EDITORIAL

ADVANCED GLYCATION END PRODUCTS: POSSIBLE LINK BETWEEN METABOLIC SYNDROME AND PERIODONTAL DISEASES

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Received June 30, 2011 – Accepted November 23, 2011

On a planetary scale, Metabolic Syndrome (MetS) is the third cause of inability after malnutrition and nicotinism, even higher than water shortage and sedentariness. In the USA, the prevalence is estimated at over 25% of the population; in Italy, it involves approximately 25% of men and even 27% of women. These are very high figures, corresponding to approximately 14 million affected individuals. The prevalence is alarming and must not be underestimated, particularly in the dental field, where more than one patient out of four sitting in a dentist's chair is affected. The etiology of periodontal disease has not yet been clarified, and recently the idea to consider it as a multifactor pathology has been developed. Cofactors such as the formation of free radicals of oxygen (ROS), oxidative stress, lipid peroxidation, and formation of glycation end-products (AGEs) probably play an important role in the onset of periodontal disease. The AGEs are compounds physiologically produced by the cells. However, they accumulate and cause pro-inflammatory conditions, when the cellular clearance fails, or in hyperglycemic and oxidative states. All these conditions can be clinically summarized as Metabolic Syndrome. The purpose of this literature review is to establish a relationship between two pathologies with very high prevalence: Metabolic Syndrome and Periodontal Disorder. The literature seems to have clarified that MetS involves a pro-oxidation status, which induces AGE formation. AGEs play a very important role in the course and severity of periodontal diseases.

Metabolic syndrome

Metabolic Syndrome – MetS – (also known as X-syndrome, insulin-resistance syndrome, or Reaven's syndrome) refers to a clinical condition involving a high cardio-cerebrovascular (CVD) risk, which includes a number of risk factors and symptoms of simultaneous appearance in individuals. These are often related to the individual's lifestyle (overweight, sedentary habits), or existing pathological conditions (e.g. obesity and hypercholesterolemia) (1-4).

Studies confirm that individuals affected by MetS who do not dramatically change their life style have a high mortality related to CVD (4). The accepted definition of MetS, which is broadly applied at the international level, is given by the Third Report of the National Cholesterol Education Program (NCEP- III). According to the NCEP-III, a diagnosis of MetS is applicable when at least 3 out of 5 of the following elements are identified:

- Abdominal Obesity (abdomen circumference

Key words: metabolic syndrome, periodontal disease, advanced glycation end products, AGE, ROS, oxidative stress, AGEs

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0394-6320 (2012)

>102 cm in Men, >88 cm in Women)

- Triglyceridemia >150 mg/dl
- Plasma HDL cholesterol <40 mg/dl in Men, <50 mg/dl in Women
- Arterial blood pressure ≥130 and/or ≥85 mm Hg
- Fasting plasmatic glycaemia ≥110 mg/dl (5).

More recently (2005), the International Diabetes Federation reviewed the diagnostic criteria, proposing the presence of two of the following disorders in the same patient as a method to identify the disease:

- Triglyceridemia >150 mg/dl
- Plasma HDL cholesterol <40 mg/dl in Men, <50 mg/dl in Women, or hypolipemizing treatment
- Arterial blood pressure ≥130 and/or ≥85 mm Hg, or anti-hypertension treatment
- Fasting plasmatic glycaemia ≥100 mg/dl (IFG stage), associated with waist circumference of more than 94 cm in men and 80 cm in women for Caucasoid patients (the parameters vary, based on the patient's ethnic group) (6). Substantially, these two definitions are the same. However, in the most recent review, the International Diabetes Federation associated the diagnostic factors with above-normal waist circumference and classified it as a required condition for diagnosis.

