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*Literature Review Article*

# The interface between metabolic syndrome and periodontal disease

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## Abstract

**Introduction:** Metabolic syndrome (MS) is a complex pathology that combines several risk factors for cardiovascular disease. It is defined by the presence of visceral obesity, elevated triglycerides, decreased HDL, elevated blood pressure and blood glucose. The presence of at least three of these factors characterizes the syndrome. Periodontal disease (PD) is a chronic infection that produces a local and systemic inflammatory response. PD has been suggested as a possible risk factor for some of the components of MS, such as diabetes, obesity and dyslipidemia. **Objective:** The aim of this study was to review the literature about the possible association between periodontal disease and metabolic syndrome and to identify the components of this syndrome that may contribute to this association. **Literature review:** PD in the body produces a subclinical inflammatory state characterized by the release of inflammatory cytokines. **Conclusion:** It is plausible that these substances may contribute to the development of metabolic syndrome.

## Introduction

Metabolic Syndrome (MS) is the denomination proposed by the World Health Organization (WHO) [42], which designates a set of risk factors for cardiovascular diseases (CVDs), such as visceral obesity, dyslipidemia, high hypertension, glucose intolerance and insulin resistance [32], which frequently are presented together.

MS definition is performed through biochemical, anthropometric and hemodynamic indicators [42].

WHO and the National Cholesterol Education Program's Adult Treatment Panel III (NCEP – ATP – III, 2001) [27] have been some of the international organizations formulating criteria for MS definition. The definition by WHO demands the evaluation of the insulin resistance. On the other hand, the definition by NCEP-ATP III does not demand the measurement of the insulin resistance, making its use ease for epidemiological studies [5]. Accordingly, NCEP-ATP III criteria were employed in the execution of the I Brazilian Guideline for the Diagnosis and Treatment of Metabolic Syndrome [5], according to table I:

**Table I** – Criteria for the definition of the metabolic syndrome according to the I Brazilian Guideline for the Diagnosis and Treatment of Metabolic Syndrome

| Components | Gender | Levels |
|---|---|---|
| Visceral obesity (waist circumference) | Men | >102 cm |
| | Women | >88 cm |
| Triglycerides | Men | >150 mg/dL |
| | Women | >150 mg/dL |
| HDL cholesterol | Men | <40 mg/dL |
| | Women | <50 mg/dL |
| Blood pressure | Men | ≥130 mm/Hg or 85mm/Hg |
| | Women | ≥130 mm/Hg or 85mm/Hg |
| Fasting glucose | Men | ≥110 mg/dL |
| | Women | ≥110 mg/dL |

According to NCEP ATP III, an individual should be considered as having MS when he or she presents at least three of the following factors: visceral obesity, hypertriglyceridemia, HDL (reduced cholesterol), altered hypertension and fasting glycemia [27].

The International Diabetes Federation (IDF) conducted a consensus conference on MS definition, in which the ethnic differences were included in the criteria of diagnosis [1], and it emphasized the focus on the visceral obesity as the main component. The fat tissue itself is capable of producing several hormones and proteins involved in the development of diseases related to obesity [32, 33].

The main difference between the guidelines from NCEP ATP III and that from IDF is that the waist circumference cutoffs for Caucasian, Blacks and Hispanics are greater in NCEP ATP III than in IDF [16].

The relatively high prevalence of the metabolic syndrome is a worldwide phenomenon that seems to be increasing in parallel with the obesity prevalence [16]. In USA, 20 to 30% of the adults have MS [16]. In the Japanese population, more than 20% of the population shows insulin resistance and in the adult population with diabetes mellitus type 2 the prevalence of metabolic syndrome ranges from 38 to 53%, depending on the gender and the criterion used [16].

In Brazil, most of the studies have exhibited data of population segments, such as a rural area of the semi-arid region of the state of Bahia (30%) [31]; in the city of Vitória/ES (29.8%) [35]; and in a Japanese-Brazilian population (57%) [14].

The insulin resistance and the proinflammatory states play a key role in the MS pathogenesis [36].

