CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

Metabolic Syndrome and Periodontitis: Is Oxidative Stress a Common Link?

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ABSTRACT

A review of pathological mechanisms that can explain the relationship between periodontitis and cardiovascular disease (CVD) is necessary to improve the management of both conditions. Metabolic syndrome is a combination of obesity, hypertension, impaired glucose tolerance or diabetes, hyperinsulinemia, and dyslipidemia. All these have been examined in recent years in terms of their relationship to periodontitis. Reviewed data indicate an association between some of them (body mass index, high-density lipoprotein-cholesterol [HDL-C], triglycerides, high blood pressure, among others) and periodontitis. Oxidative stress may act as a potential common link to explain relationships between each component of metabolic syndrome and periodontitis. Both conditions show increased serum levels of products derived from oxidative damage, with a pro-inflammatory state likely influencing each other bidirectionally. Adipocytokines might modulate the oxidant/anti-oxidant balance in this relationship.

KEY WORDS: metabolic syndrome, oxidative stress, periodontitis, hypertension, dyslipidemia, insulin resistance.

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INTRODUCTION

Cardiovascular disease (CVD) is the major cause of death in western countries (World Health Organization [WHO], 2005). Metabolic syndrome (MetS) is a clinical entity that encompasses several risk factors for CVD (Semenkovich, 2006; N Pischon *et al*., 2008). MetS consists of a combination of impaired glucose regulation, abdominal obesity, dyslipidemia, and high blood pressure (Eckel *et al.*, 2005). It is estimated that around a quarter of the world's adult population is affected by MetS (Cameron *et al.*, 2004).

It is generally accepted that the origin of all those metabolic disorders is a "pro-inflammatory" state derived from excessive caloric intake and overnutrition, and, perhaps, other chronic inflammatory conditions (Dandona *et al.*, 2004; Ghanim *et al.*, 2004; Hotamisligil, 2006). This hypothesis states that this pro-inflammatory state, being characterized by an increase in inflammatory mediators such as tumor necrosis factor alpha (TNF-α), induces insulin resistance, promoting further inflammation through an increased free fatty acid (FFA) concentration (essentially, derived from lipolysis) and a resultant interference with the anti-inflammatory effects of insulin. This pro-inflammatory state also leads to an increase in oxidative stress, with the potential to impair several crucial biological mechanisms (Tripathy *et al.*, 2003; Dandona *et al.*, 2004; Hansel *et al.*, 2004). Therefore, insulin resistance could act as the common link among all the components of MetS (Dandona *et al.*, 2002, 2004).

Oxidative stress is defined as a persistent imbalance between the production of highly reactive molecular species (*e.g*., reactive oxygen species [ROS], reactive nitrogen species [RNS]) and anti-oxidant defenses (Halliwell, 1991). There is an increase in ROS in the pre-diabetic stage, likely due to obesity-related elevations of FFA, and several studies have shown that reversal of the imbalance between ROS and anti-oxidants improves insulin resistance in mice and humans (Ceriello and Motz, 2004; Wright *et al.*, 2006).

Periodontitis is a generally chronic disorder characterized by the breakdown of the tooth-supporting tissues and the impaired host inflammatory immune response. This condition is due fundamentally to an ecological imbalance between the normal microbial biofilm on teeth and the host tissues (Newman, 1974). There is increasing evidence linking periodontitis to systemic diseases (Kuo *et al*., 2008), such as diabetes (Herring and Shah, 2006), rheumatoid arthritis (Pischon *et al*., 2008b), and, especially, CVD (Ford *et al*., 2007; Paquette *et al*., 2007; Fardi and Papadimitriou, 2008)—hence the search for factors that may explain such relationships. A potential factor which could increase insulin resistance is the production of oxidative stress-enhancing ROS in affected periodontal tissues (Battino *et al.*, 1999; Chapple and Matthews, 2007).

Table 1. Current Definitions of Disorders with Impaired Glucose Regulation (World Health Organization, 1999; American Diabetes Association, 2005; Nichols *et al.*, 2007)

Type 2 Diabetes	Impaired Glucose Tolerance (IGT)	Impaired Fasting Glycemia (IFG)
• Single raised glucose reading with symptoms, or • Raised values on 2 occasions, of either fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) or with a glucose tolerance test, 2 hrs after an oral dose of 75 g, a plasma glucose ≥ 11.1 mmol/L (200 mg/dL)	• 2-hour glucose levels of 140-199 mg *per* dL (7.8-11.0 mmol/L) on a 75-g oral glucose tolerance test • Fasting glucose may be either normal or mildly elevated	• Fasting glucose level > 5.6 mmol/L (100 mg/dL) and < 6.9 mmol/L (125 mg/dL)

Table 2. Definitions of Metabolic Syndrome by WHO and NCEP-ATP-III

WHO (Alberti and Zimmet, 1998)	NCEP-ATP-III Criteria (NCEP-ATP, 2001)
Presence of DM, IGT, IFG, or insulin resistance, and 2 of the following features:	At least three of the following:
• blood pressure ≥ 140/90 mm Hg; • dyslipidemia, defined by TG ≥ 1.695 mmol/L and/or HDL-C ≤ 0.9 mmol/L in males or ≤ 1.0 mmol/L in females; • central obesity, defined by waist:hip ratio > 0.90 in males or > 0.85 in females, and/or BMI* > 30 kg/m^2; • microalbuminuria, defined by a urinary albumin excretion ratio ≥ 20 mg/min or albumin: creatinine ratio ≥ 30 mg/g	• central obesity, measured as waist circumference ≥ 102 cm in males or ≥ 88 cm in females; • TG ≥ 1.695 mmol/L (150 mg/dL); • HDL-C < 40 mg/dL in males or < 50 mg/dL in females; • blood pressure ≥ 130/85 mmHg; • fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL)

* BMI, body mass index; DM, diabetes mellitus; HDL-C, high-density lipoprotein-cholesterol; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; TG, triglycerides.

Therefore, our goal in this review is to analyze the published data to consider the hypothesis for a potential relationship between MetS and periodontitis, with oxidative stress acting as a putative link between both conditions.

METABOLIC SYNDROME: CURRENT DEFINITIONS

MetS as originally described (Reaven, 1988) is a combination of obesity, hypertension, impaired glucose tolerance or diabetes, hyperinsulinemia, and dyslipidemia (elevated triglycerides and decreased high-density lipoprotein-cholesterol [HDL-C] levels). These same features are also considered as risk factors for atherosclerosis, therefore leading to the deduction that MetS constitutes a risk for coronary heart disease (Ninomiya *et al.*, 2004).