Despres et al. assessed the lipid profile (total cholesterol, HDL cholesterol, triglycerides, plasmatic values of apolipoprotein B) and glucide profile (fasting insulin haematic values) of 2,103 male patients, aged 45-76 years, representative of a sample population of Québec. The analysis was carried out to determine the association between cardiovascular risk factors and ischemic cardiopathy during a five-year period (7). During the study, significantly higher fasting insulinaemia ($p < 0.001$) was observed in patients affected by ischemic events. The hyperinsulinaemia-arterosclerotic cardiopathy association kept this high rate also after a correction of triglycerides, apolipoprotein B, LDL cholesterol, and HDL cholesterol levels. Therefore, high insulin plasmatic concentrations in non-diabetic individuals – which can be classified as 'insulin-resistant' – were associated with an ischemic cardiopathy increase, independently from the lipid profile (although a lipid profile alteration in pro-atherogen sense has a synergic effect with hyperinsulinaemia) (7).

In addition to the role played in glucidic metabolism, insulin contributes to regulating lipid and protein metabolism and arterial blood pressure, interfering with platelet function and the balance between pro-thrombotic factors and endogenous fibrinolysis modulators. It also regulates the proliferative stimuli on smooth muscle cells of vascular walls and influences the endothelial function: all this explains the possible role played by insulin-resistance in determining MetS (8).

The mechanisms of insulin-resistance, or the insulin-cell surface-intracellular compartment interaction sites, in which the chain of signals produced by the hormones stops, preventing an appropriate use of circulating glucose, are not yet known. Insulin-resistance almost certainly develops long before MetS and other more advanced clinical diseases, such as type-2 diabetes mellitus and atherosclerosis, appearing in all contexts as a multifactor reality in terms of both its onset and potential harm (8).

It is clear that, in a person affected by MetS, a hyperglycaeima status triggers cellular damage with repercussions at the systemic level and also on periodontal tissue. Periodontal diseases of diabetic origin are a clear example of this (9).

New studies focus on the etiology of periodontal diseases and the role of oxidative stress, starting a cascade of molecular signals from inflammation mediators, which cause loss of attachment, reabsorption of alveolar bone and, ultimately, tooth loss, through the activation of osteoclasts (2). As a source of oxidative stress, MetS could provide an alternative etiological explanation to the development of periodontal disease, as suggested by Bullon (9).

The purpose of this study is to extend this vision, which includes the residual products of non-enzymatic glycosylation, originated from oxidative metabolism conditions, as factors promoting periodontal disease.

Metabolic syndrome and oxidative stress

It is known that all MetS triggering factors play a clear role in the onset of oxidative stress, in the subsequent formation of Reactive Oxygen Species (ROS), and probably also in the activation

of the pro-oxidising, pro-inflammatory AGE-RAGE system (10). Many inflammatory pathways are activated by these conditions. The excess of visceral fat (high waist circumference) is certainly one of the most important factors in activating these signalling molecular cascades through the TNF-alfa pathway (6).

Visceral fat, unlike subcutaneous fat, induces lipolysis increase, when stimulated, with release of Free Fatty Acids (FFA) in the blood circulation. Excess FFAs significantly contribute to inducing hyperinsulinemia, as they reduce insulin clearance, increase hepatic gluconeogenesis, reduce glucose uptake in the muscle tissues, and facilitate a pro-inflammatory status (11).

TNF-alfa increase, in turn, contributes to triggering the molecular processes that lead to the development of insulin-resistance, which would apparently play a key pathogenetic role in all MetS conditions (12). When calorie intake is higher than body consumption, ROS excess is created due to hyper-activity of the citric acid cycle, hence oxidative stress (13). This oxidative stress alters intracellular signalling and contributes to the development of insulin-resistance (11). On the other hand, Ceriello et al. 2000 showed that insulin-sensitivity improves after administration of anti-oxidizing substances (14).

Soory et al. claim that ROS increase causes a hyper-inflammatory status in its most aggressive forms of periodontal disease and causes an unbalance of redox status, which results in damage (15). In accordance with this vision, the hyper-inflammatory condition associated with periodontal disorder could overload the body with Reactive Oxygen Species, which are in turn able to contribute to the development of other pathologies, such as metabolic, articular, neoplastic, or geriatric diseases (15). In addition to lipid peroxidation, the AGEs are another emerging marker of oxidative stress. The AGEs are a set of heterogeneous products constantly formed in physiological conditions, but significantly increasing in the presence of hyperglycaeima and excessive oxidative stress (3). The recent literature hypothesizes that the AGEs are the cause of a large number of adverse conditions established in systemic diseases, where the oxidative component is strong, as in diabetes (2).