Periodontitis is a chronic infectious disease affecting the world adult population, characterized by the loss of gingival insertion and bone resorption as a result of the infection by periodontal pathogens, such as *Porphyiromonas gingivalis* (Pg), *Prevotella intermedia* (Pi), *Tannerella forsythia* (Tf) and *Aggregatibacter* (Actinobacillus) *actinomycetemcomintans* (Aa) [13].

The local inflammation may initiate a systemic response by the host; therefore, subjects with periodontitis would be more prone to CVDs and other systemic diseases. Risk factors for CVDs, such as the metabolic factors may be affected by the periodontal status [29].

By considering the aforementioned discussion, the aim of this study was to analyze through a literature review the possible association between periodontal disease and metabolic syndrome and to identify the MS component that may contribute to this association.

## Literature review

### The periodontal disease and the components of the metabolic syndrome

Although the bacterial biofilm is necessary for the development of the periodontal disease, it alone is not enough to produce the disease. The host response, through the releasing of a large spectrum of proinflammatory mediators, is responsible for great part of the periodontal tissue destruction observed in the disease [3].

Several other factors possibly contribute to the development of the periodontal disease. Obesity [15, 32, 37], hypertension [30, 39], dyslipidemia [10, 11] and

insulin resistance or diabetes [21, 24-26] – components of the metabolic syndrome – has been suggested as risk factors for periodontal disease.

To study the relationship between the metabolic syndrome and its components with the periodontal disease, as well as the mechanisms behind this association, it is important for helping to clarify how other possible association would occur, that is, among the periodontal disease and the systemic conditions as diabetes type 2 and CVDs [3].

## Periodontal disease and obesity

The obesity, defined by the body mass index (BMI) greater than 30.0 kg/m$^2$, is currently a major public health problem. The obesity prevalence has substantially increased in the last decades in most of the industrialized countries; however, the underlying biological mechanisms of the association between obesity and periodontal disease have not been well known. Cytokines and hormones from the fat tissue may play an important role [32].

The fat tissue, especially the visceral type, acts as an important endocrine organ secreting several bioactive substances, such as adipocytokines. Among the most important ones are the tumor necrosis factor-alpha, leptin, adiponectin and resistin, which may modulate the periodontal response [23, 33].

Leptin controls the appetite, regulates the immune response and the production of inflammatory cytokines. The obesity is associated with the reduction of the sensibility to the effects of the leptin [32], which stimulates the immunological system since it increases the production of cytokines and the phagocytosis by the macrophages [33]. It is a specific hormone of the adipocyte acting as a signaling molecule in the hypothalamus to complete the *feedback* of the lipostatic theory of weight control [23].

In periodontitis, there is a negative correlation among the levels of leptin in the gingival crevicular fluid (GCF), significantly associated with the increasing of the loss of clinical insertion [20]. Two explanations have been proposed for the increase of the serum levels of leptin in periodontitis: firstly, the gingival inflammation would result in vasodilatation, which would increase the serum levels of leptin; secondly, the serum levels of leptin would increase as a defense mechanism of the body, to fight the periodontal inflammation [6].

In the inflammatory periodontal disease, the leptin regulation still needs to be further studied, especially regarding to the epidemiological association between obesity and periodontitis [32, 34].

Other substance secreted by the fat tissue is the adiponectin. Unlikely to other hormones from the fat tissue, the levels of adiponectin are reduced in people with obesity, insulin resistance or diabetes type 2 [32], acting as an inhibitor of the inflammatory process [18].

Experimental models have suggested that adiponectin plays a mediator role in inflammatory diseases [34], acting as a predictor of the insulin resistance and of the diabetes type 2 [18].

Resistin is a specific hormone from the fat tissue recently discovered and it directly induces the insulin resistance in the muscle and liver [12].

Resistin had its role in periodontitis proved by two studies, in which the serum levels were higher in people exhibiting periodontitis than in control subjects, showing a positive correlation with bleeding on probing [12, 34].

Moreover, the releasing of the tumor necrosis factor-alpha both by the liver and the periodontal tissues in response to LPS, endotoxins of gram-negative periodontal pathogens, would contribute to the insulin resistance [37]. Data of a study in humans have suggested that the reduction in the serum concentration of LPS may contribute to the control of the metabolic diseases [2].