Insulin resistance is a condition in which normal amounts of insulin are inadequate to elicit a normal response from fat, muscle, and liver cells (Di Filippo *et al.*, 2007). This condition leads to an eventual hyperglycemia which has systemic deleterious effects, mainly acting over the vasculature. The current definitions of the main disorders presenting with impaired glucose regulation are shown in Table 1.

There are currently several definitions in use to characterize MetS. The most frequently used are from the WHO, the US National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III, 2001) (Table 2), and the International Diabetes Federation (IDF, 2005) (Table 3). Other definitions come from the European Group for the Study of Insulin Resistance (Balkau *et al.*, 2002) and the National Heart, Lung, and Blood Institute/American Heart Association (Grundy *et al.*, 2004).

The rationale for the WHO definition was that a diabetic or prediabetic individual who developed certain CVD risk components should be considered as suffering from MetS, because this is a well-defined clinical entity. The WHO stated that each component conveyed a greater CVD risk, and their mixed occurrence increased the overall risk. Therefore, the reason for diagnosing MetS was to identify persons at undue risk of CVD (Reaven, 2006). Subsequently, the goal of the NCEP-ATP III was focused less on type 2 diabetes and more on CVD risk, and thus, an additional aim was to focus on primary prevention in persons with multiple risk factors. The NCEP-ATP III considered MetS to represent multiple, interrelated factors that raise CVD risk, and stated that the root causes were overweight or obesity, physical inactivity, and genetic factors (Reaven, 2006). The most recent characterization of MetS was the result of a consensus conference organized by the IDF. This definition gives more importance than others to ethnic differences in diagnostic criteria (IDF, 2005).

Nevertheless, there is currently some disagreement as to the precise definition of MetS (Reaven, 2005; Grundy, 2006). Some authors consider that a diagnosis of MetS as a defined entity is not clinically useful (Kahn *et al.*, 2005; Kahn, 2007, 2008). They describe some weak features of this syndrome. With respect to definition, the criteria are ambiguous or incomplete, the rationale for thresholds in clinical or laboratory parameters is not clear, the inclusion of diabetes in the definition is questionable, and a clear basis for including or excluding other cardiovascular risk factors does not exist. Moreover, they argue that the cardiovascular risk associated with the syndrome seems to

be no greater than the sum of its parts, and the treatment for MetS is not different from that for each of its components. These authors consider that the hypothesis of insulin resistance as a unifying cause is uncertain.

Therefore, it will be necessary to unify the diagnostic criteria to establish the actual prevalence and influence of this condition over local (*e.g.*, periodontitis) and systemic diseases (*e.g.,* CVD).

Table 3. Definition of Metabolic Syndrome According to the International Diabetes Federation (IDF, 2005)

	Raised TG	≥ 150 mg/dL or Specific Treatment
Central obesity (defined as waist circumference**) + 2 of the following parameters	Reduced HDL-C*	< 40 mg/dL in males < 50 mg/ dL in females or specific treatment
	Raised BP	systolic BP ≥ 130 or diastolic BP ≥ 85, or treatment of previously diagnosed hypertension
	Raised FPG	FPG ≥ 100 mg/dL or previously diagnosed type 2 diabetes. OGTT is recommended but not necessary

* HDL-C, high-density lipoprotein-cholesterol; BP, blood pressure; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; TG, triglycerides.

** Their values are specific for ethnicity. If BMI (body mass index) is > 30 Kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.

OXIDATIVE STRESS AND METABOLIC SYNDROME

As previously mentioned, insulin resistance plays a key role in the pathophysiology of MetS. Several inflammatory mediators are involved in the pathogenesis of insulin resistance, with TNF-α having apparently the strongest effect (Tilg and Moschen, 2008). The most important tissues involved in the pathogenesis of this disorder are muscle and adipose tissue.

When caloric intake exceeds energy expenditure, the resultant substrate-induced increase in citric acid cycle activity generates an excess of ROS (Maddux *et al.*, 2001). Oxidative stress alters the intracellular signaling pathway, inducing insulin resistance (Evans *et al.*, 2003). Recently, a study with a murine model (Matsuzawa-Nagata *et al.*, 2008) has shown that the pathways for ROS production and oxidative stress are up-regulated in both the liver and adipose tissue of mice fed a high-fat diet before the onset of insulin resistance. Moreover, the increased ROS production was previous to the TNF-α and FFA elevation in the plasma and liver. In agreement with this hypothesis, insulin resistance is associated with reduced intracellular anti-oxidant defense in humans (Bruce *et al.*, 2003), and anti-oxidants improve insulin sensitivity (Paolisso and Giugliano, 1996; Ceriello, 2000).

There is a spectrum of potential molecular and cellular damage derived from ROS production. Lipoprotein modification takes place in the absence (glycation) and presence (glycoxidation) of oxygen (Baynes and Thorpe, 2000), and these modifications can alter their structure and function (Jenkins *et al.*, 2004). These modified lipoproteins are formed through a non-enzymatic process in which sugars bind to free amino groups of the lipoprotein (Njoroge and Monnier, 1989; Basta *et al.*, 2004).

Lipid peroxidation is the formation of lipid peroxides *via* an enzymatic and/or a non-enzymatic mechanism. ROS resulting from hyperglycemia are thought to contribute to the initiation of lipid peroxidation (Cosentino *et al.*, 1997). Once formed, lipid peroxides undergo a series of complex reactions, ultimately binding chemically to proteins. Thus, lipoxidation is the covalent binding of products of lipid peroxidation reactions to proteins (Esterbauer *et al*., 1991, 1992; Spiteller, 1998; Jenkins *et al.*, 2004).

Several studies have demonstrated a relationship between MetS and oxidative stress in humans. Thus, systemic oxidative stress is significantly higher in persons with MetS compared with non-obese normolipidemic individuals. Some HDL-C subfractions possess significantly lower specific anti-oxidative activity in affected persons than their counterparts in control individuals, and this attenuated anti-oxidative activity of HDL-C subfractions correlates with systemic oxidative stress and insulin resistance (Hansel *et al.*, 2004). In agreement with these results, persons suffering from MetS have poor anti-oxidant status and significantly increased oxidative stress (serum lipid peroxide level), compared with those without MetS (Sharma *et al.*, 2005). Moreover, obese adults with MetS have significantly higher plasma concentrations of oxidized-LDL-C, compared with obese adults without this condition (Van Guilder *et al.*, 2006). By contrast, Sjogren *et al.* (2005) found no significant differences for plasma oxidized-LDL-C and urinary 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-PGF2α) between healthy and MetS men.

