ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 01, pp.9534-9541, January, 2020

DOI: https://doi.org/10.24941/ijcr.37782.01.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

BIDIRECTIONAL INTERFACE BETWEEN PERIODONTITIS AND METABOLIC SYNDROME – A BRIEF SYNOPSIS

[1,*]Dr. Shaik Sharmila Sufia, [2]Dr. Shabnam Sufia Shaik and [3]Dr. Madhavi Kondeti

[1]M.D.S, Dept of Periodontology, Kadapa, Andhra Pradesh, India
[2]M.B.B.S, M.D. Biochemistry Final Year Post Graduate, Sri Venkateswara Medical College, DR .N.T.R.U.H.S. University, Tirupati, India
[3]M.D. Professor & H.O.D. Department of Biochemistry, Sri Venkateswara Medical College, Dr .N.T.R.U.H.S. University, Tirupati, India

ARTICLE INFO

Article History:
Received 12th October, 2019
Received in revised form
28th November, 2019
Accepted 09th December, 2019
Published online 30th January, 2020

Key Words:
Periodontitis, Metabolic syndrome, Hypertension, Triglycerides, Diabetes Mellitus.

ABSTRACT

Periodontitis is the most common multifactorial oral disease of microbial origin characterized by loss of attachment apparatus of tooth leading to edentulism if left untreated. It releases systemic and local inflammatory byproducts which are the possible risk factors for major components of the metabolic syndrome such as Diabetes, obesity, hypertension. Metabolic syndrome is a complex pathology that constitutes of increased plasma glucose, hypertension, hypertriglyceridemia, low HDL cholesterol, elevated abdominal circumference. The presence of above any 3 factors constitute this syndrome. Therefore, this reviewarticle will emphasize on iniquitous relationship between periodontitis &metabolic syndrome, their pathophysiology and evidence / lack of evidence in supporting their association in disease progression.

Citation: ***Dr. Shaik Sharmila Sufia, Dr. Shabnam Sufia Shaik and Dr. Madhavi Kondeti.*** **2020.** "Determinants of Adoption of Improved Chicken Packages: The Case of Wolaita Zone, Southern Ethiopia", *International Journal of Current Research*, 12, (01), 9534-9541.

INTRODUCTION

Periodontitis is a chronic inflammatory disease, the initial phase of disease process is called "gingivitis", which clinically presents as swelling & bleeding gums. The disease process is reversible if maintained proper oral hygiene, if neglected gingivitis may extend into "periodontitis", an irreversible process resulting in gradual deterioration of periodontium. Clinically periodontitis presents with supra/sub gingival calculus, diastema, halitosis, edematous gingiva, suppuration from periodontal pockets. Clinically it is evaluated by periodontal probe and radiographically evidenced by horizontal / vertical bone loss. The transition of gingivitis to periodontitis is a complex process, involving a qualitative change in microbial flora and other local, genetic factors[1].

Periodontitis case definition& diagnostic criteria: In the context of 2017 World Workshop, suggested that patient with the below following criteria considered as periodontitis (Tonetti, 2018):

- Interdental CAL is detectable at ≥2mm in non-adjacent teeth
- Buccal or labial CAL ≥3 mm with pocketing >3 mm is detectable at ≥2 teeth and the observed CAL cannot be ascribed to non-periodontal causes such as: gingival recession of traumatic origin, dental caries extending in the cervical area of the tooth, the presence of CAL on the distal aspect of a second molar and associated with malposition or extraction of a third molar, an endodontic lesion draining through the marginal periodontium and the occurrence of a vertical root fracture.

In summary, diagnosis for a periodontitis patient should encompass three dimensions:

- Definition of periodontitis is based on detectable CAL loss at two non-adjacent teeth.
- Identification of the form of periodontitis: necrotizing periodontitis, periodontitis as a manifestation of systemic disease or periodontitis.
- Description of the presentation and aggressiveness of the disease by stage and grade.

Corresponding author: **Dr. Shaik Sharmila Sufia,**
M.D.S, Dept of Periodontology, Kadapa, Andhra Pradesh, India.

Prevalance: Periodontitis is a globally widespread pathology of the human oral cavity. Approximately 10% of the global adult population are highly vulnerable to severe periodontitis, and 10–15% appears to be completely resistant to it, while the remainder varies between these two situations.

Etiopathogenesis of periodontitis: Periodontitis is a chronic multifactorial disease characterized by an inflammation of the periodontal tissue, which is associated with dysbiotic plaque biofilms mediated by the host, resulting in the progressive destruction of the toothsupporting apparatus and loss of periodontal attachment. The bacterial biofilm constitutes of different strains and specieswhich initiates gingival inflammation; however, periodontitis initiation and progression depend on dysbiotic ecological changes in the microbiome in response to nutrients from gingival inflammatory and tissue breakdown products and anti-bacterial mechanisms. This leads to the activation of several key molecular pathways, which ultimately activate host-derived proteinases that enable loss of marginal periodontal ligament fibers, apical migration of the junctional epithelium, and allows apical spread of the bacterial biofilm along the root surface. The development of gingivitis and periodontitis can be divided into a series of stages: initial, early, established, and advanced lesions (Page, 1976).