A study investigated the role of oral bacterias in the obesity epidemic. The bacterial population in the saliva of overweight women and normal weight women were measured. The percentage of Selenomonas noxia was capable of identifying 98.4% of the overweight women, suggesting the possibility that the bacterial species act as biological indicators for the development of weight gain and participate in the etiology of obesity [15].

## Periodontal disease and dyslipidemia

Among the main factors involved in the increase of the lipid levels in the blood are: the genetics, a diet rich in fat, the metabolic disturbs and the lack of the physical exercises [17]. One issue raised recently is whether the periodontal diseases may be a risk factor for the hyperlipidemia development [4].

Hyperlipidemia has a deregulating effect on the immune-system cells and tissue healing, increasing the susceptibility to infections, such as periodontitis [9]. Current researches have been studied the association of the periodontal disease with systemic diseases, and in this relationship the alterations of lipid metabolism has been shown as a potentially inducing factor [4, 9, 17].

Studies showed that individuals with periodontal disease have higher serum levels of total cholesterol (TC), low density lipoprotein (LDL) cholesterol and triglycerides (TRG), when compared with periodontally healthy individuals [10, 17]. A study showed that women diagnosed with hyperlipidemia had significantly highest levels of the periodontal parameters than control women with normal metabolic status [4].

The alteration in the phenotype of immune cells because of the lipids and the serum elevation of proinflammatory cytokines, such as TNF-α and IL-1β from chronic periodontitis, evidenced the bidirectional relationship between the two conditions [9].

The hyperactivity of the white blood cells caused by the hyperlipidemia increases the production of oxygen radicals, frequently associated with the periodontitis progression in adults [6, 9]. The reduction of the antioxidant capacity in individuals with periodontitis could facilitate the appearance of the insulin resistance [6].

It is still not clear whether the association with periodontal disease and dyslipidemia is an inter-relationship of cause-effect, that is, the periodontitis induces the highest lipid levels or the highest lipid serum levels are predisposing factors for periodontitis [9].

## Periodontal disease and hypertension

Hypertension is a highly prevalent multifactorial disease affecting 30% of adults and it is one of the main causes of cardiovascular mortality and morbidity [40].

The periodontal disease may stimulate the systemic inflammation linked to CVDs. Moreover, the chronic inflammation and the inflammatory cytokines may cause endothelial dysfunction, establishing a connection between inflammation and risk for CVDs. This connection could be mediated by alterations in the vascular resistance and blood pressure (BP) [40].

The Oral Infections and Vascular Disease Epidemiology Study (INVEST) was a research designed to study the hypothesis that periodontal infections would predispose to the accelerated progression of the carotid atherosclerosis, incidence of cerebral vascular accident, myocardial infarction and other cardiovascular diseases [8].

Results of 653 patients in the United States showed that the participants in INVEST exhibited high levels of systolic and diastolic blood pressure and increase the probability of hypertension after the adjustment for conventional risk factors [8].

According to the authors, these data provide the first direct evidence of the relationship between periodontal disease and hypertension through the evaluation of the periodontal bacterial burden. Clinical parameters showing past infection, such as tooth loss, loss of insertion and probing depth were not used. There was a strong positive association between the increase of the subgingival colonization by periodontopathogens, such as *A. actinomycetemcomitans*, *P.gingivalis*, *T. forsythia* and *T. Denticola*, and the hypertension prevalence [8].

Other large-scale study in USA that employed the data from Third National Health and Nutrition Examination Survey (NHANES III) demonstrated that the gingival bleeding – a marker of periodontal inflammation – was significantly associated with high systolic blood pressure and greater chance of hypertension among adults, even after the adjustment for sociodemographic, behavioral, physiologic, and chronic disease factors [39].

Maybe both conditions may be linked to a third common factor, such as genetic predisposition. Only randomized clinical studies can reach a definitive response [30].

## Periodontal disease and insulin resistance/ diabetes type 2

The world is facing a diabetes type 2 pandemic, a fact that has drawn attention not only of the scientists and health professionals, but also of the communication media [19]. Previously considered as a disease from rich countries, diabetes type 2 is now a truly global affliction [19].