Advanced glycation end-products (AGE) are important markers for oxidative stress, and their endogenous secretory receptor (esRAGE) in plasma, as a soluble decoy receptor for AGE, is significantly and inversely correlated with components of the MetS, including body mass index, blood pressure, triglyceride, glycated hemoglobin (HbA1c), and an insulin resistance index (Koyama *et al.*, 2005).

METABOLIC SYNDROME AND PERIODONTITIS

In spite of extensive clinical research on MetS, relatively little attention has been directed to its possible relationship to periodontitis. The available data come from epidemiological studies. In a group of 1315 affected individuals (30-92 yrs old), the prevalence of MetS was higher among individuals with advanced periodontitis (66.7%) than in periodontally healthy individuals (48.8%) (Borges *et al.,* 2007). Analysis of data from 13,710 participants in the NHANES III (Third National Health and Nutrition Examination Survey) showed a direct relationship between periodontitis and the prevalence of MetS (37% in those with severe periodontitis *vs*. 18% in those with mild or no periodontitis), and, particularly, higher prevalence of obesity (48-54% *vs*. 31%), hypertension (51-56% *vs*. 27%), and high

glucose levels (18-24% *vs.* 8%) were stated to be in the moderate to severe periodontitis group compared with the mild periodontitis or periodontally healthy group (D'Aiuto *et al*., 2008). In another paper (Shimazaki *et al.,* 2007), larger waist circumference, decreased HDL-C levels, and higher fasting glucose levels were associated with significantly higher odds ratios (OR) for greater pocket depth values (1.8, 2.2, and 2.2, respectively) in 584 Japanese women.

To study the pathological aspects behind this epidemiological relationship, one must analyze the different aspects of MetS in relation to periodontitis.

Impaired Glucose Regulation and Periodontitis

There are many papers on the relationship between diabetes and periodontal disease (Liu *et al*., 2006; Graves *et al*., 2007; Mealey and Ocampo, 2007; Nishimura *et al.*, 2007; Preshaw *et al.*, 2007), and evidence of the relationship between a major marker of diabetes, glycated hemoglobin (HbA1c), and periodontal parameters (Grossi *et al.*, 1997; Iwamoto *et al.*, 2001; Stewart *et al.*, 2001; Tsai *et al.*, 2002; Navarro- Sanchez *et al.*, 2007) exists.

As previously mentioned, one of the main common factors between both diseases is oxidative stress. The main studies relating oxidative stress as a common feature in periodontitis and diabetes are shown in Table 4. With respect to neutrophil function, there is no remarkable variation in oxidative burst and chemotaxis (De Toni *et al.*, 1997; Christgau *et al*., 1998; Fontana *et al*., 1999). However, a decreased superoxide-dismutase (SOD) activity, an anti-oxidant enzyme, in gingival tissue from persons with periodontitis but without diabetes (Akalin *et al*., 2008), compared with those with periodontitis and diabetes, might be explained by a potential compensating mechanism in this enzymatic system derived from hyperglycemia. Individuals with periodontitis and diabetes also show decreased activity of one pro-oxidant enzyme, myeloperoxidase, in gingival crevicular fluid (GCF), compared with those without diabetes (Gonçalves *et al.,* 2008). Analysis of these data suggests a dysregulation in oxidative balance derived from neutrophil leukocytes, with a concomitant influence by both conditions. Nevertheless, a critical point in the assessment of neutrophil function is the diversity and variability in assays, so concluding data in this respect are difficult to obtain.

With respect to substances derived from oxidative damage, a correlation exists between plasma lipid peroxidation and periodontal parameters in diabetic individuals (Collin *et al*., 2000; Sonoki *et al*., 2006). Moreover, there is increasing evidence of the deleterious effect of AGE on the pathogenesis (Schmidt *et al*., 1996) and progression of periodontitis (Takeda *et al*., 2006), and this effect could be mediated through the highly expressed RAGE in periodontal tissues (Katz *et al*., 2005). This last study found a similar expression of RAGE between diabetic and non-diabetic individuals by immunohistochemistry, but a higher mRNA level in diabetic individuals. A possible alternative splicing of mRNA from this molecule may explain this finding, and could elucidate differences in this regard between periodontal tissues and other body structures.

Dyslipidemia and Periodontitis

In recent years, several papers have considered the possible relationships between periodontitis and lipid parameters (Table 5). In general, although differences among studies exist, there is an association between increased LDL-C and triglyceride levels, as well as decreased HDL-C levels, and periodontitis. It is important to note the potential importance of oxidative stress in this relationship, because of the correlation existing between clinical periodontal status and plasma levels of anti-oxidized-LDL-C antibodies (Montebugnoli *et al*., 2004). Nevertheless, another report found no association between oxidized LDL-C and periodontal status (Türkoğlu *et al*., 2008). More research focused on the relationship between lipid peroxidation markers and periodontitis is warranted.

Hypertension and Periodontitis

The first report (Perlstein and Bissada, 1977) relating high blood pressure with periodontitis in animals found hyperplasia/hypertrophy in the blood vessel walls from a chronically irritated gingiva in hypertensive and obese-hypertensive rats. However, hypertension alone was not a significant factor. In contrast to this, another report (Leite *et al.*, 2005), in which an experimental ligature-induced periodontitis model was used in spontaneously hypertensive and normotensive rats, found that the ligated sides in the experimental group showed moderate to severe collagen degradation in the alveolar process, compared with mild degradation in controls.

The main studies relating hypertension and periodontitis in humans are shown in Table 6. In general, there is increasing evidence of a relationship between high blood pressure and more severe periodontal parameters, in such a way that individuals with hypertension show a poorer periodontal state (Wakai *et al*., 1999; Khader *et al*., 2003; Al-Emadi *et al*., 2006; Gołebiewska *et al*., 2006; Holmlund *et al*., 2006; Salcedo-Rocha *et al*., 2006; Engström *et al*., 2007), and periodontitis can negatively influence certain features of hypertension, such as an increase in the left ventricular mass (Angeli *et al*., 2003; Valentaviciene *et al*., 2006).

