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Oxidative stress in the pathophysiology of metabolic syndrome: which mechanisms are involved?

Estresse oxidativo na fisiopatologia da síndrome metabólica: quais mecanismos estão envolvidos?

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ABSTRACT

Metabolic syndrome (MS) is a combination of cardiometabolic risk factors, including obesity, hyperglycemia, hypertriglyceridemia, dyslipidemia and hypertension. Several studies report that oxidative condition caused by overproduction of reactive oxygen species (ROS) plays an important role in the development of MS. Our body has natural antioxidant system to reduce oxidative stress, which consists of numerous endogenous and exogenous components and antioxidants enzymes that are able to inactivate ROS. The main antioxidant defense enzymes that contribute to reduce oxidative stress are superoxide dismutase (SOD), catalase (CAT) and gluthatione peroxidase (GPx). The high-density lipoprotein cholesterol (HDL-c) is also associated with oxidative stress because it presents antioxidant and anti-inflammatory properties. HDL-c antioxidant activity may be attributed at least in part, to serum paraoxonase 1 (PON1) activity. Furthermore, derivatives of reactive oxygen metabolites (d-ROMs) also stand out as acting in cardiovascular disease and diabetes, by the imbalance in ROS production, and close relationship with inflammation. Recent reports have indicated the gamma-glutamyl transferase (GGT) as a promising biomarker for diagnosis of MS, because it is related to oxidative stress, since it plays an important role in the metabolism of extracellular glutathione. Based on this, several studies have searched for better markers for oxidative stress involved in development of MS.

Key words: metabolic syndrome X; reactive oxygen species; antioxidants; HDL cholesterol; gamma-glutamyl transferase.

INTRODUCTION

Metabolic syndrome (MS) is a conjunction of cardiometabolic risk factors, including obesity, hyperglycemia, hypertriglyceridemia, dyslipidemia (high levels of cholesterol linked to low-density lipoprotein [LDL-c] and low level of cholesterol associated with high-density lipoprotein [HDL-c]) and hypertension. However, a better understanding of the mechanisms that correlate MS with increased cardiovascular risk is required[1].

MS diagnosis, according to I Brazilian guidelines on diagnosis and treatment of metabolic syndrome (2005), which adopted the definition of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII), 2001[2], is based on the presence of at least three of the following components: waist circumference (WC) > 102 cm in men and > 88 cm in women; triglycerides (TG) ≥ 150 mg/dl, or use of medication to treat hypertriglyceridemia; HDL-c < 40 mg/dl in men and < 50 mg/dl in women, or drug use for low HDL-c; fasting blood glucose levels ≥ 110 mg/dl, or use of medication to treat hyperglycemia; systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg blood pressure (BP), or on antihypertensive medication use[3]. The Joint Interim Statement (JIS) (2009) represents an attempt to integrate MS diagnostic criteria most widely used in the international literature and determines the adjustment of blood glucose and WC cutoff points. Therefore, such classification differs from NCEP-ATPIII while considers as MS component fasting blood glucose levels ≥ 100 mg/dl and adjusts WC according to ethnicity (WC ≥ 90 cm for men and ≥ 80 cm in women, for the Latin American ethnicity). The values for HDL-c, TG and BP remain the same[4].

Althought insulin resistance is not considered in the diagnosis of MS, it is a common condition, and several clinical

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manifestations of the syndrome[5] are explained from this dysfunction. Furthermore, the release of adipokines by adipose tissue may affect insulin signaling in liver, skeletal muscle and blood vessels[1]. The increased visceral adiposity appears to be related to the establishment of insulin resistance and low-grade chronic proinflammatory state of patients, through inflammatory cytokines release[6].

Several studies report that oxidative condition caused by the overproduction of reactive oxygen species (ROS) plays an important role in the development of MS and in appearance of related symptoms, including obesity, systemic arterial hypertension (SAH), atherosclerosis, and type 2 diabetes *mellitus* (T2DM)[7-11]; the increase of oxidative stress associated with decreased antioxidant defenses can lead to metabolic upsets and changes in cell signaling[10]. In MS, the pro-oxidative state may impair insulin signal pathway and lead to harmful action on the endothelium. Thus, we can observe that this condition causes insulin resistance and promotes acceleration of the atherogenic process[7, 10, 12]. The increased oxidative stress associated with insulin resistance appears to be a major cause of accelerated atherosclerosis[13] and also may lead to development of T2DM[10].