The International Diabetes Federation (IDF) foresees that the world incidence of diabetes among individuals aging from 20-79 years-old will increase about 70% in the next 20 years, from 194 million in 2003 to 333 million in 2025 [19].

Diabetes and periodontal disease are two chronic diseases that have been considered as biologically connected [26]. Löe [22] reported periodontitis as the sixth complication from diabetes. It is estimated that the prevalence of diabetic individuals would be the twice or even three times greater than that of the normal population [25].

Hyperglycemia and the formation of the advanced glycation end-products (AGEs) are some of the several possible ways leading to the classical vascular complications of diabetes, also involved in the physiopathology of periodontitis in diabetic individuals [25].

Diabetic patients are more susceptible to develop periodontal disease because of the polymorphonuclear leukocytes and alterations in the collagen metabolism. The formation of AGEs affects the collagen stability and the vascular integrity. AGEs aggregate macrophage and monocyte receptors and they may also stimulate the releasing of interleukin-1 and TNF-α, which provokes an increase of the susceptibility to periodontal disease [21].

Inflammatory cytokines induce the insulin resistance and the chronic inflammatory diseases, including periodontitis [24]. Additionally, both TNF-α and IL-6 are produced in the fat tissue, and one third of circulating IL-6 is derived from the fat tissue, suggesting that obesity, diabetes and periodontitis be mutually related [26].

The degree of the glycemic control is an important variable in the relationship between diabetes and periodontal disease, with greater prevalence and gravity of gingival inflammation and periodontal destruction in those individuals with poor glycemic control [25].

The effect of periodontal treatment on the glycemic control of diabetic patients has been shown in interventional studies [24, 38].

A current meta-analysis systematic review concluded that the periodontal therapy for diabetes type 2 patients may reduce the mean levels of glycated hemoglobin in 40% more than in control individuals that did not received any intervention [38].

Insulin resistance is present in most of the individuals with MS, strongly associated with a series of other components. However, the association with hypertension is weak. Insulin resistance is correlated with the risk of diabetes type 2 and CVDs [1].

The innate immune response is active in periodontitis, which explains the mediator role of the periodontal disease in the etiology of the insulin resistance and diabetes type 2 [21].

MS components have currently shown a considerable prevalence in populations, mainly in industrialized countries where obesity and diabetes have been already an epidemic condition. The relationship of these components with a chronic inflammatory state, common to the periodontal disease, either becomes plausible the interface among each one of these alterations and the periodontal disease or characterizes the syndrome when three or more conditions are together,

In the future, with the standardization of the diagnosis criteria of both conditions, it will be possible to establish whether this biological plausibility will be proven as a real association and therefore improve the preventive and therapeutic measurements. It is highlighted that this evidence will contribute for the prevention of CVDs.

## Discussion

The evaluation of data from NHANES III revealed a greater number of individuals with periodontal disease that were also smokers. The periodontal disease participants had more metabolic syndrome (26%) than those without periodontal disease (17%). There were no differences between these groups regarding to the familiar history of diabetes or coronary artery disease or osteoporosis. The tests of correlation among the variables studied, such as gender, scholarity, and age, in the association with periodontal disease did not show significant results, except for gender ($p = 0.02$) [13].

Another study whose participants showed advanced periodontal disease exhibited more dysmetabolic parameters (2.5 times) than those without periodontitis. The odds ratio observed between periodontitis and metabolic syndrome in the population studied (homogenous, of high socioeconomic status and educational level) was similar to that derived from NHANES III. Most of the participants diagnosed with periodontitis were males. Unlikely to the findings of the literature, there was no significant association between periodontitis and waist circumference [28].

On the other hand, a case-control study with 302 patients exhibiting severe periodontitis and 183 healthy patients (control) had as main finding that the inflammatory and metabolic parameters were associated with their periodontal status. When compared with healthy patients, the severe periodontitis patients showed leukocytosis because of the increase of the number of circulating neutrophils and lymphocytes. Additionally, these individuals also presented dysmetabolic state characterized by the decrease of the serum levels of HDL, and increase of the insulin resistance and LDL [29].