Obesity and Periodontitis

Recently, two exhaustive reviews have presented the main studies relating obesity and periodontitis (Pischon *et al*., 2007; Saito and Shimazaki, 2007), and readers are referred to these valuable sources. Briefly, both papers corroborate an influence of body mass index (BMI) and other anthropometric parameters on periodontitis, although the authors consider several limitations in previous studies. In the future, it would be necessary to use samples stratified by age, gender, and ethnicity, as well as by number of remaining teeth, to confirm those results, and in addition to design longitudinal studies to verify a potential causal relationship. Both reviews also consider adipocytokines as a potential link between obesity and periodontitis. In this respect, several reports relate leptin, adiponectin, and resistin with periodontitis, and are discussed below.

Table 4. Main Studies about Oxidative Stress Parameters in Diabetes Mellitus and Periodontitis in Humans

Reference	Study Population	Country	Age Range (yrs)	Assessment of Periodontitis	Oxidative Parameters	Major Results
Akalin *et al.*, 2008	17 type-2 DM persons with CP (DMCP group) 18 type-2 DM PH persons (DMPH group) 17 persons with CP (CP group) 17 PH control individuals (PH group)	Turkey	29-68	• ≥ 30% ABL* and ≥ 3 teeth with PD ≥ 5 mm	• Gingival SOD (measured as U/mg-protein)	• Gingival SOD activity was decreasing in this order: DMPH > PH > DMCP > CP, with significant difference between DMCP and DMPH, and between CP and DMCP and PH • Inverse correlation between gingival SOD activity and PD, AL, GI, PI
De Toni *et al.*, 1997 Fontana *et al.*, 1999	All participants with CP: 40 DM persons 40 SH individuals	Italy	45-64	• ≥ 16 remaining teeth, excluding 3rd molars • Criteria for CP are not detailed	• NADPH-oxidase activity in PMN by two different assays • Neutrophil chemotaxis	• Depending on the technique used, = NADPH-oxidase activity in both groups, or < in DM persons • No differences in chemotaxis between groups
Christgau *et al.*, 1998	Persons with moderate to severe CP: 20 DM persons 20 SH control individuals	Germany	30-67	• ≥16 remaining teeth • ≥ 6 teeth with PD ≥ 4 mm	• Oxidative burst response of PMN to TNF-α and FMLP, before and after non-surgical periodontal therapy	• No differences between both groups in relation to oxidative burst response. • > oxidative burst response after periodontal therapy, in both groups
Gonçalves *et al.*, 2008	Persons with CP: 20 type-2 DM persons with inadequate metabolic control 20 SH persons	Brazil	30-60	• ≥ 15 natural teeth, excluding 3rd molars and ≥ 4 teeth with ≥ 1 sites exhibiting PD ≥5 mm, clinical AL ≥4 mm, visible plaque and BOP	• Total salivary peroxidase activity • Myeloperoxidase (MPO) antivity in the GCF	• < MPO activity in the GCF for the DM persons, at both baseline and after periodontal therapy
Collin *et al.*, 2000	45 type-2 DM persons 77 control persons	Finland	45-64	• ≥ 1 periodontal pockets > 4 mm	• Salivary MMP-8 and MMP-9 activities • Plasma lipid peroxidation	• Poor metabolic control in DM group was associated with > salivary MMP-8 but < plasma lipid peroxidation
Sonoki *et al.*, 2006	Persons with periodontitis: 5 type-2 DM persons 6 SH persons	Japan	> 40	• ABL > 50% for ≥ 1 tooth and PD > 4 mm for ≥ 1 tooth	• Plasma lipid peroxidation (LPO) • Serum anti-malondialdeyde-modified LDL-C (anti-MDA-LDL-C)	• > LPO in DM compared with control persons, but no differences in anti-MDA-LDL-C between both groups • < LPO in DM persons after periodontal therapy, but not in control individuals

(continued)

Table 4. (continued)

Reference	Study Population	Country	Age Range (yrs)	Assessment of Periodontitis	Oxidative Parameters	Major Results
						• < anti-MDA-LDL-C in both groups after periodontal therapy • In DM persons, BOP tended to correlate with LPO
Katz *et al.*, 2005	Persons with CP: 8 well-controled type-2 DM persons 14 SH persons	USA	Not detailed	• AL ≥ 30% with BOP in the remaining dentition	• Protein expression (immunohistochemistry) and mRNA transcription by RT-PCR of RAGE from gingival biopsies	• Immunohistochemical staining for RAGE in endothelium and basal and spinous layer of gingival epithelium in both groups • mRNA for RAGE was increased in DM persons
Takeda *et al.*, 2006	97 DM persons: 69 CP 28 SH	Japan	57.8 ± 12.1 (mean ± SD)	• ≥ 10 functional teeth • 1 tooth with AL > 5 mm	• plasma AGE	• Plasma AGEs showed a positive correlation to periodontal deterioration (% of teeth with AL > 5 mm) in DM persons
Yoon *et al.*, 2004	52 DM persons 40 SH persons	Germany	57 ± 13, 41 ± 14, respectively (mean ± SD)	• Periodontal parameters not detailed	• Analysis of AGE in saliva by nuclear magnetic resonance (NMR) spectroscopy	• Saliva in DM persons contained AGE, and these products were associated with approximal plaque index

* ABL, alveolar bone loss; AGE, advanced glycation end-products; AL, attachment loss; BOP, bleeding on probing; periodontitis, CP, chronic periodontitis; DM, diabetes mellitus; FMLP, formyl-methyonyl-leucyl-phenylalanine; GCF, gingival crevicular fluid; GI, gingival index; LPO, lipid peroxidation; PD, probing depth; PH, periodontally healthy; PI, plaque index; RAGE, receptor for AGE; RT-PCR, reverse-transcription polymerase chain-reaction; SD, standard deviation; SH, systemically healthy; SOD, superoxide-dismutase; TNF-α, tumor necrosis factor alpha.

ADIPOCYTOKINES AND PERIODONTITIS

The role of adipose tissue in the regulation of glucose homeostasis through insulin action has led to its consideration as a new endocrine organ. Adipocytes secrete a diversity of molecules, currently named adipocytokines, which influence metabolic and immune functions. Leptin and adiponectin are the most studied. Another molecule weakly related to adipocytes in humans, but very important in the inflammatory response and insulin resistance, is resistin (Juge-Aubry *et al.*, 2005; Koerner *et al.*, 2005; Rosen and Spiegelman, 2006).