During the initial lesion, an acute exudative vasculitis in the plexus of the venules lateral to the junctional epithelium and migration of polymorphonuclear (PMN) cells through the junctional epithelium into the gingival sulcus, loss of perivascular collagen were observed. The early lesion characterized by a dense infiltrate of T lymphocytes and other mononuclear cells, as well as by the pathological alteration of the fibroblasts. Subsequently, the established lesion dominated by activated B cells (plasma cells) and accompanied by further loss of the marginal gingival connective tissue matrix, but no bone loss is yet detectable. Several PMN continue to migrate through the junctional epithelium, and the gingival pocket is gradually established. Finally, in the advanced lesion, plasma cells continue to predominate as the architecture of the gingival tissue is disturbed, together with the destruction of the alveolar bone and periodontal ligament. It is characterized by a conversion of junctional epithelium to the pocket epithelium, formation of denser inflammatory infiltrate composed of plasma cells and macrophages, loss of collagen attachment to the root surface, and resorption of the alveolar bone (Kornman, 2000). However, when the balance between the infection control mechanisms and the subgingival biofilm is lost, innate and adaptive immune responses are triggered.

Innate immune response in periodontal disease: The most important characteristic of periodontitis is the inflammatory reabsorption of the tooth-supporting alveolar bone and persistence of a chronic and exacerbated inflammatory immune response. The inflammatory response consists of four main components: (1) endogenous or exogenous factors, such as molecular patterns associated with pathogens (PAMP) and damage (DAMP), which are derived from bacteria, viruses, fungi, parasites, and cell damage, as well as toxic cellular components or any other harmful condition; (2) cellular receptors that recognize these molecular patterns (PRR), for example, Toll-like receptors (TLR); (3) proinflammatory mediators, such as cytokines, chemokines, the complement system, etc.; and (4) target cells and tissues, where these proinflammatory mediators act. The inflammatory immune response is triggered by the interaction of resident cells with the bacterial biofilm attached to the tooth surface, making it impossible for the immune system to eradicate the infecting microorganisms efficiently, perpetuating the insult to the periodontal tissues. Bacteria are capable to cross the junctional epithelium and pass to the gingival conjunctive tissue, where they stimulate the gingival epithelial cells and fibroblasts to trigger the initial inflammatory responses. These resident periodontal cells detect bacterial PAMP, such as lipopolysaccharide (LPS), which binds to the Toll-like receptors (TLR4/2), triggering the recruitment of several protein kinases in the cytoplasmic end of the receptors, ultimately causing the activation of proinflammatory transcription factors, such as nuclear factor kappa B (NFκB) and activator protein 1 (AP-1), which induces the synthesis and release of mediators to trigger the inflammatory response. Likewise, the gingival fibroblasts and the periodontal ligament are responsible for the destruction and disorganization of the fibrous component of the extracellular matrix of the periodontal tissue by increasing the local production and the activity of the matrix metalloproteinases (MMPs).

The periodontal lesion is initiated as acute inflammation characterized by increased numbers of neutrophils migrating into the gingival crevice through the junctional epithelium, which have the de novo biosynthetic capacity for chemokines and cytokines with proinflammatory, anti-inflammatory, or immunoregulatory properties. Neutrophils, through the release of chemokines, can induce the recruitment of interleukin-17-producing CD4-positive T-helper 17 cells to sites of infection or inflammation. In addition, they can promote the survival, proliferation, and development of B cells into antibody-secreting plasma cells. Likewise, it was shown that activated neutrophils express membrane-bound receptor activator of nuclear factor kappa B ligand (RANKL), a key osteoclastogenic cytokine and, thereby able of inducing osteoclastic bone resorption. These recent concepts suggest that neutrophils could contribute to periodontitis not only by initiating the lesion but also by participating in its progression, by recruiting T-helper 17 cells or promoting the accumulation of B cells and plasma cells in the established and advanced lesions. Macrophages are an important source of proinflammatory and potentially destructive molecules for tissues, such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), MMP, and prostaglandin E2, which play an important role and are elevated in the gingival tissue and in the gingival crevicular fluid of patients with chronic periodontitis. Therefore, studies have shown a direct correlation of macrophage infiltration with the severity of periodontal disease, contributing greatly to the intensification of the degradation of the collagen matrix in the connective periodontal tissue. These macrophages may undergo a classical (M1) or alternative (M2) activation. M1 macrophages are induced by microbial agents or by Th1 cytokines and show high phagocytic capacity and an increased expression of proinflammatory cytokines, costimulatory, and antimicrobial molecules. In contrast, M2 macrophages are induced by Th2 cytokines and secrete high levels of IL-10 and transforming growth factor beta 1 (TGF-β1). Therefore, they have immunoregulatory properties and promote cell proliferation and tissue regeneration (José Luis Muñoz-Carrillo, 2019).

Adaptive immune response in periodontal disease: When the inflammatory response becomes chronic, the lymphocytes of the adaptive immune system invade the periodontal tissues releasing inflammatory and immune molecular mediators,

which alter the balance of bone metabolism, marking the transition from gingivitis to periodontitis. The activation of lymphocytes requires two types of signals: a signal induced by the antigen receptor itself when recognizing its related antigen and a costimulatory signal by professional antigen presenting cells (APCs). Therefore, the activation of adaptive immunity has a great influence on the bone loss in periodontitis, associated with B and T lymphocytes. RANKL is a cytokine member of the TNF family that can be bound or secreted to the membrane and stimulates the differentiation of osteoclasts, cell fusion, and activation that leads to bone resorption. Osteoblasts and stromal cells of the bone marrow predominantly express RANKL, which induces osteoclastogenesis through cell contact with osteoclast precursors.