The activation of these pathways is not restricted to limited areas of the body, but their signalling triggers systemic responses, which are also visible at the level of teeth-supporting tissues. Since the 1970s, it has been known that obesity and hypertension increase the severity of the periodontal disease (16). In fact, it is known that overweight individuals have a worse periodontal status than individuals with a normal body weight, with evident histological changes on dental tissues (17). To support this proposition, Pischon et al. clearly stressed that inflammation caused by obesity markedly affects the status of periodontal tissues. In these cases, the activation of pro-inflammatory cytokines has been broadly supported by scientific literature. In fact, TNF-alfa, Interleukin 6 and 10 (IL-6, IL-10), and C-Reactive Protein (CRP) are certainly involved in individuals with high Body Mass Index (BMI) (18).

The activation of these complexes leads to the interaction between AGEs and RAGE cellular receptors (found in many cell populations), which amplify the release of cytokines, metalloproteinase (MMPs), and ROS.

It is worth stressing that diet certainly contributes to the action of inflammatory cytokines. Obese individuals eat several times during the day, without caring too much for oral hygiene, thus facilitating the onset of dental plaque and tartar. This condition is the basis of periodontal disease aetiology.

Advanced Glycation End-Products (AGEs)

AGEs are a heterogeneous group of physiologically formed compounds, which accumulate when cellular clearance fails, and in hyperglycaeima and oxidative stress conditions (3). The accumulation of AGEs may also be dependent on exogenous sources, such as tobacco smoking, vegetarian diet, alcohol, consumption of browned foods, and high lipid/glucide quantities (2). Approximately one-third of AGEs intake through diet is excreted with urine, whereas the remaining part is supposedly incorporated in tissues (2). These compounds are produced through an enzymatic pathway from monosaccharide substances, such as glucose and fructose, but also dicarbonyls originating from Maillard's reaction, sugar self-oxidation, and other molecular pathways, such as glycolysis, which involves the formation of glyoxal

and methylglyoxal (19).

The non-enzymatic post-translational glycosilations of proteins occur through reductive amination reaction between the non-reducing end of a carbohydrate and primary amino groups located on macromolecules containing lysine or arginine residues (amino acids, proteins, phospholipids, lipids, and nucleic acids). These reactions lead to the formation of a number of reversible intermediate products called Schiff's bases and Amadori products (e.g. Glycated haemoglobin; HbA1C). Any subsequent rearrangement of these complexes leads to the formation of much more stable products, the AGEs, which affect the functionality and properties of proteins, lipids, and DNA (19, 20).

A key role in the formation of these adducts can be referred to oxidative stress and aging. Oxidising conditions and Reactive Oxygen Species (ROS) facilitate the formation of AGEs, which in turn increase the production of free radicals. Schiff's bases and Amadori products increase ROS production, and hyperglycaemia promotes glucose self-oxidation, which involves OH radicals. Several studies clearly show that AGEs are involved in the development of diabetic problems, as well in CVD and renal and neurodegenerative disease pathogenesis (2, 19, 20).

Throughout life, the AGEs produced accumulate in the tissues and can be found in plasma (21). The pathogenetic action of these compounds performs directly, damaging the tissues, or indirectly, binding a specific receptor, called RAGE, which belongs to the family of immunoglobulins (20).

This receptor is physiologically found in small quantities in many cells, but it is over-expressed in conditions such as diabetes, vasculopathy, and cancer (20). The AGE-RAGE bond involves a cascade of pro-inflammatory signalling with subsequent activation of redox-sensitive transcription factors, such as NF-kB (22). This interaction involves hyper-permeability, at the level of endothelial cells, and activates the VCAM-1 molecule, whereas on monocytes it involves chemotaxis and cytokine increase, such as the Tumor Necrosis Factor (TNF), and interleukins IL-1 and IL-6 (23). Collagen synthesis by fibroblasts is also reduced (24).