Leptin and Periodontitis

Leptin negatively regulates the appetite and weight, mainly through a central mechanism involving the hypothalamus. It also can interact with other hormones, such as insulin (Margetic *et al.*, 2002; Guzik *et al.*, 2006). Obesity appears to be a condition of relative leptin resistance, with an elevated circulating level of leptin reported due to an enlarged fat mass (El-Haschimi *et al.*, 2000). Moreover, there is some evidence that leptin is involved in the pathogenesis of atherosclerotic vascular disease (Wolk *et al.*, 2004).

A decreasing leptin level in GCF and gingival tissue is associated with a more deteriorated periodontal status (Johnson and Serio, 2001), and smokers also show reduced GCF leptin levels (Bozkurt *et al.,* 2006), suggesting a protective role of leptin for the periodontium. The relationship between GCF and serum levels of leptin has been recently reported (Karthikeyan and Pradeep, 2007a,b). GCF leptin levels are proportional to BMI. In periodontitis, there is a significant negative correlation between GCF and serum leptin concentration, and these changes are significantly associated with increasing clinical attachment loss. The two possible mechanisms to explain this inverse correlation are shown in Fig. 1. By contrast, a study of periodontitis and MetS (Borges *et al*., 2007) found a higher serum leptin level in healthy and chronic gingivitis individuals than in those with initial/moderate or advanced periodontitis. It is difficult to draw conclusions from this disagreement, because this latter study used pooled data from healthy and MetS individuals.

Adiponectin and Periodontitis

Adiponectin levels remain relatively constant in normal circumstances (Trujillo and Scherer, 2005), but are decreased in

Table 5. Main Studies about Plasma Lipid Parameters and Periodontitis in Humans

Reference	Study Participants	Country	Age Range (yrs)	Assessment of Periodontitis	Serum Lipid Parameters	Major Results
Cutler *et al.*, 1999	6 SH PH 7 SH CP 6 well-controlled DM and PH 5 well-controlled and CP 5 poorly-controlled DM and PH 6 poorly-controlled DM and CP	USA	28.2 ± 4.6 42.9 ± 11.9 52 ± 6.4 65.8 ± 6.3 45 ± 5.3 42.5 ± 13.6 respectively (mean ± SD)	• ≥ 4 periodontal pockets with ≥ 6 mm with BOP and radiographic evidence of ABL* > 50%	• Total cholesterol • HDL-C • LDL-C • TG	• TG levels tended to be higher in those groups without CP
Wakai *et al.*, 1999	517 males 113 females	Japan	23-83	• CPITN	• Total cholesterol • HDL-C • LDL-C • TG	• > HDL-C level was associared with < CPITN
Lösche *et al.*, 2000	39 moderate CP 40 PH control individuals	Germany	50-60	• > 3 pockets with a PD ≥ 4 mm	• Total cholesterol • LDL-C • TG	• > Total cholesterol, LDL-C and TG for CP group
Noack *et al.*, 2000	56 individuals with IGT 17 individuals with hyperlipidemia 27 SH control individuals	Germany	40-70	• PD • AL • BOP • PI	• Total cholesterol • TG	• > No. sextants with increased PD in hyperlipidemia group compared with control individuals • + correlation between serum TG levels and PD in the overall sample
Wu *et al.*, 2000	10,146 participants from NHANES III	USA	40.37 ± 17.28 (mean ± SD)	• No disease: no tooth examined with PD ≥ 2 mm or AL ≥ 3 mm • Mild CP, ≥ 1 examined tooth with PD ≥ 2 mm or AL ≥ 3 • CP ≥ 1 tooth with PD ≥ 3 mm or AL ≥ 4 mm	• Total cholesterol • HDL-C	• There was a weak association between cholesterol level and periodontal status • There was no association between HDL-C and periodontal status
Katz *et al.*, 2001	151 individuals diagnosed as having CHD, DM or hypertension 943 SH individuals	Israel	26-53	• CPITN	• Total cholesterol • TG	• Persons with hypercholesterolemia had more severe CP, according to CPITN score • There was no association between TG and periodontal status
Katz *et al.*, 2002	9421 military men 1169 military women	Israel	19-61	• CPITN	• Total cholesterol • HDL-C • LDL-C • TG	• A CPITN score of 4 is strongly associated with total and LDL-C cholesterol and negatively associated with HDL-C in men
Craig *et al.*, 2003	25 PH persons 44CP persons	USA	29.9 ± 1.1 38.7 ± 1.3 respectively (mean ± SD)	• ≥ 20 teeth and ≥ 4 sites with PD > 3 mm and ≥ 4 sites with AL > 3 mm	• Total cholesterol • HDL-C • LDL-C • TG	• > Total cholesterol and LDL-C levels for CP group • < HDL-C for CP group • > TG levels for CP persons, but without a statistical significance

(continued)

Table 5. (continued)

