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Advanced Glycation End Products: Possible Link Between Metabolic Syndrome and Periodontal Diseases

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1. Introduction

At a planetary scale, the 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 (Ford et al. 2002). 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 aetiology of periodontal disease has not been clarified yet, and recently the idea to consider it as a multifactor pathology has been developed. Cofactors such as the formation of reactive oxygen species (ROS), oxidative stress, lipid peroxidation, and formation of glycation end-products (AGEs) probably play an important role in the onset of periodontal disease (Pietropaoli et al. 2010). The AGEs are compounds physiologically produced by all metabolically active cells. However, they accumulate and cause pro-inflammatory statuses, when the cellular clearance fails, or in hyperglycaemic and oxidative statuses (Peppa et al. 2008). 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 Diseases.

The literature seems to have clarified that the Metabolic Syndrome involves a pro-oxidation status, which induces AGE formation. AGEs play a very important role in the course and severity of periodontal diseases.

2. The Metabolic Syndrome

The 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 life style (overweight,

sedentary habits), or existing pathological conditions (e.g. obesity and hypercholesterolemia) (Lakka et al. 2002).

The studies confirm that individuals affected by Metabolic Syndrome, who do not dramatically change their life style, have a high mortality related to CVD (Lakka et al. 2002).

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 Metabolic Syndrome is applicable when at least 3 out of 5 of the following elements are identified:

- Abdominal Obesity (abdomen circumference >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 Expert Panel on Detection and of High Blood Cholesterol in Adults (2001).

More recently (2005), the International Diabetes Federation has 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 ≥110 mg/dl (IFG stage),

associated with waist circumference of more than 94 cm in men and 80 cm in women for Caucasian patients (the parameters vary, based on the patient's ethnic group) (Alberti et al. 2005).

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. (2000) assessed the lipid profile (total cholesterol, HDL cholesterol, triglycerides, plasmatic values of apolipoprotein B) and glucide profile (fasting insulin haematic values) of 2103 male patients, aged 45-76 years, representative as 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 (Després et al. 2000). During the study, significantly higher fasting insulinemia ($p < 0.001$) was observed in patients affected by ischemic events. The hyperinsulinemia-artherosclerotic 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 – who 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 hyperinsulinemia) (Després et al. 2000).

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 the Metabolic Syndrome (Harano et al. 2002).

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 known yet. Insulin-resistance almost certainly develops much before the Metabolic Syndrome 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 (Harano et al. 2002).

It is clear that, in a person affected by MetS, a hyperglycaemia 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 (Bensley et al. 2011).

New studies focus on the aetiology 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 activation of osteoclasts (Pietropaoli et al. 2010). As a source of oxidative stress, the MetS could provide an alternative etiological explanation to the development of periodontal disease, as suggested by Bullon et al. (2009).

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.

3. 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 (Koyama et al. 2005). 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 (Boden 2006).

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 (Liu et al. 2011).

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 (Odrowaz-Sypniewska 2007). When calorie intake is higher than body consumption, ROS excess is created, due to hyper-activity of the citric acid cycle, hence oxidative stress (Maddux et al. 2001). This oxidative stress alters intracellular signalling and contributes to the development of insulin-resistance (Evans et al. 2003). On the other hand, Ceriello et al. (2000) showed that insulin-sensitivity improves after administration of anti-oxidizing substances (Ceriello and Motz 2004).

Soory et al. (2009) claim that ROS increase causes a hyper-inflammation status in its most aggressive forms of periodontal disease and causes an unbalance of redox status, outcome of which is damage. In accordance with this vision, the hyper-inflammation status 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 (Soory, 2009). 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 hyperglycaemia and excessive oxidative stress (Peppa et al., 2008). The recent literature suggests 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 (Xue et al., 2011).

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 is known that obesity and hypertension increase the severity of the periodontal disease (Perlstein and Bissada, 1977). It is also suggested that overweight individuals have a worse periodontal status than individuals with a normal body weight, with evident histological changes on dental tissues (Suvan et al., 2011). To support this suggestion, Pischon et al. (2007) clearly emphasised 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) (Pischon et al., 2007).

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, metalloproteinases (MMPs), and ROS.

It is worth stressing that the nature of an individual's 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 accumulation of dental plaque and dental calculus. This condition is the basis of periodontal problems in these subjects.

4. Advanced Glycation End-Products (AGEs)

The AGEs are a heterogeneous group of physiologically formed compounds, which accumulate when cellular clearance fails, and in hyperglycaemia and oxidative stress conditions (Peppa et al., 2008).