Likewise, activated T and B cells produce both the membrane-bound and soluble RANKL forms. Soluble RANKL can induce osteoclastogenesis independently of direct contact between infiltrating lymphocytes and osteoclast precursors on the bone surface. However, 17 T-helper cells expressing RANKL, but not T-helper 1 cells, activate osteoclasts also by direct cell-cell contact. In periodontitis, the increase in RANKL/OPG promotes the recruitment of osteoclast precursors, their fusion, and subsequent activation, leading to bone resorption. On the other hand, Th1 lymphocytes have a fundamental role in the establishment and progression of periodontitis, through the increase of IFN-γ levels. Th2 lymphocytes are the main cellular source of IL-4, which promotes the change of class to the secretion of IgE in B cells and favors the alternative activation of macrophages in an IFN-γindependent pathway. These effector functions of the Th2 lymphocytes negatively regulate the inflammatory and Th1 lymphocyte responses, so that the polarization of a Th2-type immune response in periodontitis may represent a damaged adaptive immune response. Finally, RANKL can also be secreted by Th17 lymphocytes, which in cooperation with inflammatory cytokines derived from Th1 lymphocytes are capable to tilt bone metabolism favoring bone resorption.

Thus the ulcerated pocket surface acts as a portal entry for the periodontal bacteria its toxic productsand inflammatory mediators are plunged into systemic circulation which leads to a shift in localized periodontitis to a potential systemic condition. Thus severe periodontitis is capable of eliciting low grade systemic inflammation. This association of periodontitis with systemic health led to the emergence of periodontal medicine which establishes substantial relationship between periodontal disease and systemic health.Various pathogenesis have been proposed for association of periodontitis with metabolic syndrome. This review article is amassed with various studies depicting a relation with periodontitis and metabolic syndrome (José Luis Muñoz-Carrillo, 2019).

Metabolic syndrome case definition & diagnostic criteria: Metabolic syndrome is defined by constellation of an interconnected physiological, biochemical, clinical and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease, type II Diabetes mellitus and all-cause mortality. This collection of unhealthy body measurements and abnormal laboratory tests result include atherogenic dyslipidemia, hypertension, and glucose intolerance, proinflammatoryand prothrombic state (Jaspinder Kaur, 2014).

THE DIAGNOSIS OF MS WAS BASED ON TWO CASE DEFINITIONS (IDF, 2005; National Cholesterol Education Program. Expert panel on detection, 2002):

- The National cholesterol education program's adult treatment panel III (NECP-ATP III) and
- International Diabetes federation (IDF).

Prevalence: Worldwide prevalence of MS ranges from <10% to 84% depending on region (urban / rural) and sex, age, race, ethnicity. Based on NCEP-ATP III criteria, 2001 varied from 8% to 43% in men and 7% to 56% in women (R. M. Mabry, 2010; Desroches, 2007; Kolovou, 2007; Cameron, 2004).

Etiopatogenesis of MS: MS is a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, chronic stress are the several factors which constitute the syndrome.

The following conditions have all been described as riskfactors for the development of MS (Lipińska, 2014; Sun , 2012; Green, 2014; Amy, 2008):

- Positive family history
- Smoking
- Increasing age
- Obesity
- Low socioeconomic status
- Mexican American ethnicity
- Postmenopausal status
- Physical inactivity
- Sugary drink and soft drink consumption
- Excessive alcohol consumption
- Western dietary patterns
- Low cardiorespiratory fitness
- Excessive television watching
- Use of antiretroviral drugs in human immunodeficiency virus infection
- Atypical antipsychotic drug use (e.g. clozapine)

There are several hypothesized mechanisms for the underlying pathophysiology of MS, and the most widely accepted of these is insulin resistance with fatty acid flux. Other potential mechanisms include low-grade chronic inflammation and oxidative stress (McCracken, 2018).

Insulin Resistance: Reduced responsiveness to normal insulin levels is an obvious precursor to the development of type 2 diabetes. Considering the main tissues targeted by insulin, insulin resistance in skeletal muscle results in a reduction in glycogen synthesis and glucose transport, whereas insulin resistance in the liver appears to lead to reduced effectiveness of insulin signaling pathways; however, discordant to this observation is evidence that hepatic lipogenesis continues. Precise mechanisms have not been definitively confirmed, and research in this area is ongoing. An alternative hypothesis is that of mitochondrial dysfunction, namely a defect in the process of mitochondrial oxidative phosphorylation. During insulin resistance, the effects of insulin are reduced and the rate of lipolysis will increase, resulting in increased fatty acid production.

