinflammatory cytokine and appears to be important in the regular control of the amount of body fat. It is a peptide hormone, a product of the *ob* gene, that functions as an afferent signal in a negative feedback loop regulating the size of adipose tissue mass.[28] The leptin concentration, which is also a known satiety factor,[48] is proportional to the number and size of adipocytes.[49] Recently, it has been the subject of research to elucidate how obesity stimulates systemic inflammation through the action and connection of several cytokines, including the very own increased leptin[50] and decreased adiponectin.[45,46,47]

Still regarding leptin, recent studies have shown that insulin and leptin act as regulators of a type of protein called aquaglyceroporins, which allow the movement of water and other smaller solutes, in particular glycerol, across cell membranes. Glycerol is a metabolite acting in the control of lipid accumulation and the glucose homeostasis, with an important role as a substrate for hepatic gluconeogenesis, in pancreatic insulin secretion and in cardiac ATP production. Aquaglyceroporins (AQP3, AQP7, AQP9 and AQP10) comprise a subfamily of aquaporins.[50,51] Through a metabolic pathway known by the acronym PI3K/Akt/mTOR (Phosphatidylinositol 3-Kinase/Akt/mammalian target of rapamycin), and considering that adipose tissue is a major source of glycerol via AQP7,[49,53] it has been recently reported that aquaglyceroporins (in particular AQP3 and AQP7) may facilitate glycerol efflux from adipose tissue while reducing glycerol influx into hepatocytes via AQP9, thus preventing the excessive lipid accumulation and the subsequent aggravation of hyperglycemia in human obesity.[51,52] As shown in Figure 1, taken from Rodríguez et al.'s paper,[51] these versatile and significant functions of the aquaglyceroporins reveal the unexpected and emerging roles of these glycerol channels.

Other adipokines recently reported[54,55] are: vaspin, visfatin, apelin, omentin, fractalkine, acylation stimulating protein (ASP) and retinol-binding protein 4 (RBP4). The role – sometimes beneficial, sometimes detrimental – of these adipokines in obesity and atherosclerosis has been extensively studied. Vaspin (an acronym for visceral adipose tissue-derived serine protease inhibitor) was identified as a member of the protein family of serine protease inhibitors, and may have anti-atherogenic effects through its insulin-sensitizing properties.

Similarly, visfatin also has these properties, but it seems to destabilize atherosclerotic plaques, which is a detrimental effect. Apelin, via inhibition of food intake and increases in physical activity and body temperature, may promote weight loss, resulting in a beneficial anti-atherogenic effect, which is associated with other positive effects on vasodilation and blood pressure. Considering its increased levels in atherosclerotic subjects, RBP4 may be a valuable biomarker. Also, ASP, often increased in obesity and MS, may contribute to efficient lipid storage, and decreasing or blocking it may provide a potential anti-obesity target.

As for omentin-1, the most common isoform, it has been identified as a new adipokine predominantly secreted by visceral stromal vascular cells, although it is not exactly produced by adipocytes.[55] *In vitro* experiments have shown that treatment with recombinant omentin-1 enhances insulin-stimulated glucose uptake in subcutaneous and omental human adipocytes while increasing the phosphorylation of Akt/PKB. Studies with human patients with T1DM showed a decrease in plasma omentin-1 levels, which are not affected by glucose intake. Furthermore, the plasma concentration and gene expression of omentin in visceral adipose tissue appear to decrease in obesity.

Visceral adipose tissue and adipokines

Numerous clinical and experimental studies, especially over the last decade, have focused on visceral adipose tissue and abdominal obesity.[45,46] Abdominal fat is composed of subcutaneous fat and visceral fat, and, depending on the predominant fat, is classified as subcutaneous or visceral abdominal obesity, with the latter posing the highest risk for health. As reviewed,[56] omental or visceral adipose tissue (VAT) is the most active, i.e., more sensitive to lipolysis, via catecholamines and β-adrenoreceptors, and more insulin-resistant, releasing a higher concentration of free fatty acids (FFA) directly into the portal vein. In addition, VAT secretes the highest concentrations of adipokines linked to pro-inflammatory processes, such as resistin, angiotensin I, plasminogen activator inhibitor-1 (PAI-1), PCR, IL-6, followed by subcutaneous abdominal adipose tissue (SAAT) and subcutaneous femoral-gluteal adipose tissue (SFGAT).

Regarding specific body fat stores, two- to three-fold expressions of resistin, one of the aforementioned adipokines, are found in visceral adipose tissue, followed by subcutaneous abdominal tissue and subcutaneous gluteal-femoral adipose tissue, and an increase in resistin expression can be an important link between abdominal obesity and T2DM. Besides, its expression is three times higher in preadipocytes than in mature adipocytes, and it also functions as a potential regulator of adipogenesis.[57]

Waist circumference is a recommended measurement for representing an anthropometric index representative of intra-abdominal fat and for being simple and reproducible.[58] This index is obtained by measuring halfway between the iliac crest and the lower costal border (Brazilian Society of Cardiology, 2005). For abdominal waist circumferences between 80 and 88 cm and between 94 and 102 cm in women and men, respectively, more frequent monitoring of risk factors for coronary heart diseases is recommended.[58]

It is known that adipokines can act as a link between visceral adiposity and atherosclerosis.[34] In visceral fat stores, turnover is faster than in other areas, which increases concentrations of PAI-1, inflammatory cytokines and non-esterified fatty acids (NEFA, according to the trilingual and structured vocabulary DeCS – Health Sciences Descriptors) in the portal system. The increased release of NEFA from adipose tissue stimulates gluconeogenesis, inhibits hepatic insulin clearance and causes accumulation of triglycerides in the liver and muscles, resulting in hyperglycemia and consequent hyperinsulinemia. Thus, the accumulation of fat in muscles leads to insulin resistance, whereas in the liver it promotes atherogenic dyslipidemia.[33,59]

Final remarks

MS has shown a high global prevalence, occurring in groups of sedentary and obese individuals. The knowledge of the molecular bases that regulate inflammation, obesity and its comorbidities may provide new therapeutic approaches in the treatment or prevention of these pathologies.

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