Metabolic syndrome, atherosclerosis and inflammation: an inseparable triad?

Síndrome metabólica, aterosclerose e inflamação: tríade indissociável?

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Abstract

Populations all over the world are increasingly inactive and are consuming increasing quantities of fats and sugars, which is generally linked to industrially processed foods. The consequences have rapidly manifest as an increase in overweight/obesity and in physiological and metabolic changes, such as the Metabolic Syndrome, which is a series of changes in glycemia, lipids and blood pressure. There is evidence of a close relationship between these changes and inflammatory processes, which can also be linked to oxidative stress. These conditions lead to the pathogenesis of vascular abnormalities or intensify metabolic processes that accompany the metabolic syndrome. The objective of this review is to compare the large number of bibliographic references that show correlations between components of the Metabolic Syndrome and increases in the mediators of inflammation. The publications reviewed were located using the *Pubmed*, *Scopus*, *Lilacs* and *Scielo* databases and the majority of the articles selected were published within the last 5 years.

Keywords: metabolic syndrome ; arteriosclerosis; inflammation.

Resumo

Observa-se, nas populações mundiais, aumento do sedentarismo e aumento do consumo de gorduras e açúcares, sendo estes vinculados normalmente aos alimentos industrializados. A consequência disso rapidamente se manifestou no aumento do sobrepeso/obesidade e na instalação de alterações fisiológicas e metabólicas, como a Síndrome Metabólica, que é representada por alterações na glicemia, nos lipídeos e na pressão arterial. Há evidências de ligação estreita entre estas alterações e os processos inflamatórios, que também podem estar associados ao estresse oxidativo. Estas condições levam à patogênese das alterações vasculares ou intensificam os processos metabólicos que acompanham a Síndrome Metabólica. O objetivo desta revisão foi comparar as inúmeras referências literárias que mostram correlação entre os componentes da Síndrome Metabólica e o aumento dos mediadores de inflamação. Para isso, utilizou-se *Pubmed, Scopus, Lilacs* e *Scielo* como base de dados, sendo que os artigos selecionados dataram principalmente dos últimos cinco anos.

Palavras-chave: síndrome metabólica; arteriosclerose; inflamação.

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INTRODUCTION

The modern world has brought many benefits and comforts for humans, but has also led to considerable changes to lifestyles. Whereas in times past humans had to expend large quantities of calories attempting to feed themselves, the modern scenario is very different. Populations all over the world are increasingly inactive and consume increasing quantities of fats and sugars, which is generally linked to industrially processed foods. The consequence of this was a rapid transition, manifest as a reduction in malnutrition and underweight and an increase in overweight/obesity. It is estimated that the proportion of the Brazilian population that is obese is 17.1% and the figures for overweight are also alarming at 49.1% of Brazilian women and 56.5% of Brazilian men.[1]

Other metabolic and physiological abnormalities are associated with overweight and obesity, manifest in the form of Diabetes Mellitus type 2 (DM2) and the Metabolic Syndrome (MS). These conditions exacerbate the risk of developing cardiovascular diseases (CVDs) and cancer, which are the chronic degenerative diseases responsible for most morbidity and mortality today. These metabolic abnormalities involve changes to carbohydrate metabolism, resulting from a reduction in the response to insulin, primarily in muscle and adipose tissues (AT), leading to hyperglycemia and changes in metabolism of lipids, resulting in dyslipidemias. Moreover, they also change immunoresponse patterns, the consequence of which is initiation of an inflammatory process that culminates in a vicious circle of exacerbation of biochemical alterations and increased production of inflammatory mediators.[2,3]

There is growing concern with the increased incidence of chronic degenerative diseases and the many different studies investigating them have taken the most varied approaches to their complexity and etiopathogenic factors; but there is consensus that lifestyle changes are the most effective way of improving or preventing their risk factors. Changes to the diet and regular physical exercise modify the metabolic and inflammatory profile, leading to a state of metabolic equilibrium.[4]

This bibliographic survey covers the most important features of the inflammatory processes involved in obesity, the metabolic syndrome (MS) and the CVDs.