The relationship between degrees of oxidative stress and the number of MS components is also valid. Sánchez-Rodriguez *et al*. (2010) report that there is a greater risk of exacerbation of oxidative stress in individuals who have more MS components[14]. Thus, we suggest that treatment for the reduction or disappearance of each component should reduce the pro-oxidant status in these patients.

Intervention studies show that lifestyle change, balanced diet, and exercise positively affects oxidative stress in patients with MS and can decrease the chances of developing other chronic diseases associated with the syndrome and hyperoxidative condition[10]. The molecular mechanism for generating these improvements is still not well understood, as well as the relationship between MS and oxidative stress markers is not consistent. Several studies seek to establish the best markers of oxidative stress, its variations in different populations, gender and age, in addition to variations suffered due to nutrition and external factors[9].

ANTIOXIDANT ENZYMES

The natural antioxidant system consists of numerous endogenous and exogenous components (acquired by diet) and antioxidant enzymes, which are able to inactivate ROS. The main enzymes participating in the oxidative stress reduction process are: superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). SOD function is catalyse the dismutation of superoxide anions ($O_2^{\bullet -}$) into hydrogen peroxide (H_2O_2), which is less reactive than the previous species. H_2O_2 also has oxidizing ability and easily diffuse across cell membranes and cytosol. To reduce this action, the presence of CAT and GPx enzymes is required, which are able to neutralize this reactive species, producing water (H_2O) and molecular oxygen[9] (**Figure**).

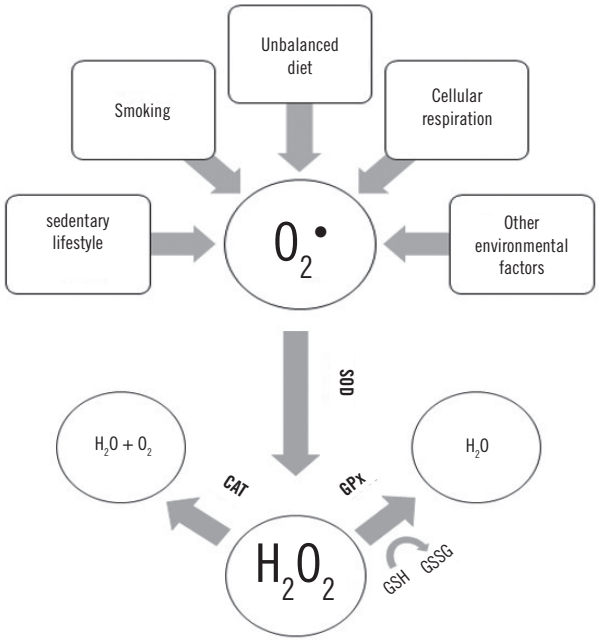

FIGURE – *Generation and neutralization of ROS by activity of antioxidant enzymes SOD, CAT and GPx leading to transformation of GSH into GSSG*

ROS formation is induced by cellular respiration and external factors, such as physical inactivity, smoking and unbalanced diet. In order to reduce oxidative stress, SOD catalyzes the dismutation of superoxide anion ($O_2^{\bullet -}$) into hydrogen peroxide (H_2O_2). CAT and GPx play an important role converting this reactive species into water (H_2O) and molecular oxygen (O_2). Modified from Roberts, 2009.

ROS: reactive oxygen species; SOD: superoxide dismutase; CAT: catalase; GPx: glutathione peroxidase; GSH: reduced glutathione; GSSG: oxidized glutathione.