In addition to persistent hyperglycaeima states, transient hyperglycaemia is also a risk condition, as it induces pro-inflammatory signalling and activates the long-lasting expression of p65, which is a fraction of the above-mentioned NF-kb (25). Recently, interest in this condition has grown, as a few studies report that the 'cell memory' – thus, pro-inflammatory signalling – continues up to 16 hours after the end of the hyperglycemic condition (26).

Contemporary literature suggests that the RAGE is also the receptor for other ligands: the EN-RAGE (recently identified as extracellular receptor) and other members of inflammatory cytokines of the S100/calgranulin family (27). These intracellular proteins may have access to the extracellular space in inflammatory conditions. After release, the capacity to interact with RAGE seems to be an important tool through which the inflammation spreads and causes cellular damage (27).

Long-survival proteins, such as collagen, are the most vulnerable molecules exposed to cross-links and forming AGEs, with subsequent subtraction to proteolysis and tissue remodeling (24). Vascular collagen is also irreversibly modified by AGEs, and contributes to the formation of atherosclerosis and development of kidney failure (22, 28). AGEs have a higher predictive value of micro-vascular complication development than the value of other risk predictors, such as the duration of diabetes and HbA1c.

On the other hand, reduced clearance of serum AGEs can further increase the accumulation of AGEs in tissues and their new formation, which worsens kidney failure (28).

Aetiology and pathogenesis of periodontal disorder

The aetiology of periodontal disease has not yet been totally clarified. However, it is commonly accepted that it may result from an opportunistic infection. The bacteria cross the epithelial pocket and invade the sub-epithelial connective tissue. A crucial role is played by the increase in the number of dental plaque microorganisms, their capacity to penetrate the tissues, and the host's immunological status. The damage is only partially reversible, even after professional treatment (29).

The hyper-inflammation following these events determines the failure of the immunological response: it not only removes the pathogens, but it also involves the prolonged release of proteolytic enzymes by the neutrophils, pro-inflammatory

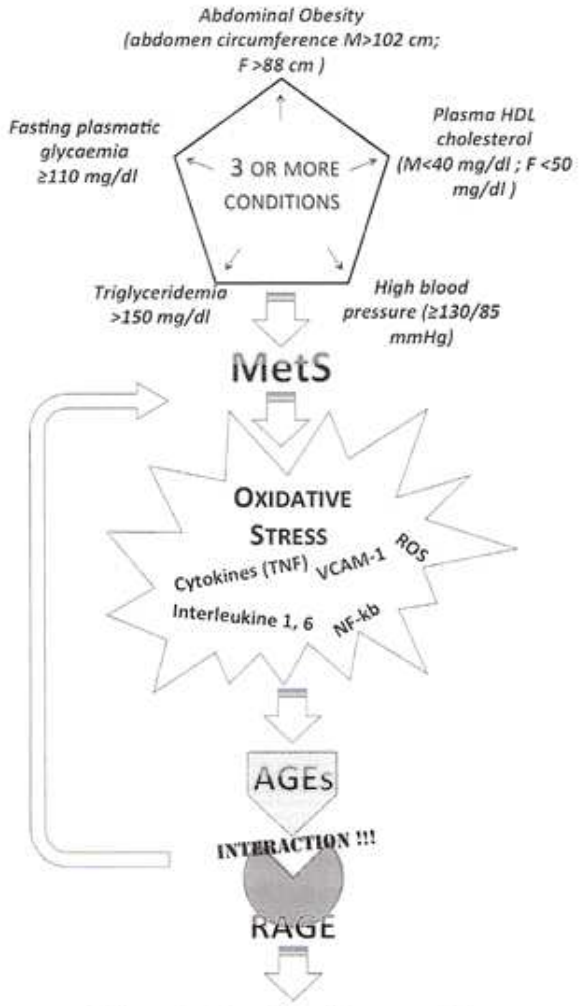

Fig. 1. *Conditions that can cause MetS promote Oxidative Stress, which induces the release of inflammatory mediators. These molecules induce the AGEs formation and RAGE expression over the cell's membranes. Their interaction, in a vicious circle, on the one hand induces inflammatory mediators and, on the other hand, promotes osteoclast activation, resulting in alveolar bone loss.*

mediators, and ROS (30). These elements determine periodontal attachment destruction. *Fusobacterium Nucleatum* and the other oral pathogens induce an increase in intracellular production and ROS release in neutrophils (30). Higher ROS levels are, in fact, found in saliva and gingival crevicular fluid in patients with periodontal disease as compared with healthy controls (31).