The accumulation of AGEs may also be dependent on environmental sources, such as tobacco smoking (Yamagishi et al., 2008), vegetarian diet (Sebeková et al., 2006), alcohol (Kalousová et al., 2004), consumption of browned foods, and high lipid/glucide quantities (Krajcovicová-Kudlácková et al., 2002). Approximately one third of AGEs intake through diet is excreted with urine, whereas the remaining part is supposedly incorporated in tissues (Bohlender et al., 2005).

These compounds are produced through 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 (Fu et al., 1996). 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 lead to the formation of much more stable products, the AGEs, which affect the functionality and properties of proteins, lipids, and DNA (Thornalley, 2005; Fu et al., 1996).A key role in the formation of these adducts can be referred to oxidative stress and aging (Baynes, 2001). Oxidising conditions and Reactive Oxygen Species (ROS) facilitate the formation of AGEs, which in turn increase the production of free radicals (Wen et al., 2002; Yin et al., 2001). Schiff's bases and Amadori products increase ROS production, and hyperglycaemia promotes glucose self-oxidation, which involves OH radicals (Noiri and Tsukahara, 2005). Several studies clearly show that the AGEs are involved in the development of diabetes problems, andin CVD and renal and neurodegenerative disease pathogenesis (Goldin et al., 2006; Zhang et al., 2009).

Throughout life, AGEs produced accumulate in the tissues and can be found in plasma (Ulrich and Cerami, 2001). 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 (Ramasamy et al., 2005).

This receptor is physiologically found in small quantities in many cells, but it is over-expressed in conditions such as diabetes, vasculopathy, and cancer (Ramasamy et al., 2005). The AGE-RAGE bond involves a cascade of pro-inflammatory signalling with subsequent activation of redox-sensitive transcription factors, such as nuclear factor kappa B (NF-κB) (Schmidt and Stern, 2000). This interaction involves hyper-permeability, at the level of endothelial cells, and activates the vascular cell adhesion molecule-1 (VCAM-1) molecule, whereas on monocytes it involves chemotaxis and cytokine increase, such as the tumour necrosis factor (TNF), and interleukins IL-1 and IL-6 (Vlassara et al., 1988). Collagen synthesis by fibroblasts is also reduced (Hollá et al., 2001).

In addition to persistent hyperglycaemia statuses, 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-κB (Siebel et al., 2010). Recently, the 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 hyperglycaemic condition (El-Osta et al., 2008).

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 remodelling (Verzijl et al., 2000). Collagen irreversibly modified by the AGEs is also the vascular collagen, which contributes to the formation of atherosclerosis and development of kidney failure (Bohlender et al., 2005). The AGEs have a higher predictive value of microvascular 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 (Miyata et al., 1997).

5. Aetiology and pathogenesis of periodontitis

The aetiology of periodontitis has not been fully clarified yet. However, it is commonly accepted that it may result from an opportunistic infection. The bacteria cross the epithelial barrier 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 (Needleman et al., 2006).

The hyper-inflammation following these events determines the failure of the immunological response: it does not only remove the pathogens, but it also involves the prolonged release of proteolytic enzymes by the neutrophils, pro-inflammatory mediators, and ROS (Sheikhi et al., 2000). These elements determine periodontal attachment destruction (Chapple and Matthews, 2007). *Fusobacterium nucleatum* and the other oral pathogens induce an increase in intracellular production and ROS release in neutrophils (Sheikhi et al., 2000). Higher ROS levels are, in fact, found in saliva and gingival crevicular fluid of patients with chronic periodontitis as compared with healthy controls (Tsai et al., 2005).

Lee et al. (2008) 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 (Lee et al., 2008). This event should not be underestimated and should be taken into consideration during periodontal surgery.

Soory et al. (2009) proposed 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 (Soory, 2008). A broad body of literature documenting a link between periodontal diseases and other pro-oxidative inflammatory diseases support this hypothesis. 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 its severity (Soory, 2009).

Based on these observations, it is clear that many conditions may worsen periodon- tal disorders or promote new onset. Contemporary literature supports the assumption that, in addition to inflammation and oxidative stress, other conditions such as cigarette smoking (Bagaitkar et al., 2009), vitamin deficits, alcohol abuse, diet (Dye, 2010; Hujoel, 2009), 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 new onset of a periodontal disease (Liu et al., 2011; Soory, 2009; Boden, 2006).