SODs are part of a family of ubiquitous enzymes and three isoenzymes present in the body of all mammals can be described: SOD1 (or CuZn-SOD), mainly found in the cytoplasm and nucleus of cells; SOD2 (or Mn-SOD), found in mitochondria; and SOD3 (EC-SOD), present in the extracellular environment[15]. The SOD isoenzymes performance prevents the accumulation of $O_2^{\bullet -}$, since this superoxide anion may react with nitric oxide ($NO^{\bullet}$) to form peroxynitrite ($ONOO^-$) and thus, preventing the oxidant effect[16]. These enzymes are the frontline defense against oxidative stress and, its altered activity has been related to the presence of MS in several studies[17-21].

Isogawa *et al*. (2009) showed that SOD activity is decreased in patients with cardiovascular disease (CVD), suggesting that this decrease is related to blood vessel aging. Obese individuals also showed negative relationship with enzymatic activity of SOD. In individuals with MS, decreased enzymatic activity was inversely proportional to the number of components of the syndrome. In contrast, it was observed that a slight increase in SOD activity is associated with plaque formation in the carotid arteries from platelet aggregation[19]. Nakao *et al*. (2010) demonstrated that the ingestion of hydrogen-rich water, for eight weeks, increased 39% the levels of SOD enzyme in subjects with MS; hydrogen-rich water ingestion can be regarded as an attempt to decrease ROS[22].

GPx is a tetrameric enzyme containing selenium. It is not only responsible for the decrease of H_2O_2, but also transforms lipoperoxide and other organic hydroperoxide into their corresponding hydroxylated compounds, which are less reactive. For this, GPx uses reduced glutathione (GSH) as a proton donor (H^+), which, after the reaction, becomes oxidized glutathione (GSSG)[10]. GPx is found in the cytoplasm and in the mitochondrial matrix, and there is also an insoluble form that is associated with the membrane that acts in the neutralization of lipid hydroperoxides[16].

According to Chen *et al*. (2012), GPx has significantly lower activity levels in individuals with MS, associated with increased oxidative stress and proinflammatory state. The decrease in GPx activity was also associated with increased body mass index (BMI) and WC. SOD and CAT activity levels were also reduced in these individuals[17], reinforcing the establishment of pro-oxidant condition.

Yubero-Serrano *et al*. (2013) study demonstrated the relations between the activities of antioxidant enzymes in accordance with the number of MS components. The authors found that the SOD activity was higher in subjects with three, four or five MS components, when compared with the group that had only two components of the syndrome. Furthermore, they reported that insulin resistance and WC have been considered independent predictors of SOD activity. Regarding GPx activity in plasma, they found similar results. Individuals with four or five components showed increased enzyme activity compared with those who had two or three components. From these results, we can argue that, in contrast to what has been described above, the mechanism used to prevent oxidative damage to cells would be to "strengthen" the body's frontline of antioxidant defense, which would result in increased activity of antioxidant enzymes in individuals with more severe metabolic changes[21].

It is suggested that the increased production of ROS is associated with high-fat intake, one of the contributing factors to the onset of MS and other diseases, such as diabetes, hypertension, obesity and atherosclerosis. A high-fat diet can lead to decreased GPx antioxidant enzyme activity, and this reduction is far greater among MS individuals[23]. Perez-Martinez *et al*. (2010) found that high-fat diets may decrease the plasma levels of SOD, observing a lower H_2O_2 concentration in individuals who have adopted this type of diet. Also noted increased GSH/GSSG ratio, which indicates low GPx activity[24]. Cardona *et al*. (2008) suggest that this association is observed together with hypertriglyceridemia, raising the hypothesis that oxidative stress increased after fat intake, occurs due to production of ROS by mitochondria-dependent induction, which requires mitochondrial fatty acid uptake[25].

CAT, together with GPx, has the function of inactivating peroxides also by H^+ ion donors to facilitate the reduction of organic hydroperoxides. It is present at higher levels in peroxisomes and vesicles attached to the plasma membrane, and is still found in significant levels, mainly in the liver and erythrocytes. Vávrová *et al*. (2013) also measured the activity of antioxidant enzymes in patients with MS and, together with GSH and plasma paraoxonase 1 (PON1), CAT levels were reduced, and this condition has been described in patients with obesity, hypertension, and insulin resistance. Unlike other studies, this group demonstrated an increase in SOD1 activity, suggesting that there is an increase of H_2O_2 levels, which would lead to erythrocytic damage[26].