Lee et al. suggest that hydrogen peroxide (oxygenated water) deposited in periodontal tissues to reduce the inflammation caused by bacteria accelerates their destruction by activating the IL-8 pathway in periodontal cells (32). This event should not be underestimated and should be taken into consideration during periodontal surgery.

Soory et al. propose that during periodontal disease, increased ROS production may worsen an inflammatory condition, causing an alteration of the redox status and inducing damage from oxidative stress, which involves a more rapid evolution of the disease (33). To support this hypothesis, a broad body of literature documents a link between periodontal disorders and other pro-oxidative inflammatory diseases. In fact, it has been confirmed that diseases inducing oxidative metabolic changes, such as diabetes, arthritis, neoplasias, and aging, are associated with periodontal disease, increasing their severity (15).

Based on these observations, it is clear that many conditions may worsen periodontal disorders or promote new onset. Contemporary literature supports the assumption that, in addition to inflammation and oxidative stress, other conditions such as cigarette smoking, vitamin deficits, alcohol abuse, diet, and other pro-oxidation conditions, such as MetS, play a key role in the activation of signalling pathways, which act in promoting ROS development and probably also in worsening or producing a new onset of a periodontal disease (2, 15).

SO, WHY IS METS INVOLVED IN PERIODONTAL DISORDERS?

Certainly this is because a disease including all pro-oxidation conditions (hyperglycaemia, hyperlipaemia, obesity, and hypertension), coexisting in a vicious circle, establishes and supports the production of free radicals and non-enzymatic glycosylation products.

To date, there is not much in literature to support this assumption, except for a note-worthy epidemiological analysis, which helps to provide the background on the relationship between MetS

and periodontal disorders, i.e. the analysis of the American study, Third National Health and Nutrition Examination Survey (NHANES) III (34).

NHANES III analysed 13,994 individuals (men and women) aged over 17. The study assessed their periodontal condition through plaque and bleeding indexes, and testing depth, as well as the Metabolic Syndrome parameters. The patients aged over 45 affected by MetS had a risk 2.31 times higher than healthy individuals of being affected by periodontal disorders. The study authors concluded that serious periodontal disease is associated with middle-aged individuals affected by MetS (34).

Further investigations are required to support and extend this hypothesis. However, it is clear enough that MetS negatively influences the health of tissues supporting the teeth.

Metabolic syndrome, AGEs, and periodontal diseases

Hypertension, obesity, dyslipidemia, and hyperglycaeima, which coexist in MetS, play an incremental role in ROS and AGE production (35). This is probably on the basis of a potential MetS role in the destruction of periodontal tissues. In fact, the AGEs create damage by directly modifying proteins (24), or indirectly, activating signalling through its RAGE receptors (27).

The interaction AGE-RAGE results in proinflammatory signalling and in the generation of intracellular oxidative stress and subsequent activation of the redox-sensitive transcription factors such as NF-kB (22). Formation of AGEs is a way to maintain the signal of a short oxidative burst in much longer-lived post translational modified proteins (36). Interaction of RAGE with AGEs in endothelial cells results in hyperpermeability and enhanced expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1). This interaction on monocytes induces chemotaxis, as well as an increased generation of cytokines such as tumor necrosis factor (TNF), interleukin IL-1, or IL-6 (23).