Table 1. Periodontitis case definition system based on staging and grading

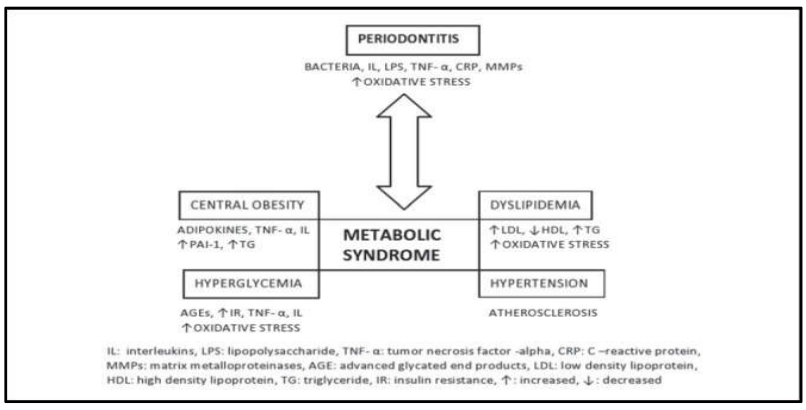
PERIODONTITIS STAGE		STAGE I (Initial Periodontitis)	STAGE II (Moderate Periodontitis)	STAGE III (Severe Periodontitis With Potential For Tooth Loss)	STAGE IV (Advanced Periodontitis With Extensive Tooth Loss And Potential For Loss Of Dentition)
SEVERITY	Interdental CAL Loss	1-2mm	3-4mm	≥5mm	≥5mm
	Radiographic Bone Loss	Coronal Third (<15%)	Coronal Third (15% To 33%)	Extending To Mid-Third Of Root & Beyond	Extending To Mid-Third Of Root & Beyond
	Tooth Loss	No Tooth Loss		Tooth Loss ≤ 4 Teeth	Tooth Loss ≥ 5 Teeth
COMPLEXITY	Local	PD ≤ 4mm Mostly Horizontal Bone Loss	PD ≤ 5mm Mostly Horizontal Bone Loss	In Addition To Stage II Complexity: PD ≥6mm Vertical Bone Loss ≥ 3mm, Furcation Involvement Class II Or III, Moderate Ridge Defect	In Addition To Stage III Complexity: Need For Complex Rehabilitation Due To: Masticatory Dysfunction, Secondary Occlusal Trauma, Tooth Mobility ≥2, Severe Ridge Defect, Bite Collapse, Drifting, Flaring, Less Than 20 Remaining Teeth
EXTENT & DISTRIBUTION		Localized (<30% Teeth Involved), Generalized Or Molar / Incisor Pattern			

Periodontitis grade			Grade a: Slow rate of progression	Grade b: Moderate rate of progression	Grade c: Rapid rate of progression
Primary criteria	Direct Evidence Of Progression Longitudinal Data (Radiographic Bone Loss Or CAL)		Evidence of no loss over 5 years	<2mm over 5 years	≥2mm over 5 years
	Indirect Evidence Of Progression	%Bone Loss/Age	<0.25	0.25 to1.0	>1.0
		Case Phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds biofilm deposits, periods of rapid progression, early onset of disease (molar/ incisor pattern; lack of response to bacterial control therapies
Grade modifiers	Risk Factors	Smoking	Non – smoker	Smoker < 10 cigarettes/day	Smoker ≥ 10 cigarettes/day
		Diabetes	No Diabetes	HbA1c < 7.0%	HbA1c ≥ 7.0%
Risk of systemic impact of periodontitis	Inflammatory Burden	High Sensitivity CRP	<1 mg/L	1 to 3 mg/L	>3mg/L
Biomarkers	Indicators of CAL/ Bone Loss	Saliva, Gingival Crevicular Fluid, Serum	?	?	?

Table 2. MS Diagnostic criteria according to NCEP & IDF criteria

COMPONENTS	REFERENCE LEVELS
Abdominal obesity by abdominal circumference	
men	>102cm
women	>88cm
European men	>94cm
Asian men	>90cm
women	>80cm
Triglycerides (men & women)	≥150mg/ dL
HDL cholesterol	
Men	<40mg/dL
Women	<50mg/dL
Arterial pressure (Men & Women)	≥130mm/Hg or 85mm/Hg
Fasting glucose (Men & Women)	≥110mg/dL

Fig 1. The following hypothesis are suggested to explain the bidirectional relationship between periodontitis and metabolic syndrome



This will potentiate the negative cycle of inhibiting the antilipolytic properties of insulin, leading to further lipolysis (McCracken, 2018; DeFronzo, 1991).

Inflammatory and oxidative mediators: MS is recognized to be a proinflammatory and prothrombic state with adipose tissue being central to its pathophysiology. Adipocytes undergo hypertrophy and hyperplasia in response to nutritional excess that can lead the cells to outgrow their blood supply with induction of a hypoxic state. Hypoxia can lead to cell necrosis with macrophage infiltration and the production of adipocytokines, which include the proinflammatory mediator's interleukin-6 (IL-6) and tumor necrosis factor α, as well as the prothrombic mediator plasminogen activator inhibitor-1 (PAI-1). IL-6 is a potent inflammatory cytokine that plays a vital role in the pathogenesis of insulin resistance and type 2 diabetes. Elevated IL-6 levels have been measured in adipose tissue of patients with diabetes mellitus and obesity and also, notably, in patients with features of MS; further, epidemiologic studies have reported increased IL-6 concentrations in association with hypertension, atherosclerosis, and cardiovascular events. Tumor necrosis factor α, a proinflammatory cytokine named after its antitumor activity, is a significant mediator of numerous cardiovascular pathologic conditions, including atherosclerosis and heart failure. It has been reported to act as a paracrine mediator to reduce insulin resistance in adipocytes.