OVERPRODUCTION OF REACTIVE OXYGEN SPECIES

The production of ROS is related to the formation of free radicals, and are generated mainly by the production of superoxide anion ($O_2^{\bullet -}$). Therefore, $O_2^{\bullet -}$ is strongly associated to the oxidative stress, since its overproduction can cause cell dysfunction and biological alterations, besides causing atherosclerosis, diabetes *mellitus* and insulin resistance[22, 27].

The action of xanthine oxidase can also lead to overproduction of free radicals, since this enzyme catalyzes the conversion of hypoxanthine into uric acid and $O_2^{\bullet -}$. Feoli *et al*. (2014) found a significant correlation between the activity of xanthine oxidase and the components of MS. In addition, they observed that C-reactive protein levels were associated with xanthine oxidase activity. Thus, it is justified by: a) the increasing number of reports that demonstrate the growing association between MS, pro-oxidant status and chronic low-grade inflammation; b) the pharmacological treatment with inhibitors of this enzyme, such as allopurinol, that can be administered for the prevention of cardiovascular diseases (CVD)[18].

Although physical activity is related to improved cardiovascular function, changes in body composition, blood pressure and other organism positive changes, it has been reported that physical exercise is related to production of free radicals, reflecting undesirably contribution to the organism. The production of free radicals related to physical exercise may be due to increased oxygen consumption, associated with increased circulating catecholamines. This effect is also associated with lipid peroxidation, a process that is due to fatty acids oxidation in plasma membranes, generating mainly alkyl radical ($L^{\bullet}$) and peroxyl radical ($LOO^{\bullet}$). The alkyl radical reacts with O_2 to form the peroxyl, which can be combined with other similar radicals and cause damage to the membrane structure and, consequently, adverse effects on the transport of substances and ions[28].

Another major product of lipid peroxidation is malondialdehyde (MDA), a highly reactive dialdehyde, formed from the reaction of the lipid hydroperoxide (LOOH) with alkoxyl radical ($LO^{\bullet}$), which can cause changes in biological structures[27]. Skalicky *et al*. (2009) demonstrated that obese patients have higher levels of MDA and free radicals, when compared to normal weight individuals. This suggests that obesity may be involved with increased products of lipid peroxidation[28]. Demircan *et al*. (2008) observed that MDA levels are higher in MS patients, asserting the hypothesis that oxidative stress is involved in the pathogenesis of this syndrome[29]. Moreover, oxidative stress plays an important role in the development of CVD and diabetes by imbalance of ROS production, and has close relationship with inflammation. It was observed that the lipid peroxidation are increased in patients with MS and it is directly related with the development of atherosclerosis together with establishment of pro-inflammatory state[21, 30]. Likewise, diabetes can be regarded as a pro-oxidant state caused by increased lipid oxidation[31].

Another major source of ROS is nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, an enzyme present in renal and cardiovascular tissue, which catalyzes a single-electron transfer to O_2, producing superoxide anion. The increase of its expression is associated with elevated levels of ROS and, consequentely, with oxidative stress[11, 32]. The pro-inflammatory state and hyperglycemia, both observed in MS, increase the production of ROS, which results in overactivation of o NADPH oxidase, resulting in production of $O_2^{\bullet-}$ and decreased $NO^{\bullet}$ bioavailability[8].

In a study performed in human mononuclear cells, it was observed that the increase of NADPH oxidase activity in vascular endothelial cells is associated with the development of atherosclerosis[16]. Apocynin (4-hydroxy-3-methoxyacetophenone) is a NADPH oxidase inhibitor. Oral administration positively regulates the SOD, associating it to decrease of oxidative stress by suppressing of NADPH oxidase, thus reducing the current level of ROS. Studies have shown in experimental models of Parkinson's disease that apocynin may be used in the treatment of insulin resistance caused by increased ROS[33].