<p align="center">SO, WHY IS METS INVOLVED IN PERIODONTAL DISEASES?</p>

Certainly this is because a pathological range including all pro-oxidation conditions (hyperglycaemia, hyperlipaemia, obesity, and hypertension), which coexist in a vicious circle, and establish and support the onset of free radicals and products from non-enzymatic glycosilation. As yet, 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 diseases, i.e. the analysis of the American study NHANES III (D'Aiuto et al., 2008). NHANES III (Third National Health and Nutrition

Examination Survey) 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 diseases. The study authors concluded that serious periodontal disease is associated with middle-aged individuals affected by MetS (D'Aiuto et al., 2008). Further investigations are required to support and extend this hypothesis. However, it is clear enough that the MetS negatively influences the health of tissues supporting the teeth.

6. Metabolic Syndrome, AGEs, and periodontal diseases

Hypertension, obesity, dyslipidemia, and hyperglycaemia, which coexist in MetS, play an incremental role in ROS and AGEs production (Turco et al., 2011). 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 (Verzijl et al., 2000), or indirectly, activating signalling through its RAGE receptors (Schmidt et al., 2000). The interaction AGE-RAGE results in pro-inflammatory signalling and in generation of intracellular oxidative stress and subsequent activation of the redox-sensitive transcription factors such as NF-κB (Schmidt and Stern, 2000). Formation of AGEs is a way to maintain the signal of a short oxidative burst in a much longer-lived post translational modified proteins (Andrassy et al., 2006). 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 tumour necrosis factor (TNF), interleukin-1 (IL-1), or IL-6 (Vlassara et al., 1988).

Furthermore, the engagement of RAGE results in diminished collagen synthesis in fibroblasts (Hollá et al., 2001). 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 (Hofmann et al., 1999). 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 (Schaefer and Heizmann, 1996). 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 metalloproteinases, significantly reducing the loss of alveolar bone (Schmidt et al., 1996). 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 are not valid to support the hypothesis that the AGEs are involved in the onset of periodontal disease. However, this aspect has been recently studied by Murillo et al. (2008) and Ren et al. (2009), who assessed the in vitro effect of AGEs on human gingival and periodontal fibroblasts. Both of these studies started from the premise that an important role in periodontal physiology is played by cell interaction with molecules of the extracellular matrix (Steffensen et al., 2001). 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 (Lackler et al., 2000). The

glycated proteins of the extracellular matrix can also have their pathogenic 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 the AGEs reduce the mobility of these cells and significantly inhibit the expression of type I and III collagen (Ren et al., 2009). The importance of these mechanisms in the pathogenesis of periodontal disease is emphasised 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 (Ohi et al., 2006).

In concurrence with the above-mentioned data, it seems that the AGEs participate in the pathogenesis of periodontal disease, independently from the mechanisms provoking their accumulation. This hypothesis is supported by a recent study, which has investigated the existing relationship between the development of periodontal disease and glycosylated haemoglobin (HbA1c) levels in non-diabetic individuals. The periodontal health status, analysed 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 HbA1c was significantly increased in the case of periodontal deterioration (Hayashida et al., 2009).

7. 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, and particularly in the development of chronic periodontitis.

As the MetS is defined by the presence of hyperglycaemia, dyslipidemia, obesity, hypertension – all these conditions determine ROS increase and AGEs production – it is clear that the 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 (Ramasamy et al., 2005). Considered individually, the conditions defining the MetS play an important role. However, their role is certainly at a lower level as compared with 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; whose sum defines the MetS (Martin-Cordero et al., 2011; Martínez-Clemente et al., 2011).

The AGEs that may irreversibly accumulate in periodontal tissue with age, prolonged hyperglycaemia and/or chronic inflammation statuses, such as those that may be observed in the 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 metalloproteinases, leading to osteoclast activation and bone loss.

Since AGEs are products of accumulation, all these conditions have more significance in a condition which needs long time to develop, just as chronic periodontitis.