METHODOLOGY

This review of the literature is based on a survey of articles primarily published during the last 5 years, located using the following databases: *Medline*, *Scielo*, *Pubmed*, *Scopus* and *Lilacs*. The retrospective search was restricted to indexed scientific articles describing research involving human beings and animals.

DISCUSSION

The Metabolic Syndrome

The high prevalence of MS in both sexes has made it a public health problem. The syndrome is characterized by a series of risk factors, normally associated with insulin resistance and deposition of fat in the abdominal region. These risk factors are interconnected by biochemical, physiological, clinical and metabolic features and directly increase the risk of developing DM2 and CVD. The syndrome's incidence can vary within different populations depending on ethnicity, age, sex and region (urban or rural) and according to the diagnostic criteria employed. According to the International Diabetes Federation – IDF (2005), one quarter of the global adult population has the syndrome.[5-7]

The MS was originally named Metabolic Syndrome X and there are a large number of criteria for its diagnosis, including the EGIR – European Group for the Study of Insulin Resistance (1999), the AACE – American Association of Clinical Endocrinologists (2003) and the IDF (2005), but the First Brazilian Directive on the Metabolic Syndrome (IDBSM, 2005) chose the National Cholesterol Education Program – Adult Treatment Panel III (2001) criteria. These criteria for diagnosis include glycemia disorders related to insulin resistance (IR); elevated BMI; elevated triglycerides and low HDL-c (high density lipoprotein); and high blood pressure.[5,8-10]

There is consensus in the recent literature that there are at least six criteria that define the presence of MS: obesity, waist circumference (> 102 cm in males or > 88 cm in females), IR (fasting glycemia greater than 100mg/dL), elevated triglycerides (> 150 mg/dL) and low HDL-c (< 40 mg/dL no male sex or < 50 mg/dL in female sex), arterial hypertension (BP > 130⁄85 mm Hg) and a proinflammatory and pro-thrombotic state. People who have three or more of the criteria listed above are considered to have the syndrome.[4,7,11-14]

It is possible to detect MS in people with normal BMI and so obesity can be defined as a risk factor, but is not present in all those with the syndrome.[4]

Studies show that MS can also be related to pathologies such as hepatic steatosis, cancer, depression and respiratory and rheumatic diseases.[15,16]

Inflammation: can it be measured?

For a long time it has been known that coronary diseases are among the principal causes of death in the modern world and they place an extremely high cost burden on Public Health Systems. Prevention is the best way to reduce these costs and the high rates of morbidity/mortality. With a view to this, a large number of algorithms have been developed to delineate the risk factors of these diseases. Among the most widely known are the Framingham and Reynolds scores, while ultra-sensitive C-reactive protein (CRP-us), also known as high sensitivity C-reactive protein (CRP-hs) and carotid intima-media thickness are also used.[17] However, use of many of these tools may not be feasible in daily clinical practice. Notwithstanding, some of them can be useful for predicting cardiovascular events.

Some studies indicate that CRP can be used as an inflammatory marker to detect the initial stages of atherosclerotic disease.[10,15,18] In this review, special attention will be paid to CRP because it is the marker of inflammation that is most studied and most used for prediction of cardiovascular events.

Some cytokines, such as Interleukin-1 (IL-1), IL-6 and Tumor necrosis factor-α (TNF-α), can regulate synthesis of CRP. Studies have shown that this protein can have important pro-inflammatory effects and, when it binds with molecules produced during inflammation or infection, it triggers activation of the complement, leading to tissue damage.[19-21]

Published data show that there is a strong correlation between high CRP levels and overweight or obesity. Overweight/obesity in children also affects the presence of hyperglycemia, dyslipidemia, elevated CRP levels and the risk of MS, conferring a risk of future comorbidities.[22,23]

Moreover, it has been demonstrated that CRP-us results are strongly correlated with recurrent vascular events. There is also evidence in the literature of a positive correlation between elevated CRP-us levels and hyperglycemia, hypertension, smoking and presence of MS or abnormal plasma lipid levels.[6,15,23-25]