Youn *et al*. (2014) study observed in animal models increased ROS production associated with development of obesity and MS, probably due to regulation of vascular inflammation and an increase in adipogenesis. The researchers reported increased T lymphocyte infiltration in adipose tissue and increased levels of monocyte chemotactic protein-1 (MCP-1) in mice fed high-fat diet. As many obese patients do not maintain a balanced diet, the presence of oxidative stress associated with underlying medical conditions, such as hypertension and hypercholesterolemia, may contribute to the development of MS[11].

PRODUCTION OF DERIVED REACTIVE OXYGEN METABOLITES (d-ROMs)

The d-ROMs have been studied as oxidative stress markers and can be quantified by measuring the levels of organic hydroperoxide compounds, such as proteins, lipids, nucleic acids and others. These metabolites have been associated with C-reactive protein and then related with high risk of developing CVD and MS. Studies show that there is a greater relationship between inflammation and oxidative stress in patients with MS, compared to those individuals without the syndrome[34].

Kotani *et al*. (2011) used tests that measure d-ROMs to investigate the association between oxidative status and MS in asymptomatic Japanese men. They reported that individuals with MS have d-ROMs levels significantly higher, compared to control group. Fat and ROS that are originated from the adipocytes of obese individuals and individuals with unfavorable lifestyle, are associated with increased NADPH oxidase concentration and suppression of antioxidant enzymes. These pathways may directly lead to the genesis/development of MS by cell damage and, indirectly, by disrupting of adipokines production. In the study, the authors also observed a significant increase of d-ROMs levels in the group of patients with MS under the age of 60 years, compared to individuals of the same category without the syndrome. No difference was observed between d-ROMs levels in the absence or presence of MS when age was over 60 years. It was also noted that older ones showed higher d-ROMs levels when compared with younger ones. Due to the fact that aging is itself a pro-oxidant condition, it can become confusing or difficult to distinguish the resulting oxidative state of pathologies in the elderly. Previous studies have established a weak relationship between MS and CVD

in elderly populations, whereas others showed significant positive relationship. Consequently it is required more research involving different populations, using different markers related to oxidative stress[9].

It was also confirmed, in female population, the direct relationship between the hyperoxidative state and the presence of MS. The increased oxidative capacity by d-ROMs was associated with the amount of MS components present, and it was observed that the more factors contributing to the MS development present in the individual, the greater the oxidizing ability of d-ROMs[9]. Thus, it is suggested that the pathophysiology of MS is closely associated with increased oxidative stress, and that the measurement of derivatives of oxygen metabolites can be helpful in identifying and monitoring the course of the disease[35].

HDL-c AND OXIDATIVE STRESS

HDL-c has been considered an important plasma antioxidant defense system. It acts by preventing the oxidation of LDL-c, protects against cytotoxicity induced by LDL-c and also has anti-inflammatory properties, such as supression of cytokines-induced endothelial adhesion molecules function[12].

The hypothesis of atherosclerosis pathogenesis (Williams and Tabas, 1995) postulates that cholesterol-rich lipoproteins, primarily low-density lipoprotein (LDL-c) molecules, are trapped in the arterial wall and oxidized under the action of resident cells. The oxidation of the arterial intimal layer results of the local oxidative stress, which is the imbalance between pro- and anti-oxidants, in favor of the former. Cellular oxidative systems *in vivo* include myeloperoxidase (MPO), NADPH oxidase, NO synthase, and lipoxygenase. These enzymes produce a variety of reactive species of chlorine, nitrogen and oxygen as one or two electrons. High density lipoprotein (HDL-c) can protect LDL-c and other lipoproteins from oxidative stress induced by both free radical species, since it powerfuly inhibits the accumulation LOOH in LDL-c. LOOH removal from LDL-c (or cells), mediated by HDL-c, is a crucial step in protecting the oxidative damage induced by free radicals. HDL-c particles are the major LOOH transporter in human plasma, working effectively as ''remover'' of oxidized lipids, because they can accumulate them in their particles when their inactivation capacity is overloaded. Therefore, the accumulation of oxidized lipids in HDL-c most probably results not only from its transfer from LDL-c, but also from remnant triglyceride-rich lipoproteins and/or arterial wall cells[36].

