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

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 over-nutrition, and, perhaps, other chronic inflammatory conditions (Dandona et al., 2004, 2007; Fardi and Papadimitriou, 2008). 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).

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

<table>
<thead>
<tr>
<th>Type 2 Diabetes</th>
<th>Impaired Glucose Tolerance (IGT)</th>
<th>Impaired Fasting Glyceria (IFG)</th>
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<tbody>
<tr>
<td>• Single raised glucose reading with symptoms, or</td>
<td>• 2-hour glucose levels of 140-199 mg per dl (7.8-11.0 mmol/L) on a 75-g oral glucose tolerance test</td>
<td>• Fasting glucose level &gt; 5.6 mmol/L (100 mg/dl) and &lt; 6.9 mmol/L (125 mg/dl)</td>
</tr>
<tr>
<td>• 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)</td>
<td></td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Presence of DM, IGT, IFG, or insulin resistance, and 2 of the following features:</td>
<td>At least three of the following:</td>
</tr>
<tr>
<td>• blood pressure ≥ 140/90 mm Hg;</td>
<td>• central obesity, measured as waist circumference ≥ 102 cm in males or ≥ 88 cm in females;</td>
</tr>
<tr>
<td>• 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;</td>
<td>• TG ≥ 1.695 mmol/L (150 mg/dl);</td>
</tr>
<tr>
<td>• central obesity, defined by waist:hip ratio &gt; 0.90 in males or &gt; 0.85 in females, and/or BMI* &gt; 30 kg/m²;</td>
<td>• HDL-C &lt; 40 mg/dL in males or &lt; 50 mg/dL in females;</td>
</tr>
<tr>
<td>• microalbuminuria, defined by a urinary albumin excretion ratio ≥ 20 mg/min or albumin:creatinine ratio ≥ 30 mg/g</td>
<td>• blood pressure ≥ 130/85 mmHg;</td>
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<tr>
<td></td>
<td>• fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL)</td>
</tr>
</tbody>
</table>

* BMI, body mass index; DM, diabetes mellitus; HDL-C, high-density lipoprotein-cholesterol; IFG, impaired fasting glyceria; 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).

**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 (Paolasso 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; Spitteler, 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 sub-fractions 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, Bjorg et al. (2005) found no significant differences for plasma oxidized-LDL-C and urinary 8-iso-prostaglandin F₂α (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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Raised TG</td>
<td>≥ 150 mg/dL or Specific Treatment</td>
</tr>
<tr>
<td>Central obesity</td>
<td>Reduced HDL-C* &lt; 40 mg/dL in males &lt; 50 mg/dL in females or specific treatment</td>
</tr>
<tr>
<td>+ 2 of the following parameters</td>
<td>Raised BP systolic BP ≥ 130 or diastolic BP ≥ 85, or treatment of previously diagnosed hypertension</td>
</tr>
<tr>
<td></td>
<td>Raised FPG FPG ≥ 100 mg/dL or previously diagnosed type 2 diabetes. OGTT is recommended but not necessary</td>
</tr>
</tbody>
</table>

* 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/m², central obesity can be assumed and waist circumference does not need to be measured.**
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; Golebiewska 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