Reference	Study Participants	Country	Age Range (yrs)	Assessment of Periodontitis	Serum Lipid Parameters	Major Results
Saito *et al.*, 2003	179 men	Japan	50-54	• ≥ 10 remaining teeth • ABL (panoramic Rx)	• Total cholesterol • HDL-C • TG	• There was a negative correlation between HDL-C levels and ABL
Joshipura *et al.*, 2004	377 PH men 91 CP men	USA	43-80	• The participant reported being professionally diagnosed with CP	• LDL-C	• LDL-C showed a positive correlation with CP, and this result persisted after subsequent adjustment for dietary factors
Montebugnoli *et al.*, 2004	63 men with CHD 50 healthy men	Italy	40-65	• CPSS (clinical periodontal sum score): the sum of the No. sites with PD ≥ 4mm, No. gingival sites with BOP, visible suppuration on probing, No. furcation lesions exceeding grade 1	• Total cholesterol • HDL-C • LDL-C • TG • Serum antibodies against oxidized LDL-C (anti-Ox-LDL-C)	• There was a significant relationship between CPSS and anti-Ox-LDL-C • There was no association between periodontal status and total cholesterol, LDL-C, HDL-C, or TG levels
Morita *et al.*, 2004	133 persons from Japanese rural communities, with and without CP	Japan	NA	• CPI	• Total cholesterol • HDL-C • LDL-C • TG	• > TG level for CP group • < HDL-C for CP group, but without a statistical significance
Lösche *et al.*, 2005	32 persons with CP receiving periodontal treatment	Germany	23-69	• Criteria for periodontitis are not detailed	• Total cholesterol • HDL-C • LDL-C • TG	• No association between lipid parameters and BOP, PD, or AL • No variation in lipid levels before/after periodontal therapy (6-8 weeks later)
Machado *et al.*, 2005	30 moderate to severe CP 30 PH control individuals	Brazil	43.3 ± 9,2 44.3 ± 9,7 respectively (mean ± SD)	• ≥ 2 sites with PD ≥ 5 mm	• Total cholesterol • HDL-C • LDL-C • TG	• No significant differences between groups
Nishimura *et al.*, 2006	131 non-obese type-2 DM persons	Japan	36-84	• Periodontal examination was not performed	• HDL-C • LDL-C • TG	• Association between LDL-C and serum antibody titer to *Porphyromonas gingivalis*
Valentaviciene *et al.*, 2006	140 women 121 men	Lithuania	38 (mean)	• CPITN	• Total cholesterol • HDL-C • LDL-C • TG	• No association between lipid parameters and CPITN
Furukawa *et al.*, 2007	100 type-2 DM persons	Japan	29-77	• PD	• Total cholesterol • HDL-C	• Total cholesterol was significantly correlated with mean PD • HDL-C was inversely correlated with PD (but no statistical significance)
Nibali *et al.*, 2007	302 persons with severe periodontitis (aggressive and chronic forms) 183 PH control individuals	United Kingdom	38-48	• Aggressive period • (Armitage 1999) • Chronic period: ≥ 20 teeth and 50% of sites exhibiting PD ≥ 5mm and marginal ABL > 30%	• Total cholesterol • HDL-C • LDL-C • Cholesterol/ HDL-C ratio • TG	• LDL-C levels were significantly increased in periodontitis persons • HDL-C levels were significantly decreased in periodontitis persons • Cholesterol/HDL-C ratio was significantly higher in periodontitis persons

(continued)

Table 5. (continued)

Reference	Study Participants	Country	Age Range (yrs)	Assessment of Periodontitis	Serum Lipid Parameters	Major Results
Oz *et al.*, 2007	51 periodontitis persons assigned to the treatment or control groups	Turkey	36-66	• > 3 sites with PD ≥ 4 mm	• Total cholesterol • HDL-C • LDL-C • TG	• There was a significant decrease in cholesterol and LDL-C levels after treatment (3 months later)
Türkoğlu *et al.*, 2008	72 persons, divided into healthy control individuals, PH-EHT, G-EHT, CP-EHT	Turkey	44.83± 8.4454.35± 11.14 49.71±7.30 54.38±6.76 respectively (mean ± SD)	• ≥ 4 non-adjacent teeth with sites with AL ≥ 4mm and PD ≥ 5 mm, BOP at >50% of sites	• Oxidized LDL	• No differences in oxidized-LDL-C between groups

* ABL, alveolar bone loss; AL, attachment loss; BOP, bleeding on probing; CHD, coronary heart disease; CP, periodontitis; CPITN, community periodontal index of treatment needs; DM, diabetes mellitus; EHT, essential hypertension; G, gingivitis; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NA, not available; NHANES III, Third National Health and Nutrition Examination Survey; PD, probing depth; PH, periodontally healthy; PI, plaque index; SD, standard deviation; SH, systemically healthy.

Table 6. Published Reports about Arterial Hypertension and Periodontitis in Humans

Reference	Study Participants	Country	Mean Age (yrs ± SD)	Assessment of Periodontitis	Vascular Parameters	Major Results
Al-Emadi *et al.*, 2006	210 moderate or severe CP 210 PH or mild CP	USA	46.95 (± 16.17)	• ≥ 20 remaining teeth • Moderate/severe CP: mean ABL* ≥ 2.5 mm	• Self-reported HBP	• > HBP prevalence in subjetcs with moderate to severe ABL (34.3% vs. 7.6%)
Angeli *et al.*, 2003	104 persons with EHT	Italy	57 (± 10)	• CPITN	• Echocardiography	• Association between > CPITN score and LVM
Engström *et al.*, 2007	54 persons with known HBP 141 persons with diastolic BP > 90 mmHg during study 195 control persons	Sweden	Mean age in case groups: 49 and 54, respectively	• No. sites ≥ 5 (excluding the third molar)	• Diastolic and systolic blood pressure	• > No. sites ≥ 5 mm in HBP persons • Association between prevalence of deep periodontal pockets and BP status
Gołebiewska *et al.*, 2006	47 persons HBP 57 persons, myocardial infarction (MI), treated with angioplasty	Poland	50-90 (range)	• OHI index • Russell's PI and CPI • Tooth loss according to Eichner's class	• Previous medical diagnosis	• < OHI and poorer periodontal status in persons with HBP, specially those with MI
Higashi *et al.*, 2008	32 CP+, HBP- 20 control individuals 38 CP+, HBP+ 24 CP-, HBP+	Japan	25 ± 3, 26 ± 3, respectively 54 ± 13, 56 ± 12, respectively	• Self-reported periodontal status	• Forearm blood flow (FBF) response to acetylcholine (ACh)	• < FBF response to ACh in both CP groups • Periodontal therapy ↑ ACh-induced vasodilation in CP individuals
Holmlund *et al.*, 2006	3,352 persons with history of HBP or myocardial infarction 902 control individuals	Sweden	45 ± 17	• Periodontal disease severity index (PDSI), combining ABL and BOP	• HBP was defined as drug treatment for this disease	• Association between severity of CP and No. of periodontal pockets with HBP

(continued)

Table 6. (continued)