Enzymatic components greatly contribute to the antioxidant properties of HDL-c, including PON1, platelet-activating factor acetylhydrolase (PAF-AH) and lecithin-cholesterol acyltransferase (LCAT), all acting in the hydrolysis of oxidized phospholipids. In addition, HDL-c carries GPx, which detoxify LOOH, reducing them to the corresponding hydroxides[36].

The antioxidant activity of HDL-c may be attributed, at least in part, to PON1 activity. This is a pleiotropic enzyme, synthesized in the liver[12], that has at least three isoforms previously identified (PON1, PON2, PON3), all apparently related to the antioxidant action[13]. PON1 is the most studied and has intense antioxidant activity associated with HDL-c. It is a glycoprotein named after one of its functions: the ability to hydrolyze toxic exogenous organophosphorus compounds, such as insecticide paraoxon. Other functions include protection against oxidative stress and lipid peroxidation, contribution to processes of innate immunity, detoxification of reactive molecules, and drug bioactivation (for example, clopidogrel)[12, 36]. Among all these functions, the metabolism of pro-inflammatory lipids formed during the oxidation of LDL-c plays an important role against atherogenesis[13]. The biologically relevant substrates of this hydrolytic enzyme have not been clearly determined; apparently the main are lipophilic lactones[37]. PON1 protects lipoproteins from lipid peroxidation through the degradation of oxidized cholesteryl esters and phospholipids[7, 12].

Some authors discuss other mechanisms which associate PON1 with the reduction of oxidative stress. The enzymatic activity was associated with increased antioxidant activity of monocytes/macrophages, with the ability of HDL-c to remove cholesterol from macrophages, the prevention of LDL-c oxidation mediated by macrophages, and the modulation of myeloperoxidase activity, activating these enzymes and decreasing lipid peroxidation. Thus, the activity of this enzyme is involved in pathological processes, which are related to the pro-oxidant state, such as diabetes, MS, and renal dysfunction[36].

A recent study demonstrated that, in contrast to healthy patients, HDL-c in patients with CVD has no anti-inflammatory effects on the endothelium and does not stimulates its repair, since it failure to induce endothelial production of $NO^{\bullet}$. What occurs is the reduction of PON1 activity, which apparently leads to inhibition of eNOS (constitutively expressed NO synthase-isoenzyme) and subsequently the loss of anti-inflammatory and stimulating endothelial repair action of HDL-c[7, 12].

Sentí *et al*. (2003) were the first to establish a relationship between PON1 activity and MS. They found that serum levels of PON1 activity were significantly lower in subjects with MS, compared to those of subjects not affected by the syndrome. In addition, they observed that the more associated metabolic disorders present in the individual, the greater the decrease in enzyme activity. That is,

it is concluded that a greater degree of severity of MS is associated with progressive worsening of antioxidant/prooxidant balance, which is consistent with increased oxidative stress and the lower PON1 antioxidant ability[38].

Akçay *et al*. (2011) studied the relationship between CVD and PON1 in three different groups: i) subjects with MS, stable angina and CVD confirmed by angiography; ii) individuals with MS and normal coronary arteries observed on angiography; and iii) healthy individuals in the control group. PON1 activity was significantly lower in patients with MS, compared to the control group, which is consistent due to the increase of the oxidative stress in the syndrome, observed in several studies. In both groups with MS (with and without CVD), similar levels of PON1 activity were observed, which suggests that the disturbance of oxidative balance occurs even before the development of CVD[39].

Mackness *et al*. (2006) developed a remarkable study using a mouse model deficient in both leptin-receptor and HDL-c (MS model) underwent gene therapy using an adenovirus that promoted an overexpression of human PON1. The mouse showed an increase in PON1 activity, reduction in atherosclerotic plaque volume and on macrophages and oxidized LDL-c associated with plaque, and increase in the percentage of smooth muscle cells in the plaque. However, no changes were observed in total cholesterol and plasma triglycerides concentration. This exceptional study proved that PON1 adenovirus-mediated overexpression attenuated the development of atherosclerosis in the MS mouse model, which could be used as a possible tool against atherosclerosis in humans[13].