Hyperglycemia is related to inflammation because of formation of advanced glycation end products (AGEs), which can lead to synthesis of IL-6, to activation of macrophages and to oxidative stress, which culminates in production of CRP, contributing to inflammation. Advanced glycation end products are derived from non-enzymatic reaction of glucose (in addition to oxidation of glucose) with proteins, lipids and nucleic acids, leading to oxidative stress and subsequent development of inflammatory and thrombotic processes. These conditions partially explain the relationship between DM and cardiovascular events. Advanced glycation end products also increase production of reactive oxygen species, compromising the function of antioxidant systems. Notwithstanding, AGEs are also produced in situations of oxidation, contributing to the chronic complications of DM. Their activity starts when they bind to the receptor for AGE (RAGE). This interaction leads to activation of JAK (Janus Kinase), ρ-GTPase, extracellular signal-regulated kinases and p38 mitogen-activated protein kinase. Interaction with the receptor also activates NADPH oxidases and increases intracellular formation of reactive oxygen species, which, in turn, increase formation of AGEs. There is also activation of NF-κB (nuclear factor - *kappa β*), which activates transcription of proinflammatory cytokines, such as IL-6 and monocyte chemotactic peptide-1 (MCP-1), intensifying the inflammatory response.[26-28]

Elevation of CRP is also part of the genesis of atherosclerosis and even modest increases can be predictive of cardiovascular events. Their levels approximately triple in the presence of risk of peripheral vascular diseases. Therefore, CRP can predict cardiovascular events, since it represents an independent risk factor for developing CVD. Some studies show that since they are related to multiple risk factors for cardiovascular diseases, particularly visceral fat, irrespective of the level of dyslipidemia, people with elevated CRP are at high risk of acute myocardial infarction.[6,29,30]

In conclusion, it can be inferred that CRP levels are associated with cardiovascular morbidity and are strongly related to a number of components of the MS; but there is a stronger correlation with adiposity than with insulin sensitivity or glycemic control. Notwithstanding, certain limitations should be taken into account, since serum CRP levels can increase transitorily for 2 to 3 weeks after severe infections, traumas or acute ischemic events.[6,20,22,23,31]

Testing CRP can even be important for adults with Low Density Lipoprotein (LDL-c) results that are not a cause for concern and the result is predictive of whether or not statins should be prescribed. This indication is based on the recommendations of the JUPITER study (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), which demonstrated possible beneficial effects of these drugs in apparently healthy people who have LDL-c < 130mg/dL and CRP levels over 2 mg/dL.[32,33] It should be remembered that elevated CRP-us is an independent risk factor for cardiovascular diseases.[17]

Metabolic syndrome, adipose tissue and aspects of inflammation

Metabolic system has polygenic inheritance, in which accumulation of abdominal fat plays a fundamental role in the high morbidity and mortality. This deposition of abdominal fat has a strong relationship with development of IR and consequent fasting hyperglycemia. As already mentioned, IR and increased waist circumference are accompanied by increased release of proinflammatory mediators, particularly in adipose tissue (AT), in the liver and in skeletal muscle.[17,34,35]

Adipose tissue itself is also related to inflammation and it is a long time since it was still considered a mere means of storing triacylglycerides and it is now known to be an endocrine organ that produces a wide range of adipokines such as IL-6, adiponectin, leptin, plasminogen activator inhibitor-1 (PAI-1) and TNF-α. Imbalances in the production of the chemical mediators modifies several factors associated with cardiovascular diseases (energy balance, insulin sensitivity, arterial blood pressure, lipid metabolism, immunity and homeostasis), promoting the development of a low intensity inflammatory process, which gives rise to a local immunoresponse characterized by an increase in inflammatory biomarkers, such as CRP and oxidative chemical species.[36,37]