PAI-1 is a serine protease inhibitor that acts to inhibit tissue plasminogen activator. Circulating PAI-1 is increased in obese MS patients, as well as in patients with type 2 diabetes, and there is a positive correlation between the severity of the MS and the plasma concentration of PAI-1.The mechanism of PAI-1 overexpression in MS likely involves multiple mediators, and the mechanism as yet remains unknown. Interestingly, one group has postulated that in addition to its role in atherothrombosis, PAI-1 is also involved in adipose tissue development and control of insulin signaling (McCracken, 2018). The mechanism by which adipocyte dysregulation occurs is not clearly understood, but a role for obesity-induced oxidative stress is postulated. In human and animal studies there has been a positive correlation between fat accumulation and oxidative stress, with production of reactive oxygen species and increased expression of NADPH oxidase with concomitant decreased expression of antioxidant enzymes. In vitro studies found that cultured adipocytes with increased levels of fatty acids exhibited increased oxidative stress via the NADPH pathway. Antioxidant cytokines that include adiponectin are downregulated in MS, allowing reactive oxygen species to activate an oxidative cascade that leads to apoptosis and cellular damage.When the integrity of the endothelial cell is breached, a cascade is initiated that terminates in atherosclerosis (McCracken, 2018).

Periodontal disease and components of ms: Although the bacterial biofilm is necessary for the development of periodontal disease, the host response through the release of large spectrum of proinflammatory mediators, is responsible for periodontal destruction. This pro inflammatory mediators such as TNF-α and IL-6 along with the periodontal bacteria enter the systemic circulation and produce a "low level systemic inflammation/infection". Several other factors possibly contribute to the development of periodontal disease such as Obesity, hypertension, dyslipidemia and insulin resistance or diabetes.

Periodontitis & insulin resistance: Diabetes and periodontal disease are two chronic diseases that have been considered as biologically connected. Prevalence of DM would be twice or three times greater than that of normal population. The International diabetes federation foresees the incidence of DM among individuals aging from 20-79 yrs old will increase about 70% in the next 20 yrs, from 194 million in 2003 to 333 million in 2025.Loe reported periodontitis as the sixth complication from diabetes (Löe, 1993). Type 2 DM is the most common metabolic disorder characterized by impaired glucose homeostasis, leading to a persistent deterioration of β cell function and hyperglycemia. Increased oxidative stress and chronic subclinical systemic inflammation is contributory to impaired glycemic control and increased IR; thus, paving a way for T2DM. Chronic hyperglycemia facilitates the non-enzymatic glycation of proteins with the formation of advanced glycation end products (AGEs).

AGEs are reported to prime the macrophages to express inflammatory cytokines which releases acute phase reactants CRP from the liver, further exacerbating the existing inflammation. 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. 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. Periodontitis and T2DM reveal a commonality in the pathogenesis process, featuring inflammatory response at the local and systemic level[20]. Various studies have shown a bi-directional relationship between periodontal status and diabetes (Taylor, 2001; Choi, 2011; Morita, 2012; Mealey, 2000). Diabetic patients are more susceptible to develop periodontal disease because of thepolymorphonuclear leukocytes and alterations in thecollagen metabolism. The innate immune response is active in periodontitis, which explains the mediator role of periodontal disease in the etiology of the insulin resistance and diabetes type 2 (Mealey, 2008; Nagasawa, 2010). In 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.

Periodontitis & Obesity: Obesity is defined by the body mass index (BMI) greater than 30.0 kg/m2, a chronic disease, with a multi-factorial etiology. Obesity might represent a systemic condition, cognizable of regulating the onset and progression of periodontitis. The fat tissue, especially the visceral type, acts as an important endocrine organ secreting adipocytokines. Among the most important ones are the tumor necrosis factor-alpha, leptin, adiponectin and resistin, which may modulate the periodontal response. 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, which stimulates the immunological system. The immunologic activity of these adipokines may play a significant role in the development of IR and in periodontitis. Recent cross-sectional studies and a meta-analysis have divulged positive associations between obesity and periodontal disease (Chaffee, 2010; Bullon, 2009; Pischon, 2007; Wood, 2003).

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 (Karthikyan, 2007). Twoexplanations have been proposed for the increase of the serum levels of leptin in periodontitis: firstly, thegingival 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. Recently, Han et al**.** concluded that the visceral fat area was the most appropriate indicator of obesity in relation to periodontitis and that obesity could act as a substantial risk factor for periodontitis (Han, 2010).

Although, the meta-analysis points to a positive association of obesity and periodontitis, the magnitude of the correlation is still not defined. This warrants further prospective studies to clarify the association. Resistin had its role in periodontitis which is 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.Moreover, the releasing of the TNF-α both by the liver and the periodontal tissues in response to LPS, endotoxins of gram negativeperiodontal pathogens, would contribute to the insulin resistance (Furugen, 2008).

Periodontitis & dyslipidemia: Dyslipidemia is a state of abnormal lipid profile, characterized by an increase in the serum concentrations of TGs, total cholesterol and low-density lipoprotein cholesterol, accompanied by a reduction in the levels of high-density lipoprotein (HDL) cholesterol. It has been proposed that dyslipidemia leads to an increase in levels of pro-inflammatory cytokines and oxidative stress. The association between altered lipid profile and periodontitis has been investigated in several studies (Fentoglu, 2008; Awartani, 2010). Although, it is suggested that dyslipidemia could be associated with periodontitis, its role as a risk factor is still under investigation. However, serum pro-inflammatory cytokines may orchestrate a vital role in the association between periodontitis and dyslipidemia. It is proposed that periodontitis is not only associated with the severity of lipid metabolism, but also the aggravation of hyperlipidemic state is linked with periodontal inflammation by the up-regulation of serum and gingival crevicular fluid pro-inflammatory cytokines. Studies have shown 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. 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. The reduction of the antioxidant capacity in individuals with periodontitis could facilitate the appearance of the insulin resistance. 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 (Hamissi, 2010; Cutler, 1999; Katz, 2002; Moeintaghavi, 2005).