Results from the Health 2000 Survey exhibited that the number of teeth with deep periodontal pockets (≥4 mm) was associated with BMI after the control of confounders such as gender, age, scholarity, number of teeth, smoking, and frequency of physical exercise between men and women, and also between non-smokers. The number of teeth with deep periodontal pockets was associated with the percentage of body fat (BF%) and waist circumference among non-smokers. It is concluded that obesity is at least an independent risk modifier for periodontal disease. However, because of the study design (cross-sectional), the possible causal role of the periodontal infection in the etiology of the weight gain could not be evaluated [37].

A cohort study in USA found a strong positive association between the increase of the subgingival colonization by *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia* and *T. denticola* (periodontopathogens) and the prevalence of hypertension. These associations remained positive in the subgroup gender, although the results had been stronger between men than women [40].

A study with the data from NANHES III evaluated the relationship among the different markers of inflammation/periodontal disease and blood pressure. The periodontal disease markers were associated with the results of blood pressure through regression models, with adjustment for confounders. All periodontal parameters had significant association with hypertension. Gingival bleeding was significantly associated

with the increase of the systolic blood pressure and a greater chance of hypertension. When the analysis was repeated among the participants who did not use antihypertensives, the results were replicated, allowing further evidence of the association between periodontal inflammation and high blood pressure [39].

None study, however, clearly demonstrated that the periodontal disease treatment reduces the blood pressure or that the blood pressure reduction improves the periodontal status. It would be interesting to test the effect of the periodontal treatment on the efficacy of antihypertensive drugs, or vice versa. In the prospective studies of populations or patients, the relevant co-variables should be measured, including food habits, tobacco use, alcohol consumption, and dental hygiene [30].

Concerning to hyperlipidemia, there were studies reporting significant association with the levels of serum lipids and the severity of periodontal disease [9].

A study with 30 individuals with hyperlipidemia and 30 control patients evaluated the body mass index (BMI) and the clinical periodontal parameters: plaque index (PI), bleeding on probing (BP), pocket deepness (PD) and level of clinical insertion (LCI), in addition to the biochemical parameters, including triglycerides, total cholesterol, low density lipoprotein (LDL-C) and high density lipoprotein (HDL). The results exhibited that female patients with hyperlipidemia showed higher values of the periodontal parameters in comparison with control individuals. Notwithstanding, studies with larger samples in mixed populations are necessary to determine the association with hyperlipidemia and periodontal disease [4].

Other study evaluated the effect of the periodontal treatment on the control of dyslipidemia of patients in treatment with statins. All parameters of the lipids decreased after the periodontal treatment, but only the decrease of the total cholesterol ($p = 0.002$) and of the low density lipoprotein cholesterol ($p = 0.003$) reached statistically significance compared with the basal levels. This result suggested that a better periodontal health may influence the metabolic control of hyperlipidemias [9].

The bidirectional association between periodontal disease and diabetes has been already well established in the literature [22, 26].

The systemic inflammation caused by periodontitis has an effect on the development and control of diabetes [21]. Inflammatory cytokines, including TNF-$\alpha$ and IL-6 from periodontal disease, may induce insulin resistance [26].

As part of a vicious circle, the insulin resistance seems to modulate the inflammatory process [26]. The periodontal disease affects the glucose metabolism in diabetic and non-diabetic individuals. By considering the strong causal relationship between obesity and diabetes, it can be concluded that the associations among periodontal disease, diabetes, and obesity have not been clarified yet [33].

A meta-analysis systematic review of interventional studies concluded that the periodontal therapy for diabetes type 2 patients is favorable and it can improve the glycemic control of these patients for at least three months [38].

The complex interaction of the inflammatory response of the host to the periodontal infections, obesity and to the alterations of the lipid levels may be responsible for the state of insulin resistance reported in individuals with periodontal disease. Such fact would explain the association among periodontal diseases, metabolic syndrome and increase of the future risk of CVDs and diabetes [28].

## Conclusion

The association between periodontal disease and metabolic syndrome is compatible with the hypothesis that the chronic inflammation is an important factor in the physiopathology underlying to these conditions. The local and systemic alterations initiated by the periodontal disease may contribute to a chronic inflammatory state, increasing the probability of developing metabolic syndrome and cardiovascular disease.

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