When a person has a BMI defined as characterizing obesity (greater than or equal to 30 kg/m^2), preexisting adipocytes in AT expand, primarily through storage of triacylglycerides. In lean people, liberation of anti-inflammatory adipokines is observed, reflecting good metabolic, oxidative and inflammatory control. In contrast, in moderately obese people, a different secretion pattern can be observed, with initial release of proinflammatory adipokines such as IL-6, IL-18, resistin, lipocalin-2 and TNF-α, among others, but small quantities of anti-inflammatory adipokines such as adiponectin are also still released. Increased inflammation, reduced metabolic control and changes to vascular endothelium can be observed. In people already considered obese, release of anti-inflammatory adipokines ceases and release of proinflammatory adipokines increases, leading to an exacerbated increase in inflammation, serious loss of metabolic control and severe endothelial dysfunction.[38]

The increase in AT can attain a proportion at which mediators are produced that interfere with utilization of the glucose in the diet, leading to IR. The consequence of this is a low intensity chronic inflammatory process. This process, which has a localized onset, has systemic effects because of release of countless adipocytokines. During an initial phase it can be said that the proinflammatory mediators are released by the expanded adipocytes, but the intensification of AT expansion is also the result of infiltration by macrophages.[39]

The state of obesity induced by the diet can alter the secretion pattern of the AT, changing the state of alternatively activated macrophages, termed M2 macrophages, to the state of classically activated macrophages, known as M1. The M2 macrophages have an anti-inflammatory cytokine secretion profile, whereas the M1 macrophages have a proinflammatory secretion profile. This state change leads to secretion of chemotactiles such as TNF-α, contributing further still to the inflammatory process.[36,39-42]

In addition to the macrophages, production of T killer cells, mast cells and immune system cells is also increased in AT in the obese state and contribute to the proinflammatory condition of this environment. Under these circumstances there is also a reduction in the ratio of CD8+ to Treg CD4+ cells (regulatory CD4+ T cells) in the AT. Adipose tissue of obese people also has fewer Treg CD4+ lymphocytes, which have an immunosuppressive action and are recognized as secreting anti-inflammatory cytokines, which, in turn, inhibit macrophage migration. This supports the belief that the increased AT in obesity and overweight is directly associated with activation of the innate immune system, which coordinates inflammatory responses.[39]

Both IL-4 and IL-13 primarily exhibit pro-M2-pattern properties, whereas IFN-γ (interferon gamma) and GM-CSF (Granulocyte-macrophage colony-stimulating factor), which are also secreted by AT, are related to activation of the M1 pattern. Polarization of macrophages is in turn very closely related to a transition to a T-helper cell 1 (T_H1) or T-helper cell 2 (T_H2) pattern and changes in Treg activity. In obesity, eating a high fat diet activates T_H1 proinflammatory cells and M1 macrophages, with consequent production of IFN-γ, TNF-α and IL-12, while differentiation of virgin T cells to T_H2 cells (which secrete IL-4, IL-10 and IL-13) is reduced along with Treg activity.[36]

Although more studies are needed on the relationship between release of mediators in obesity and MS, it is known that IL-2, IL-6 and TNF- α are greatly elevated in obese people, while IL-4, IL-5, IL-12, IL-13 and IFN-γ are elevated in MS. There are studies showing that both generalized and central obesity significantly increase IL-5, IL-10, IL-12, IL-13 and IFN-γ. In generalized obesity, TNF-α levels are also high and, as a consequence, so are its inflammatory

effects. Another interesting finding is that increases in IL-4, IL-12 and IL-13 levels are observed in obese people who do not engage in physical activity.[36,39,43-45]

Therefore, the secretion profile of the AT can contribute to the metabolic disorders associated with obesity and these, in turn, result in a proinflammatory metabolic state, with a direct association with endothelial dysfunction and development of CVD.[46,47]

Atherosclerosis: some inflammatory features

Just as great strides have been taken over recent years with respect to knowledge about the endocrine role of AT, what is known about atherosclerosis has also evolved. For a long time the process was considered to be simply the result of build-up of lipids on the artery wall. However, over the last two decades, the growing research interest in studies in the vascular field has resulted in countless details related to the initial definition of atherosclerotic disease.[22]