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

(continued)
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

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

(continued)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Participants</th>
<th>Country</th>
<th>Age Range (yrs)</th>
<th>Assessment of Periodontitis</th>
<th>Serum Lipid Parameters</th>
<th>Major Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saito et al., 2003</td>
<td>179 men</td>
<td>Japan</td>
<td>50-54</td>
<td>• ≥ 10 remaining teeth • ABL (panoramic Rx)</td>
<td>• Total cholesterol • HDL-C • TG • LDL-C</td>
<td>There was a negative correlation between HDL-C levels and ABL • LDL-C showed a positive correlation with CP, and this result persisted after subsequent adjustment for dietary factors</td>
</tr>
<tr>
<td>Joshipura et al., 2004</td>
<td>377 PH men, 91 CP men</td>
<td>USA</td>
<td>43-80</td>
<td>• The participant reported being professionally diagnosed with CP</td>
<td>• Total cholesterol • HDL-C • LDL-C • TG</td>
<td>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</td>
</tr>
<tr>
<td>Montebugnoli et al., 2004</td>
<td>63 men with CHD, 50 healthy men</td>
<td>Italy</td>
<td>40-65</td>
<td>• CPSS (clinical periodontal sum score): the sum of the No. sites with PD ≥ 4 mm, No. gingival sites with BOP, visible suppuration on probing, No. furcation lesions exceeding grade 1</td>
<td>• Total cholesterol • HDL-C • LDL-C • TG</td>
<td>No association between lipid parameters and BOP, PD, or AL • No variation in lipid levels before/after periodontal therapy (6-8 weeks later)</td>
</tr>
<tr>
<td>Morita et al., 2004</td>
<td>133 persons from Japanese rural communities, with and without CP</td>
<td>Japan</td>
<td>NA</td>
<td>• CPI</td>
<td>• Total cholesterol • HDL-C • LDL-C • TG</td>
<td>&gt; TG level for CP group • &lt; HDL-C for CP group, but without a statistical significance • No significant differences between groups</td>
</tr>
<tr>
<td>Löschke et al., 2005</td>
<td>32 persons with CP receiving periodontal treatment</td>
<td>Germany</td>
<td>23-69</td>
<td>• Criteria for periodontitis are not detailed</td>
<td>• Total cholesterol • HDL-C • LDL-C • TG</td>
<td>Association between LDL-C and serum antibody titer to Porphyromonas gingivalis • No association between lipid parameters and CPITN</td>
</tr>
<tr>
<td>Machado et al., 2005</td>
<td>30 moderate to severe CP, 30 PH control individuals</td>
<td>Brazil</td>
<td>43.3 ± 9.2, 44.3 ± 9.7 (mean ± SD)</td>
<td>• ≥ 2 sites with PD ≥ 5 mm</td>
<td>• Total cholesterol • HDL-C • LDL-C • TG</td>
<td>No significant differences between groups</td>
</tr>
<tr>
<td>Nishimura et al., 2006</td>
<td>131 non-obese type-2 DM persons</td>
<td>Japan</td>
<td>36-84</td>
<td>• Periodontal examination was not performed</td>
<td>• Total cholesterol • HDL-C • LDL-C • TG</td>
<td>Association between LDL-C and serum antibody titer to Porphyromonas gingivalis • No association between lipid parameters and CPITN</td>
</tr>
<tr>
<td>Valentaviciene et al., 2006</td>
<td>140 women, 121 men</td>
<td>Lithuania</td>
<td>38 (mean)</td>
<td>• CPITN</td>
<td>• Total cholesterol • HDL-C • LDL-C • TG</td>
<td>No significant differences between groups</td>
</tr>
<tr>
<td>Furukawa et al., 2007</td>
<td>100 type-2 DM persons</td>
<td>Japan</td>
<td>29-77</td>
<td>• PD</td>
<td>• Total cholesterol • HDL-C</td>
<td>Total cholesterol was significantly correlated with mean PD • LDL-C was inversely correlated with PD (but no statistical significance)</td>
</tr>
<tr>
<td>Nibali et al., 2007</td>
<td>302 persons with severe periodontitis (aggressive and chronic forms), 183 PH control individuals</td>
<td>United Kingdom</td>
<td>38-48</td>
<td>• Aggressive period (Armitage 1999) • Chronic period: ≥ 20 teeth and 50% of sites exhibiting PD ≥ 5 mm and marginal ABL &gt; 30%</td>
<td>• Total cholesterol • HDL-C • LDL-C • Cholesterol/HDL-C ratio • TG</td>
<td>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</td>
</tr>
</tbody>
</table>