Periodontitis & 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. 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. Periodontitis as a risk factor for the establishment of atherosclerosis.Studies have revealed that subjects with advanced chronic periodontitis show increased left ventricular mass. It is proposed that periodontitis induced systemic inflammation may perpetuate atherosclerosis (Huck, 2011; Angeli, 2003). A state of systemic inflammation conduces to the stiffness of large arteries and increases the pulse wave velocity. This arterial stiffness as a result of impairment in elastic properties of large arteries could be a contributory mechanism to the pathogenesis of HT. Further, increased blood pressure adds to the risk of cardiovascular events. In hypertensive subjects, periodontitis may enhance the risk and degree of target organ damage. Although, the present literature shows a possible association between periodontitis and HT, the existence of a causal relationship needs to be ascertained. The effect of periodontitis on the blood pressure of periodontitis affected subjects and the increase of blood pressure with the deterioration in the degree of periodontitis should be examined. Well-designed, prospective randomized controlled trials should be carried out henceforth (Chen, 2008; Tsakos, 2010; Khader, 2008).

DISCUSSION

MS as defined by Reaven consists of obesity, IR, HT, impaired glucose tolerance or diabetes, hyperinsulinemia and dyslipidemia characterized by elevated TG and low HDL concentrations. Two hypotheses could be suggested to explicate the relationship between periodontitis and MS. One hypothesis is a cause-effect relationship. However, longitudinal and large-sample studies are needed to corroborate, which disease is the cause. The other hypothesis proposes a commonality in risk factors (excess caloric intake, sedentary life-style and poor oral hygiene) between the two conditions. It is observed that periodontitis shares some common risk factors with MS, including hyperglycemia, obesity, dyslipidemia and elevated blood pressure. Although, the causative association of periodontitis with most of the mentioned factors is yet to be emphatically proven, periodontitis can pose as a risk factor, capable of modifying the disease course. The inflamed gingival tissue in periodontitis can act as a perennial source of pro-inflammatory cytokines, bacteria and LPS furnishing the impulse for systemic inflammation and infection. It has been reported that the association between periodontitis and MS could be bi-directional (fig 1).

Various studies have demonstrated a statistically significant association between established periodontitis and CVD (D'Aiuto, 2008; Kushiyama, 2009; Nesbitt, 2010; Khader, 2008; Morita, 2009; Li, 2009; Benguigui, 2010). Recently, Buhlin et al**.** showed that periodontal inflammation and bone loss is related to angiographically verified coronary artery narrowing in patients with stable coronary artery disease or acute coronary syndrome (Buhlin, 2011). Romagna et al**.,** in across sectional study on 150 patients, demonstrated that bone loss in periodontitis is associated with a risk of multiple coronary lesions. Studies have reported a positive association between MS and periodontitis (Romagna, 2012). Acharya et al**.** assessed the effect of PT in a sample of periodontitis patients with MS and other group of systemically healthy individuals (control group). The study design consisted of 31 subjects with chronic generalized periodontitis.

This sample was segregated into16 subjects (Group A) diagnosed with MS and 15 subjects as healthy (Group B). Non-surgical PT was instituted in both groups. In both groups; high-sensitivity C-reactive protein (hs-CRP), total leukocyte count, parameters of lipid metabolism were evaluated at baseline and 2 months later. In the MS group, PT produced a significant improvement in the levels of inflammatory metabolic markers as compared with the baseline values. Systemically healthy group showed no statistical change in these markers. Thus, PT produced beneficial effects in patients with MS and chronic periodontitis (Acharya, 2010). Periodontitis and MS shares a common risk factors like excessive caloric intake, sedentary life-style and poor oral hygiene also includes hyperglycemia, obesity, dyslipidemia and elevated blood pressure. Oxidative Stress could be a potential common link to explain the relationship between each component of MS and periodontitis. Since the metabolic alterations observed in that condition can causean exacerbated host inflammatory response, metabolic syndrome individuals could have higher chances of undergoing tissue destruction in the presence of periodontal infection.

Conclusion

Periodontitis is a widely prevalent disease, but if diagnosed in the initial stage can be managed successfully without much morbidity. Many studies point out to the positive relation of MS with periodontitis. Further longitudinal, long-term, well-designed, multi-centric studies based on a large sample sizes are mandatory to boost this relationship. In conclusion, considering its limitations, this literature review suggests an association between MS and PD. Further research in this field could include prospective studies conducted to establish cause and effect relations between these two conditions.

REFERENCES

Socransky SS, Haffajee AD, Cugini MA, Smith C. 1998. Microbial complexes in subgingival plaque. *J ClinPeriodontol.* 25:134– 144.

Tonetti MS, Greenwell H, Kornman KS. 2018. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *Journal of Periodontology.* 89(Suppl. 1):S159-S172.

Page RC, Schroeder HE. 1976. Pathogenesis of inflammatory periodontal disease. A summary of current work. 34(3):235-249.

Kornman KS, Page RC, Tonetti MS. 2000. The host response to the microbial challenge in periodontitis: Assembling the players. *Periodontology,* 1997;14(1):33-53.