The risk factors for formation of atherogenic plaques are related to lifestyle (atherogenic diet, inactivity, obesity, smoking and alcoholism) and other factors such as IR (or DM), arterial hypertension, hypertriglyceridemia, low HDL-c and oxidized LDL-c levels, and abnormal homocysteine, CRP-us, coagulation factor VII, plasminogen tissue activator and PAI-1 levels.[24,48]

Atherosclerosis is a CVD that is characterized by chronic inflammation of the artery wall and consequent formation of plaques, in addition to activation of several different cells of the innate immune system that are directly involved in genesis of deposition of the substances that comprise these plaques, primarily lipids, calcium and inflammatory cells. Atherosclerotic lesions are actually a series of highly specific cellular and molecular responses that are, by their nature, essentially inflammatory. In vulnerable patients, atherosclerosis develops via the influence of conditions that traumatize the endothelium, such as aging, smoking, systemic arterial hypertension, hypercholesterolemia, diabetes and obesity itself. These factors damage the endothelium and stimulate a proliferative/inflammatory reaction on the vascular wall. It is interesting that the relationship between risk factors has proven to be one of multiplication, and not of simple addition.[24,49]

In addition to increasing the risk of hypertension and DM2, the inflammatory process also provokes an increase in cytokine levels, which is directly related to recruitment of monocytes and infiltration of macrophages to the artery wall, with formation of plaques. Since these are slow and asymptomatic processes, the signs can take years to manifest; which is why the use of markers such as CRP-us is an important indicator. Presence of hypertension is also related to increased oxidative stress and consequent triggering of the inflammatory process in the walls of blood vessels.[24,29,50]

Hyperglycemia and development of DM are related to development of atherosclerosis via different mechanisms. One widely studied mechanism, perhaps the most studied, is that related to AGEs, which are linked with genesis of plaques, but can also accumulate in lesions. These products are mediators of endothelial injury, inflammation and lipid abnormalities, such as, for example, oxidation of LDL-c, which is highly atherogenic in this state because the macrophages involved in formation of the plaques have scavenger receptors for uptake of oxidized LDL-c and it has been observed that over time these macrophages become foam cells. The AGEs also stimulate expression of the MCP-1 gene, the intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and PAI-1. These events are followed by recruitment of inflammatory cells to the vessel walls. The AGEs also exert atherogenic effects by interfering in production of nitric oxide (NO), by reducing the activity of nitric oxide synthase. Nitric oxide plays an important role in endothelial regeneration, in vasodilation and in inhibition of platelet aggregation and so a deficiency of NO production promotes endothelial dysfunction and formation of plaques.[28,51]

An increase in visceral adipose tissue is directly linked to a rise in CRP levels and this association with CRP levels is directly proportional with the accumulation of visceral adipose tissue and the components of the insulin resistance syndrome. This relationship allows for direct correlation of the increase of visceral adipose tissue, playing a fundamental role in development of atherosclerosis. Therefore, the insulin resistance syndrome, increases in BMI (obesity, primarily visceral) and atherosclerosis are intimately related and can be determinant of the exacerbated response of vascular endothelium inflammatory events. Furthermore, CRP also stimulates expression and activity of PAI-1 in endothelial cells. This situation is exacerbated in the presence of hyperglycemia, since more mediators of inflammation are created. Elevation of PAI-1 levels in DM and MS is also the result of stimulation of monocytes and of endothelial cells by CRP, which are significantly elevated in these situations. This protein also induces expression of several other molecules, such as ICAM-1, VCAM-1, selectins and MCP-1. In monocytes, CRP-us results are also related to stimulation of production of thromboplastin, which

is an extrinsic activator of the coagulation cascade. C-reactive protein also acts to regulate production of nitric oxide in vascular endothelium and coordinates production and secretion of many proinflammatory cytokines by adipocytes.[6,20,31,35,52]