These findings support the concept that the cardiovascular impact of HDL-c is not simply related to its abundance. It is observed that HDL-c is only an integrative measure of lipoproteins, but not functional, so that new biomarkers that reflect the functionality of this lipoprotein are needed to better assess and manage cardiovascular risk[12]. Due to all these antioxidant/anti-inflammatory properties and its negative relationship with MS, some researchers invested in HDL-c as a marker of oxidative stress. Although this hypothesis has theoretical background, in practice it were observed some functional problems, and further studies over the functions of this lipoprotein are required.

GAMMA-GLUTAMYL TRANSFERASE (GGT) AS OXIDATIVE STRESS BIOMARKER IN MS

GGT, also referred to as gamma-glutamyl transpeptidase in the literature, is an enzyme found in cell membranes and in microsomal fractions involved in amino acids transport through cell membranes. Its function is to catalyze transfer of the peptides gamma-glutamyl group and other compounds to other peptides, amino acids and water[40]. Despite being found in greater quantities in the renal tissue, the enzyme present in the serum is mainly produced by the liver, but is also found in minor amounts in other organs[41].

Traditionally, GGT is considered a sensitive marker for hepatobiliary diseases as well as chronic alcohol consumption. However, GGT is not very efficient when necessary to discriminate different types of hepatopathy[41]. Additionally to diagnostic use, GGT presents relevant epidemiological significance[42], since recent studies show that elevated GGT serum levels, even within the normal range, could predict development of CVD, diabetes and hypertension, and it is associated with the risk of MS onset, regardless of the individual's alcohol consumption[43, 44]. However, the mechanisms that explain the relation between GGT serum level and such diseases are not completely understood. One possible explanation is that GGT may be closely related to the oxidative stress[45].

In recent decades, numerous evidence showed that GGT plays an important role in the catabolism of glutathione, the main intracellular "thiol" and antioxidant in most cells[45]. GGT is an enzyme responsible for the metabolism of extracellular GSH, promoting GSH hydrolysis and facilitating its reuse for intracellular synthesis. GSH is a substrate for GPx and glutathione S-transferases (GST), playing a key role in protecting against oxidative stress and detoxification/metabolism of endogenous and exogenous compounds, including carcinogens and drugs. Additionally, it also plays a role in regulating cell cycle, signaling and apoptosis[46]. However, this hydrolysis reaction also triggers production of ROS and LDL-c oxidation, this process is correlated with atherosclerotic plaques formation[45].

Increasing evidences in the literature correlate increased serum GGT with metabolic disorders, such as glucose disorders, hypertension, hypertriglyceridemia and decreased HDL-c serum levels[42]. Besides the influence of alcohol consumption, it is found that obesity has an important effect on the circulating levels of GGT, both conditions can promote a synergistic effect which contributes to the development of MS[47].

Some studies show that the risk of MS development may increase by 63% when compared to individuals included in the highest and lowest serum GGT category level, even whether those values are within the reference values. Reports indicate that circulating GGT levels are positively correlated with the risk of MS development, regardless individual alcohol intake. GGT may be a promising biomarker for the diagnosis of MS[44], and may be mainly associated with insulin resistance and WC[47]. This increase in GGT expression may occur due to an increased fat deposition in liver, which is considered one of the characteristics of the insulin resistance syndrome[42]. However,

more studies are needed to clarify the mechanisms that correlate GGT and insulin resistance, once both play a crucial role in the pathogenesis of MS.