José Luis Muñoz-Carrillo, Viridiana Elizabeth Hernández-Reyes, 2019. Oscar Eduardo García-Huerta, Francisca Chávez-Ruvalcaba, María Isabel Chávez-Ruvalcaba, Karla Mariana Chávez-Ruvalcaba and Lizbeth Díaz-Alfaro. June 6th, Pathogenesis of Periodontal Disease, IntechOpen.

Jaspinder Kaur. 2014. A Comprehensive Review on Metabolic Syndrome. Hindawi Publishing Corporation Cardiology Research and Practice, Volume.

IDF. 2005. The Internacional Diabetes Federation consensus world wide definition of metabolic syndrome.

National Cholesterol Education Program. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adults Treatment Panel III). JAMA 2002; 285:2486-2497.

Mabry, R. M., Reeves, M. M., E. G. Eakin , N. Owen.Gender differences in prevalence of the metabolic syndrome in Gulf Cooperation Council Countries: a systematic review. Diabet. Med. 27, 593–597 (2010).

S. Desroches and B. Lamarche, "The evolving definitions and increasing prevalence of the metabolic syndrome," Applied Physiology, Nutrition and Metabolism, vol. 32, no. 1, pp. 23–32, 2007.

G.D. Kolovou, K.K. Anagnostopoulou, K.D. Salpea and D.P. Mikhailidis,"The prevalence of metabolic syndrome in various populations,"The American Journal of the Medical Sciences, vol. 333,no.6,pp.362–371,2007.

A. J. Cameron, J. E. Shaw, and P. Z. Zimmet, "The metabolic syndrome: prevalence in worldwide populations," Endocrinology and Metabolism Clinics of North America, vol.33, no.2, pp. 351–375, 2004.

Lipińska A, Koczaj-Bremer M, Jankowski K, Kaźmierczak A, Ciurzyński M, Ou-Pokrzewińska A, Mikocka E, Lewandowski Z, Demkow U, Pruszczyk P. Does family history of metabolic syndrome affect the metabolic profile phenotype in young healthy individuals?.Diabetology& metabolic syndrome. 2014 Dec;6(1):75.

Sun K, Liu J, Ning G (2012) Active Smoking and Risk of Metabolic Syndrome: A Meta-Analysis of Prospective Studies. PLOS ONE 7(10): e47791.

Green AK, Jacques PF, Rogers G, Fox CS, Meigs JB, McKeown NM. Sugar-sweetened beverages and prevalence of the metabolically abnormal phenotype in the Framingham Heart Study. Obesity. 2014 May;22(5):E157-63.

Amy Z. Fan, Marcia Russell, Timothy Naimi, Yan Li, Youlian Liao, Ruth Jiles, Ali H. Mokdad, Patterns of Alcohol Consumption and the Metabolic Syndrome, The Journal of Clinical Endocrinology & Metabolism**,** Volume 93, Issue 10, 1 October 2008, Pages 3833–3838.

McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. J ClinDermatol. 2018 Jan - Feb; 36 (1):14-20.

DeFronzo RA[1], Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease.Diabetes Care. 1991 Mar;14 (3):173-94.

Löe H. Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care. 1993 Jan;16(1):329-34.

Nishimura F, Iwamoto Y, Mineshiba J, Shimizu A, Soga Y, Murayama Y. Periodontal disease and diabetes mellitus: The role of tumor necrosis factor-alpha in a 2-way relationship. J Periodontol. 2003;74:97–102.

Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: An epidemiologic perspective. Ann Periodontol. 2001;6:99–112.

Choi YH, McKeown RE, Mayer-Davis EJ, Liese AD, Song KB, Merchant AT. Association between periodontitis and impaired fasting glucose and diabetes. Diabetes Care. 2011;34: 381–6.

Morita I, Inagaki K, Nakamura F, Noguchi T, Matsubara T, Yoshii S, et al. Relationship between periodontal status and levels of glycated hemoglobin. J Dent Res. 2012;91:161–6.

Mealey BL, Ocampo Gl. Diabetes mellitus and periodontal disease. Periodontol 2000. 2007;44:127-53.

Mealey BL, Rose LF. Diabetes mellitus and inflammatory periodontal diseases. CurrOpinEndocrinol Diabetes Obes. 2008 Apr;15(2):135-41.

Nagasawa T, Noda M, Katagiri S, Takaichi M, Takahashi Y, Wara-Aswapati N et al. Relationship between periodontitis and diabetes – importance of a clinical study to prove the vicious cycle. Inter Med. 2010;49(10):881-5.

Chaffee BW, Weston SJ. Association between chronic periodontal disease and obesity: A systematic review and meta-analysis. J Periodontol. 2010;81:1708–24.

Karthikyan BV, Pradeep AR. Gingival crevicular fluid and serum leptin: their relationship to periodontal health and disease. J ClinPeriodontol. 2007 Jun;34(6):467-72.

Bullon P, Morillo JM, Ramirez-Tortosa MC, Quiles JL, Newman HB, Battino M. Metabolic syndrome and periodontitis: is oxidative stress a common link? J Dent Res. 2009 Jun;88(6):503-18.

Pischon N, Heng N, Bernimoulin JP, Kleber BM, Willich SN, Pischon T. Obesity, inflammation and periodontal disease. J Dent Res. 2007 May;86(5):400-9.

Wood N, Johnson RB, Streckfus CF. Comparison of body composition and periodontal disease using nutritional assessment techniques: Third National Health and Nutrition Examination Survey (NHANES III) J ClinPeriodontol. 2003;30:321–7.