Reference	Study Participants	Country	Mean Age (yrs ± SD)	Assessment of Periodontitis	Vascular Parameters	Major Results
Khader *et al..*, 2003	603 participants from general population	Jordan	15-65 (range)	• PD, AL, PI • Gingival recession	• Questionnaire for general health	• Having HBP was significantly associated with increased AL and gingival recession
Salcedo-Rocha *et al..*, 2006	363 persons with overweight-obesity, HBP or DM, or a combination of them	Mexico	50.05 ± 9.70	• Periodontal criteria not detailed	• Blood pressure	• In the sample, HBP group showed the poorest periodontal status
Türkoğlu *et al.*, 2008	72 individuals, divided into healthy control individuals, PH-EHT, G-EHT, CP-EHT	Turkey	44.83 ± 8.44, 54.35 ± 11.14, 49.71 ± 7.30, 54.38 ± 6.76, respectively	• ≥ 4 non-adjacent teeth with sites with AL ≥ 4mm and PD ≥ 5 mm, BOP at >50% of sites	• Serum IgM and IgG anti-cardiolipin	• > mean IgM anti-CL levels and > prevalence of persons with IgM anti-CL+ in CP-EHT group
Valentaviciene *et al.*, 2006	140 women 121 men	Lithuania	38	• CPITN	• Echocardiography	• < LVM index in PH/G persons compared to CP
Wakai *et al.*, 1999	517 males 113 females	Japan	23-83	• CPITN	• Blood pressure	• > systolic BP was associated with > CPITN

* ABL, alveolar bone lose; AL, clinical attachment level; anti-CL, anticardiolipin antibodies; BOP, bleeding on probing; BP; blood pressure; CP, periodontitis; CPI, community periodontal index; CPITN, community periodontal index of treatment needs; DM, diabetes mellitus; EHT, essential hypertension; FBF, forearm blood flow; G, gingivitis; HBP, hypertension; LDL-C, low-density lipoprotein-cholesterol; LVM, left ventricular mass; OHI, oral hygiene index; PD, probing depth; PH, periodontally healthy; PI, plaque index.

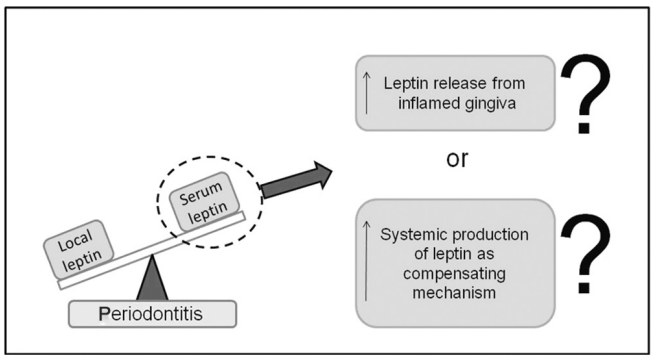

Figure 1. Increased serum leptin levels in periodontitis. Two putative explanations have been proposed. First, gingival inflammation would result in vasodilation, which might increase the net rate of leptin removal from the gingiva and increase serum leptin levels. The second hypothesis states that serum leptin levels rise as a body defense mechanism to counteract periodontal inflammation (according to Karthikeyan and Pradeep, 2007b).

obesity, insulin resistance, and diabetes, and in cardiovascular disease with increasing severity (Matsuzawa *et al.*, 2004). This reduction appears to precede these disorders, and low adiponectin levels have been shown to predict the development of insulin resistance and type 2 diabetes (Spranger *et al.*, 2003; Yamamoto *et al.*, 2004). Thus, adiponectin has a key role in the development of MetS.

Currently, there is no report of adiponectin in periodontal tissues or GCF. By an *in vitro* approach, adiponectin acts as a potent negative regulator of the osteoclast formation induced by *Aggregatibacter actinomycetemcomitans* lipopolysaccharide (LPS). Therefore, adiponectin could exert an anti-inflammatory effect in periodontitis sites, and thereby have a negative influence over the onset and progression of periodontitis (Yamaguchi *et al.*, 2007). In humans, two recent studies (Furugen *et al.*, 2008; Saito *et al.*, 2008) have found that serum adiponectin levels tended to decrease in Japanese persons with periodontitis, albeit not significantly. Moreover, adiponectin levels were negatively correlated with mean attachment loss, but not mean probing depth or percentage of sites bleeding on probing. Another study (Iwamoto *et al.*, 2003) found that serum adiponectin levels did not change significantly after periodontal therapy. However, small sample size, lack of a control group, and a longer period for additional measures are relevant limitations in this study.

Resistin and Periodontitis

In humans, resistin is mainly secreted by monocytes, macrophages, and bone marrow, but also by adipocytes. It has a potent pro-inflammatory action. This molecule has been associated with insulin resistance in mice (Koerner *et al.*, 2005). Two recent studies confirm the role of this molecule in periodontitis; serum resistin levels are higher in persons with periodontitis than in control individuals, and there is a positive correlation with bleeding on probing (Furugen *et al.*, 2008; Saito *et al.*, 2008).

OXIDATIVE STRESS AS A POTENTIAL LINK BETWEEN PERIODONTITIS AND METABOLIC SYNDROME

As previously mentioned, oxidative stress is one of the main factors studied to explain the pathophysiological mechanisms of inflammatory conditions, such as MetS and periodontitis. A recent and exhaustive review (Chapple and Matthews, 2007) has described the complex role of oxidative stress in relation to periodontal breakdown. It seems that peripheral blood neutrophil hyperactivity in chronic and aggressive periodontitis exists as a constitutional element (Matthews *et al*., 2007a,b), rather than being entirely the result of peripheral priming by cytokines or plaque bacterial LPS. In addition, there may be possible baseline hyperactivity, with low-level extracellular ROS release in the absence of any exogenous stimulus in persons with periodontitis (Gustafsson and Asman, 1996; Gustafsson *et al*., 1997; Fredriksson *et al*., 1998; Matthews *et al*., 2007b).

There is increasing evidence for compromised anti-oxidant capacity in periodontal tissues and fluids, independent of smoking, and increased AGE levels in persons with type 2 diabetes and in smokers, which are risk factors for periodontitis. Such oxidation products can increase neutrophil adhesion, chemotaxis, and priming in hyper-reactive neutrophils, and might augment the damaging effects of the resultant oxidative stress (Brock *et al.*, 2004; Palmer *et al.*, 2005; Panjamurthy *et al.*, 2005). In addition to this, the up-regulation of pro-inflammatory transcription factors, such as NF-κB and activating protein-1, in inflamed periodontal tissues contributes to reduced glutathione depletion and ROS generation (Chapple, 1997; Janssen-Heininger *et al.*, 2000).

It is important to emphasize the influence of periodontitis on serum and/or plasma oxidative markers in humans. Several studies have demonstrated an increase in products of oxidative damage in peripheral blood from persons with periodontitis compared with control individuals (Battino *et al*., 2001; Montebugnoli *et al.,* 2004; Baltacioglu *et al*., 2008). Moreover, it is evidence of a decreased anti-oxidant capacity in persons with periodontitis, evaluated by different assays (Chapple *et al*., 2002, 2007; Battino *et al.,* 2003; Brock *et al*., 2004; Panjamurthy *et al*., 2005; Baltacioglu *et al*., 2006; Akalin *et al*., 2007; Konopka *et al*., 2007; Zilinskas *et al*., 2007).