Table 5. (continued)
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<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Participants</th>
<th>Country</th>
<th>Age Range (yrs)</th>
<th>Assessment of Periodontitis</th>
<th>Serum Lipid Parameters</th>
<th>Major Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oz et al., 2007</td>
<td>51 periodontitis persons assigned to the treatment or control groups</td>
<td>Turkey</td>
<td>36-66</td>
<td>&gt; 3 sites with PD ≥ 4 mm</td>
<td>Total cholesterol, HDL-C, LDL-C, TG</td>
<td>There was a significant decrease in cholesterol and LDL-C levels after treatment (3 months later)</td>
</tr>
<tr>
<td>Türkoğlu et al., 2008</td>
<td>72 persons, divided into healthy control individuals, PH-EHT, G-EHT, CP-EHT</td>
<td>Turkey</td>
<td>44.83 ± 8.44-35 ± 11.14</td>
<td>≥ 4 non-adjacent teeth with sites with AL ≥ 4 mm and PD ≥ 5 mm, BOP at &gt;50% of sites</td>
<td>Oxidized LDL</td>
<td>No differences in oxidized-LDL-C between groups</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Participants</th>
<th>Country</th>
<th>Mean Age (yrs ± SD)</th>
<th>Assessment of Periodontitis</th>
<th>Vascular Parameters</th>
<th>Major Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Emadi et al., 2006</td>
<td>210 moderate or severe CP, 210 PH or mild CP</td>
<td>USA</td>
<td>46.95 (± 16.17)</td>
<td>≥ 20 remaining teeth, Moderate/severe CP: mean ABL* ≥ 2.5 mm</td>
<td>Self-reported HBP</td>
<td>&gt; HBP prevalence in subjects with moderate to severe ABL (34.3% vs. 7.6%)</td>
</tr>
<tr>
<td>Angeli et al., 2003</td>
<td>104 persons with EHT</td>
<td>Italy</td>
<td>57 (± 10)</td>
<td>CPITN</td>
<td>Echocardiography</td>
<td>Association between &gt; CPITN score and LVM</td>
</tr>
<tr>
<td>Engström et al., 2007</td>
<td>54 persons with known HBP, 141 persons with diastolic BP &gt; 90 mmHg during study, 195 control persons</td>
<td>Sweden</td>
<td>Mean age in case groups: 49 and 54, respectively</td>
<td>No. sites ≥ 5 (excluding the third molar)</td>
<td>Diastolic and systolic blood pressure</td>
<td>&gt; No. sites ≥ 5 mm in HBP persons</td>
</tr>
<tr>
<td>Golebiewska et al., 2006</td>
<td>47 persons HBP, 57 persons, myocardial infarction (MI), treated with angioplasty</td>
<td>Poland</td>
<td>50.90 (range)</td>
<td>OHI index, Russell’s PI and CPI, Tooth loss according to Eichner’s class</td>
<td>Previous medical diagnosis</td>
<td>Association between prevalence of deep periodontal pockets and BP status &lt; OHI and poorer periodontal status in persons with HBP, specially those with MI</td>
</tr>
<tr>
<td>Higashi et al., 2008</td>
<td>32 CP+, HBP-20 control individuals, 38 CP+, HBP+ 24 CP-, HBP+</td>
<td>Japan</td>
<td>25 ± 3, 26 ± 3, respectively</td>
<td>Self-reported periodontal status</td>
<td>Forearm blood flow (FBF) response to acetylcholine (ACh)</td>
<td>&lt; FBF response to ACh in both CP groups</td>
</tr>
<tr>
<td>Holmlund et al., 2006</td>
<td>3,352 persons with history of HBP or myocardial infarction, 902 control individuals</td>
<td>Sweden</td>
<td>45 ± 17</td>
<td>Periodontal disease severity index (PDSI), combining ABL and BOP</td>
<td>HBP was defined as drug treatment for this disease</td>
<td>Association between severity of CP and No. of periodontal pockets with HBP</td>
</tr>
</tbody>
</table>
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 et al., 2007b).

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).

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).

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 (Bouloumié 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.

ACKNOWLEDGMENTS

Funding for this research was from Università Politecnica delle Marche, Italy, and Grupo de investigación CTS113 Junta de Andalucia, Spain.

REFERENCES