GGT is also directly involved in ROS generation under physiological conditions, especially in the presence of iron molecules or other transition metals[45]. Thus, in the presence of large amounts of thiolate, iron can be released from carrier proteins, and by Fenton reaction, leading to the production of hydroxyl radicals ($OH^{\bullet}$)[46]. Thus, the circulating levels of GGT may reflect not only in the oxidative stress response, but also the generation and accumulation of oxidative stress[45]. Furthermore, GGT can predict inflammatory markers levels, including fibrinogen, C-reactive protein and F2-isoprostanes. Findings suggest that GGT may be expressed in atherosclerosis plaques, located with LDL-c oxidized and foam cells and, also, can contribute to the rupture of atherosclerotic plaques. The total leukocyte count can also increase along with the increase of circulating GGT levels, as leukocytes are the major components of the inflammatory process, and are recruited due to release of various cytokines, particularly interleukin-6 (IL-6) and interleukin-8 (IL-8). Therefore, GGT may also reflect a state of subclinical inflammation[42]. Besides the influence of hepatic fat and inflammation in the generation of oxidative stress, another factor which enhances this state is the production of cysteinylglycine, one of the GSH hydrolysis products by GGT, which can greatly promote the generation of free radicals through its interaction with iron[44].

It is suggested that elevated circulating GGT levels may be considered as markers of oxidative stress and subclinical inflammation, which are conditions inherent to the MS. Based on this evidence, it is speculated that insulin resistance, oxidative stress and inflammation may be the link between the increased GGT serum levels and the development of MS.

CONCLUSION

It is now known that several factors influence the pathogenesis of MS, and the establishment of pro-oxidant state has been increasingly related with its components, and, thereby, can increase the risk for developing symptoms and related chronic diseases, such as T2DM. The decrease in antioxidant capacity in MS individuals can be explained by overproduction of ROS and its metabolites (d-ROMS), by decreased activity of enzymes that neutralize these species (SOD, CAT and GPx) and the reduction of other antioxidants systems, such as PON1 activity.

Recently, GGT has been regarded as a promising biomarker for MS diagnosis, since its serum levels may reflect not only the oxidative stress response, but also its production and accumulation.

MS diagnostic criteria remain controversial and we can infer, using all the information provided, that the evaluation of oxidative condition of these patients should be present in assessing the risk of developing comorbidities associated with MS. To establish, in fact, the relationship between MS and oxidative stress, more studies should be conducted in different populations, in which must be made correlations between oxidative status and the presence of triggering factors and components of the syndrome.

RESUMO

A síndrome metabólica (SM) representa uma conjunção de fatores de risco cardiometabólicos, incluindo obesidade, hiperglicemia, hipertrigliceridemia, dislipidemia e hipertensão. Vários estudos reportam que a condição oxidativa causada pela superprodução de espécies reativas de oxigênio (EROs) desempenha importante papel no desenvolvimento da SM. Nosso organismo apresenta sistema antioxidante natural para diminuir o estresse oxidativo, o qual consiste em numerosos componentes endógenos e exógenos e enzimas antioxidantes que são capazes de inativar as EROs. As principais enzimas de defesa antioxidante que contribuem para o processo de redução do estresse oxidativo são a superóxido dismutase (SOD), a catalase (CAT) e a glutationa peroxidase (GPx). O colesterol associado à lipoproteína de alta densidade (HDL-c) também está relacionado com o estresse oxidativo por apresentar propriedades antioxidantes e anti-inflamatórias. A atividade antioxidante do HDL-c pode ser atribuída, pelo menos em parte, à atividade da paraoxonase 1 (PON1) sérica. Além disso, os metabólitos derivados de oxigênio reativo (d-ROMs) também se destacam como atuantes nas doenças cardiovasculares e no diabetes, pelo desequilíbrio na produção de EROs, tendo relação importante com a inflamação. Relatos recentes vêm apontando a gama-glutamiltransferase (GGT) como biomarcador promissor para diagnóstico da SM, pois esta se associa ao estresse oxidativo, uma vez que desempenha papel relevante no metabolismo extracelular de glutationa. Com base nisso, vários estudos vêm buscando melhores marcadores do estresse oxidativo e sua relação com o desenvolvimento da SM.

Unitermos: *síndrome X metabólica; espécies de oxigênio reativas; antioxidantes; HDL-colesterol; gama-glutamiltransferase.*

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