Therefore, we believe periodontal diseases , and particularly chronic periodontitis, should be considered by a multidisciplinary approach, bearing in mind that 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.
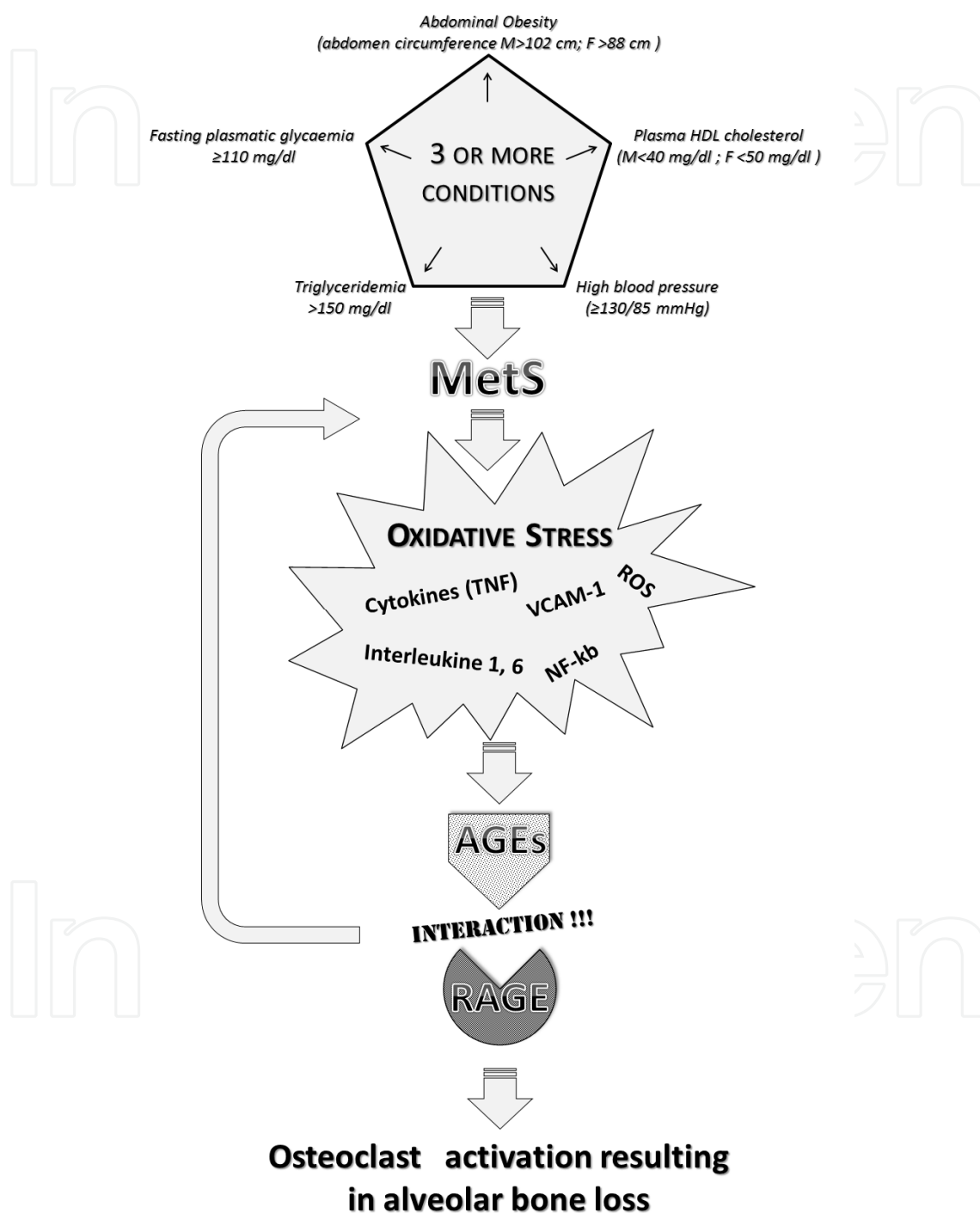
Fig. 1. In this figure has been represented the hypothesis supported in this article. MetS promote a self supporting ROS and AGEs accumulation that result in chronic inflammation signalling. This condition also promotes the osteoclast activation that result in alveolar bone loss.

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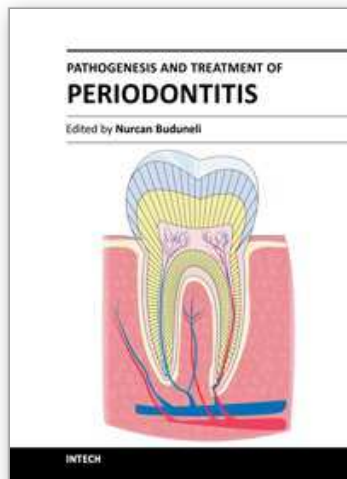
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