Han DH, Lim SY, Sun BC, Paek DM, Kim HD. Visceral fat area-defined obesity and periodontitis among Koreans. J ClinPeriodontol. 2010;37:172–9.

Furugen R, Hayashida H, Yamaguchi N, Yoshihara A, Ogawa H, Miyazaki H et al. The relationship between periodontal condition and serum levels of resistin and adiponectin in elderly Japanese. J Periodont Res. 2008 Oct;43(5):556-62.

Fentoglu O, Bozkurt FY. The bi-directional relationship between periodontal disease and hyperlipidemia. Eur J Dent. 2008 Apr;2(2):142-6.

Awartani F, Atassi F. Evaluation of periodontal status in subjects with hyperlipidemia. J Contemp Dent Pract. 2010 Mar 1;11(2):33-40.

Hamissi J, Shahsavarani MT, Shahsavarani H, Sayahpour S, Hamissi H. A comparison of the serum lipid level between patients with periodontitis and healthy individuals. J Periodontol Implant Dent. 2010;2(1):29-32.

Cutler CW, Shinedling EA, Nunn M, Jotwani R, Kim BO, Nares S, et al. Association between periodontitis and hyperlipidemia: Cause or effect? *J Periodontol.* 1999;70:1429–34.

Katz J, Flugelman MY, Goldberg A, Heft M. Association between periodontal pockets and elevated cholesterol and low density lipoprotein cholesterol levels. J Periodontol. 2002;73:494–500.

Moeintaghavi A, Haerian-Ardakani A, Talebi-Ardakani M, Tabatabaie I. Hyperlipidemia in patients with periodontitis. *J Contemp Dent Pract*. 2005;6:78–85.

Huck O, Saadi-Thiers K, Tenenbaum H, Davideau JL, Romagna C, Laurent Y, et al. Evaluating periodontal risk for patients at risk of or suffering from atherosclerosis: Recent biological hypotheses and therapeutic consequences. Arch Cardiovasc Dis. 2011;104:352–8

Angeli F, Verdecchia P, Pellegrino C, Pellegrino RG, Pellegrino G, Prosciutti L, et al. Association between periodontal disease and left ventricle mass in essential hypertension. Hypertension. 2003;41:488–92.

Chen YW, Umeda M, Nagasawa T, Takeuchi Y, Huang Y, Inoue Y, et al. Periodontitis may increase the risk of peripheral arterial disease. *Eur J VascEndovasc Surg*. 2008;35:153–8.

Tsakos G, Sabbah W, Hingorani AD, Netuveli G, Donos N, Watt RG et al. Is periodontal inflammation associated with raised blood pressure? Evidence from a National US survey. J Hypertens. 2010 Dec;28(12):2386-93.

Khader Y, Khassawneh B, Obeidat B, Hamma M, El-Salem K, et al. (2008) Periodontal Status of Patients with Metabolic Syndrome Compared to Those Without Metabolic Syndrome. Journal of Periodontology 79: 2048-2053.

D'Aiuto F, Sabbah W, Netuveli G, Donos N, Hingorani AD, et al. (2008) Association of the Metabolic Syndrome with Severe Periodontitis in a Large U.S. Population-Based Survey. J ClinEndocrinolMetab 93: 3989-3994.

Kushiyama M, Shimazaki Y, Yamashita Y (2009) Relationship Between Metabolic Syndrome and Periodontal Disease in Japanese Adults. Journal of Periodontology 80: 1610-1615.

Nesbitt MJ, Reynolds MA, Shiau H, Choe K, Simonsick EM (2010) Association of periodontitis and metabolic syndrome in the Baltimore Longitudinal Study of Aging. J Aging Clinical and Experimental Research 22: 238-242.

Khader Y, Khassawneh B, Obeidat B, Hammad M, El-Salem K, Bawadi H, et al. Periodontal status of patients with metabolic syndrome compared to those without metabolic syndrome. J Periodontol. 2008;79:2048–53.

Morita T, Ogawa Y, Takada K, Nishinoue N, Sasaki Y, Motohashi M, et al. Association between periodontal disease and metabolic syndrome. J Public Health Dent. 2009;69:248–53.

Li P, He L, Sha YQ, Luan QX. Relationship of metabolic syndrome to chronic periodontitis. J Periodontol. 2009;80:541–9.

Benguigui C, Bongard V, Ruidavets JB, Chamontin B, Sixou M, Ferrières J, et al. Metabolic syndrome, insulin resistance, and periodontitis: A cross-sectional study in a middle-aged French population. J ClinPeriodontol. 2010;37:601–8.

Andriankaja OM, Sreenivasa S, Dunford R, DeNardin E. Association between metabolic syndrome and periodontal disease. Aust Dent J. 2010;55:252–9.

Buhlin K, Mäntylä P, Paju S, Peltola JS, Nieminen MS, Sinisalo J, et al. Periodontitis is associated with angiographically verified coronary artery disease. J ClinPeriodontol. 2011;38:1007–14.

Romagna C, Dufour L, Troisgros O, Lorgis L, Richard C, Buffet P, et al. Periodontal disease: A new factor associated with the presence of multiple complex coronary lesions. J ClinPeriodontol. 2012;39:38–44.

Acharya A, Bhavsar N, Jadav B, Parikh H. Cardioprotective effect of periodontal therapy in metabolic syndrome: A pilot study in Indian subjects. Metab Syndr Relat Disord. 2010;8:335–41.

****