Therefore, it might be argued that this increased pro-oxidative state and decreased anti-oxidant capacity in persons with periodontitis could facilitate the onset of a decrease in insulin sensitivity, which could be aggravated by a high fat diet in these persons. This is in agreement with the previously mentioned report which demonstrated that an increase in ROS production precedes insulin resistance (Matsuzawa-Nagata *et al.*, 2008). Conversely, the presence of MetS or any of its components in a previously periodontally healthy person could facilitate a pro-oxidant state which would diminish anti-oxidant capacity of the periodontal tissues, and the response of these tissues to bacterial challenge could be impaired. The presence of a high RAGE expression in periodontal tissues (Katz *et al*., 2005) is an important finding supporting the sensitivity of these tissues to products derived from oxidative damage. Moreover, AGE may promote apoptosis in osteoblasts (Alikhani *et al*., 2007a) and fibroblasts (Alikhani *et al*., 2007b), and this might have an influence on alveolar bone homeostasis and the progression of periodontitis. This way, it is plausible to draw a patho-physiological picture in which a bidirectional influence exists between both conditions, with oxidative stress as a common link (Fig. 2).

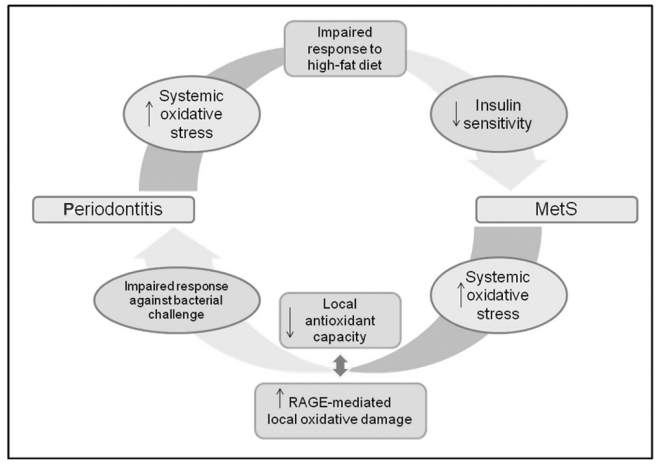

Figure 2. Hypothetic role of oxidative stress as a link between periodontitis and metabolic syndrome (MetS).

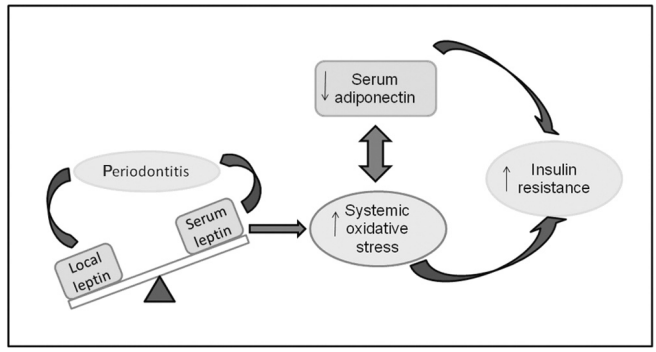

Figure 3. Proposed roles of leptin and adiponectin as putative mediators in the oxidative imbalance enhancing periodontitis and insulin resistance.

Leptin and adiponectin appear as potential candidates to influence in a positive or negative manner, respectively, over the pro-oxidative state in periodontitis and MetS. Leptin has been demonstrated to have a predominantly pro-oxidative effect (Bouloumie *et al*., 1999; Maingrette and Renier, 2003; Suzuki *et al*., 2003; Beltowski *et al*., 2004). The increased serum leptin levels existing in persons with periodontitis, possibly in an attempt to modulate the immune response, could be one of the factors that induces oxidative stress and accelerates the onset of insulin resistance. This increased oxidative stress could facilitate a relative hypoadiponectinemia (Hattori *et al*., 2005; Soares *et al*., 2005; Katsuki *et al*., 2006), like that presenting in persons with periodontitis, which could also decrease the protection against oxidative damage, since this adipocytokine has been demonstrated to have a protective effect against oxidative stress (Nakanishi *et al*., 2005; Barazzoni *et al*., 2007). This picture is ideal for the onset of features comprising MetS (Fig. 3).

CONCLUSIONS

The evidence reviewed indicates that there is a need for further research concerning the possible relationships between MetS and periodontitis, in relation to both local and systemic health and disease. But according to the available reviewed data, we can propose some pathological mechanisms that could explain this relationship. Adipocytokines may act as a link between both conditions, and relevant questions arise which could guide future research: (1) Can gingival keratinocytes or any cell type from gingiva or periodontal ligament express leptin, adiponectin, and/or resistin, or any of their respective receptors? (2) How do these molecules interact with other cytokines in periodontal tissues and influence oxidative stress derived from periodontal breakdown? (3) What is the relationship between serum and GCF levels of these molecules in systemically healthy and MetS persons, with or without chronic gingivitis and/or periodontitis?

Oxidative stress could be a common mechanism in the development of several features related to both MetS and periodontitis, and perhaps an interaction between both conditions may result in a worse evolution of both of them. To elucidate the potential association between both conditions, several approaches are suggested:

(1) Design large-scale studies to assess biomarkers of oxidative stress and anti-oxidant defenses in persons suffering from MetS, with and without periodontitis at several grades of severity, to facilitate comparisons between both conditions and to determine whether periodontitis can affect redox state in persons with MetS. Use of the new definition of this condition (IDF, 2005), applied to different ethnic groups, would be an important element, with the aim of achieving more reliable conclusions.

(2) Analysis of biomarkers of oxidative stress, to obtain a more complete view of the potential interactions between both conditions. All such markers should be analyzed in relation to each component of MetS in persons with and without periodontitis.

(3) Design an intervention study, in which the influence of periodontal therapy (conservative and surgery) on biomarkers of oxidative stress in persons with MetS would be assessed.

All data derived from these and other such approaches would increase the knowledge of the possible interrelationships among periodontitis, MetS, and CVD, with the natural aim of improving their diagnosis, treatment, and, ultimately, prevention.

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