Furthermore, the engagement of RAGE result in diminished collagen synthesis in fibroblast (37). Recent observations suggest that RAGE is a central cell-surface receptor also for EN-RAGE (extracellular newly identified RAGE binding proteins) and other members of the S100/calgranulin family of pro-inflammatory cytokines (38). These intracellular proteins may gain access to extracellular space in the inflammatory milieu. Upon release, their ability to interact with cellular RAGE appears to be an important means by which to propagate inflammatory cellular perturbation and chronic tissue injury (38).

It is important to note that a study with diabetic rats shows that RAGE inhibition prevents the progression of periodontal disease, improving the prognosis, and reduces the formation of pro-inflammatory cytokines, such as IL-6, TNF-alfa, and metalloproteinase, significantly reducing the loss of alveolar bone (39). The authors have also observed that the beneficial effect of the RAGE block is independent from glycaemic control, thus supporting the importance of signalling RAGE in periodontal disease. Observations based on the involvement of RAGEs in periodontal disease is not a valid support for the hypothesis that AGEs are involved in the onset of periodontal disease. However, this aspect has been recently studied by Murillo et al. (40) and Ren et al. (41), who assessed the effect *in vitro* of AGEs on human gingival and periodontal fibroblasts. Both these studies started from the premise that an important role in periodontal physiology is played by cell interaction with molecules of the extracellular matrix (42). In an *in vitro* model of periodontal cells, the behaviour of human gingival fibroblasts (hGFs) and human periodontal fibroblasts (hPDLs) is deeply influenced by changes in the surrounding environment (43).

The glycated proteins of the extracellular matrix can also have their pathogenetic effects interacting with RAGE. The observation that the AGEs can regulate the cellular function and hGFs' collagen metabolism supports this assumption. It was also found that AGEs reduce the mobility of these cells and significantly inhibit the expression of types I and III collagen (41). The importance of these mechanisms in the pathogenesis of periodontal disease is stressed by the observation according to which the reduction of periodontal integrity, which occurs physiologically with age, could be referred to a reduced expression of type I collagen caused by age-dependent hypermethylation in the gene-promoting area (44).

In concurrence with the above-mentioned data, it seems that AGEs participate in the pathogenesis of periodontal disease, independently from the mechanisms provoking their accumulation.

This hypothesis is supported by a recent study, which investigated the existing relationship between the development of periodontal disease and HbA1c levels in non-diabetic individuals. The periodontal health status, analyzed in these patients using modified CPI (Community Periodontal Index), was significantly correlated with HbA1c levels. After the normalisation of data, the Authors observed that mean glycosylated haemoglobin was significantly increased in the case of periodontal deterioration (34).

Final considerations and future developments

The literature analysed clearly shows that all the conditions and pathologies causing oxidative stress, production of AGEs, and activation of RAGE, are potentially involved in the aetiology and severity of periodontal diseases.

As MetS is defined by the presence of hyperglycaemia, dyslipidaemia, obesity, hypertension – all these conditions determine ROS increase and AGEs production – it is clear that MetS may worsen an existing state, or cause a new periodontal pathology, with mechanisms like those described for diabetes, where the AGEs play a key role in the onset of microangiopathy, retinopathy, nephropathy, neuropathy, and general tissue degeneration conditions (20). Considered individually, the conditions defining MetS play an important role. However, their role is certainly at a lower level compared to synergic action. It is now described by clinical evidence and scientific literature that neglecting a high BMI involves a cascade of other compensatory and dysfunctional conditions promoted by humoral signalling, the sum of which defines MetS (45).

The AGEs that may irreversibly accumulate in periodontal tissue with age, prolonged hyperglycaemia and/or chronic inflammation states, such as those that may be observed in MetS, can damage the tissues and affect the functional status of collagen fibres and increase ROS and inflammation mediator levels through the interaction with RAGE. The formation of AGEs in the extracellular matrix may contribute to increasing ROS production and release from phagocytes and periodontal ligament cells, with subsequent induction of pro-inflammatory cytokines and metalloproteinase, leading to osteoclast activation and bone loss.

This text stresses our point of view, according to which periodontal disease should be faced with a multidisciplinary approach, considering the periodontal tissues exposed not only to local bacterial onslaught, but also to systemic conditions damaging them through the same mechanisms provoking damage in other tissues.

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