Published data show that increases in the levels of fibrinogen, fibrin and products of fibrinogen degradation are related to formation and development of atheromatous plaques. Fibrinogen plays a fundamental role in formation and growth of atheromatous plaques and is also a precursor of mural thrombi. It is also involved in mechanisms of platelet aggregation and endothelial cell damage, both of which play a role in formation of thrombi. Elevated fibrinogen levels in combination with the presence of other risk factors, such as hypertension, smoking, inactivity, dyslipidemia and IR, increase the risks of formation of thrombi. In common with CRP-us results, fibrinogen levels are considered an independent risk factor for CVD. The increases in fibrinogen, fibrin and products of fibrinogen degradation can lead to sclerosis of the vessel walls and to narrowing of the lumen, in addition to contributing to plaque rupture.[52-54]

Another marker of inflammation is CD40, which is expressed by T lymphocytes and by activated platelets, in addition to being expressed by endothelial cells on the surfaces of smooth muscle cells and in macrophages. The soluble ligand of this marker, sCD40L, can also be found in the form of a transmembrane protein and elevated sCD40L levels can also be indicative of an increased risk of CVD.[42]

Exacerbation of the inflammation increases the instability of atherosclerotic plaques, increasing vulnerability to recurrent coronary events. This instability leads to obstruction of small vascular compartments or even to formation of thrombi, which in turn can lead to more severe obstructions. Degradation of the fibrous cap by the action of matrix metalloproteinases (MMPs) and neovascularization of plaques are both processes that have been implicated in plaque instability. The matrix metalloproteinases MMP-2 and MMP-8 are both directly involved in this instability, as is VEGF (vascular endothelium growth factor). In addition to contributing to revascularization through degradation of matrixes, MMP-2 has the capacity to degrade glutin protein type IV. In turn, MMP-8 is primarily linked with degradation of laminin, fibronectin, elastin and glutin protein types I-IV. This metalloproteinase activates MMP-2 and also regulates expression of IL-1b, IL-8, CD2, CD4, CD8 and TNF-α, aggravating inflammatory events.[54-56]

In view of the above, it can be stated that inflammation plays an indispensable role in genesis and progression of atherosclerosis. Another important factor (already mentioned in connection with AGES) is NF-κB, which induces expression of several chemical mediators of inflammation, contributing to formation and development of atherosclerotic plaques. It should be pointed out that, in common with NF-κB, the effects of mitogen-activated protein kinase (MAPK) and protein kinase C (PKC) have been linked as signalers of inflammatory events. Studies show that fibrinogen, fibrin and products of fibrinogen degradation can regulate the activity of MMP-2 and VEGF, by activation of PKC and MAPK via the influence of NF-κB.[54,57-59]

Several authors have shown an association between CRP and MS levels and indicators of atherosclerotic plaques. Higher plaque scores and greater thickness of the intima and media of vessels have been observed in people with MS. These parameters can also exhibit a positive correlation when CRP levels are higher.[6,15,60] Some authors have detected positive relationships between glycemia, the Castelli risk index 1 (TC/HDL-c), arterial blood pressure and body composition, when compared with carotid intima-media thickness, showing that the risk factors for MS are not only associated with the onset of development of atherosclerotic plaques, but also with progressive increases in them.[61]

As such, emergent risk factors, such as CRP-us, should also be monitored in order to achieve a more effective approach to estimation of the risks of coronary events, since atherosclerosis is an expensive condition and its complications are among the principal causes of death worldwide.

It is therefore necessary to develop effective prevention programs targeted at encouraging healthier eating patterns and increasing physical activity. It is also necessary to treat dyslipidemia, hypertension, DM and obesity, and to discourage consumption of cigarettes and alcohol.[17,52]

CONCLUSIONS

Considering the importance of controlling risk factors and of stratification of these risk factors in terms of associations between components of the MS, it is important to delineate prognostic factors, adopting them as a tool for daily use in prevention of CVD. This is in addition to analysis of the traditional anthropometric, biochemical and lifestyle parameters and should take into account inflammatory markers, such as CRP-us. This marker is associated with cardiovascular morbidity and has robust associations with many components of the MS. It should also be

considered that adoption of measures for intervention should start in childhood, so that new habits will last into adulthood, thereby increasing not only life expectancy, but also quality of life. Therefore, in addition to pharmaceutical treatments, multidisciplinary interventions are needed if the triad of metabolic syndrome, atherosclerosis and inflammation is to be separated.

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