ISSN: 2582 - 3671
Pubmed - National Library of Medicine - ID: 101766917

International Journal of Dental Science and Clinical Research (IJDSCR)

IJDSCR : Dr.Angel Vaidic Publication
Available Online at: http://www.ijdscr.org
Volume – 2, Issue – 6, November - December - 2020, Page No. : 78 - 87

Metabolic Syndrome And Periodontal Disease: A Two Way / Bidirectional Association

[1]Dr. Mukund Khushu, MDS Student, Department of Periodontology and Oral Implantology, National Dental College and Hospital Derabassi, Punjab, India

[2]Dr. Sumit Kaushal, Reader, Department of Periodontology and Oral Implantology, National Dental College and Hospital Derabassi, Punjab, India

[3]Dr. Gurpreet Kaur, Head of Department, Department of Periodontology and Oral Implantology, National Dental College and Hospital Derabassi, Punjab, India

[4]Dr. Deeksha Ahuja Jhatta, MDS Student, Department of Periodontology and Oral Implantology, National Dental College and Hospital Derabassi, Punjab, India

Corresponding Author: Dr. Mukund Khushu, MDS Student, Department of Periodontology and Oral Implantology, National Dental College and Hospital Derabassi, Punjab, India

Type of Publication: Review Paper

Conflicts of Interest: Nil

Abstract

Hardly a day goes by in the world of dentistry without some mention of oral systemic relationship. 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 (MetS) is a cluster of cardiovascular risk factors that include obesity, impaired glucose tolerance or diabetes, hyperinsulinemia, hypertension, and dyslipidemia. Many studies have been done to find the impact of systemic diseases on oral health and found that there is an association between Diabetes, Obesity and Periodontal disease. Furthermore systemic disorders have been found to have a direct effect on periodontal tissues and these represent the periodontal manifestations of systemic disease. Of late metabolic syndrome and periodontal disease have been linked. In this article definition, pathogenesis, about the components of metabolic syndrome and its association with periodontal disease has been reviewed.

Keywords: Metabolic syndrome, Periodontitis, hypertension, insulin resistance, dyslipidemia.

Introduction

Periodontitis is a family of diseases that affect dental supporting tissues, caused by infections sustained by periodontal pathogens such as Porphyromonasgingivalis, Prevotella intermedia, Tannarella forsythia, and Aggregati bacteractinomycetm comintans, which lead to soft and hard tissue destruction, dental mobility, and the loss of dental elements.(1)

Periodontitis in the United States has a prevalence of 30% to 50% of the population, but only about 10% have severe forms. It tends to be more common in economically disadvantaged populations or regions. Its occurrence decreases with a higher standard of living. Individuals of Israeli, Yemenite, North-African, South Asian, or Mediterranean origin have a higher prevalence of

periodontal disease than individuals from European areas (2)

Obesity, hypertension, impaired glucose tolerance, and abnormal lipid metabolism have received a great deal of attention as risk factors for arteriosclerotic diseases, including coronary artery disease and are now described as part of a condition termed metabolic syndrome (MetS), associated with a strong risk of developing diabetes and cardiovascular events.(3)The metabolic syndrome is also known as Syndrome X, dysmetabolic syndrome, deadly quartet and plurimetabolic syndrome.(4)The changes in lifestyle has led to the increased prevalence of metabolic syndrome from developed countries to developing countries like India.

Metabolic syndrome comprises insulin resistance(fasting blood sugar>100mg/l), dyslipidaemia (triacylglycerol >15mg/l, HDL15mg/l), essential hypertension(blood pressure of >130mmHg for systolic and >85mm Hg for diastolic)and visceral obesity(waist circumference of >1020mm for men and >890mm for women)(4). It is estimated that around a quarter of the world's adult population is affected by MetS(5)

There is increasing evidence linking periodontitis to systemic diseases(7)) i.e. The low-grade inflammatory status induced by untreated PD creates a systemic inflammatory phenotype that has been associated with several systemic diseases/disorders, including cardiovascular diseases, insulin resistance and metabolic syndrome (MS).(6)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 (8).

Therefore, the purpose of writing this review is to analyze for a potential relationship between MetS and periodontitis, with oxidative stress acting as a putative link between both conditions.

Metabolic syndrome: current definitions

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 (NCEPATP-III, 2001) (Table 1), and the International Diabetes Federation (IDF, 2005) (Table 2)

Table 1. Definitions of Metabolic Syndrome by WHO and NCEP-ATP-III

WHO (Alberti and Zimmet, 1998)	NCEP-ATP-III Criteria (NCEP-ATP, 2001)
Presence of DM, IGT, IFG, or insulin resistance, and 2 of the following features: • blood pressure ≥ 140/90 mm Hg; • dyslipidemia, defined by TG ≥ 1.695 mmol/L and/or HDL-C ≤ 0.9 mmol/L in males or ≤ 1.0 mmol/L in females; • central obesity, defined by waist: hip ratio > 0.90 in males or > 0.85 in females, and/or BMI* > 30 kg/m2 ; • microalbuminuria, defined by a urinary albumin excretion ratio ≥ 20 mg/min	At least three of the following: •central obesity, measured as waist circumference ≥ 102 cm in males or ≥ 88 cm in females; • TG ≥ 1.695 mmol/L (150 mg/dL); • HDL-C < 40 mg/dL in males or < 50 mg/dL in females; • blood pressure ≥ 130/85 mmHg; • fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL

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

Table 2. Definition of Metabolic Syndrome According to the International Diabetes Federation (IDF, 2005)

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

* HDL-C, high-density lipoprotein-cholesterol; BP, blood pressure; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; TG, triglycerides. ** Their values are specific for ethnicity. If BMI (body mass index) is > 30 Kg/m2 , central obesity can be assumed and waist circumference does not need to be measured.

Oxidative stress and metabolic syndrome

Oxidative stress plays an important role in the ethiopathogenesis of MetS and its characteristic signs is widely supported.(9) Reactive oxygen species (ROS) are physiologically produced by the cellular metabolism that allow interaction with a great number of biomolecules, causing their oxidation (10).They act by creating an adequate environment for phagocytic vacuole and enzymatic digestion, and by mediating cellular signaling. Various studies have demonstrated a real correlation between oxidative stress and MetS. An extended activity of ROS resulting from hyperglycemia implies a large spectrum of molecular and cellular damage, such as lipoxidation (Cosentino et al., 1997). In patients suffering from MetS, systemic oxidative stress seems to be more elevated than in healthy controls, and antioxidant defense seems to be decreased, as demonstrated by the diminished rate of Vit C, α-tochopherol, and superoxide dismutase activity in serum compared with non-obese normolipidemicindividuals(11).

Insulin resistance plays a key role in the pathophysiology of MetS. Insulin resistance is a condition in which the normal amount of insulin is insufficient to obtain an adequate response from muscular and adipose tissues and from hepatic cells, and this leads to a severe hyperglycemia with deleterious systemic effects (12-15), such as lower intracellular antioxidant defenses(14, 15). A Large number of studies have focused on molecules that can reduce oxidative stress. Recently, for example, some tetracycline, minocycline. (16) In addition, a recent study focused on the antioxidant, anti-human immunodeficiency virus, anticarcinogenic, and antiinflammatory properties of Gomisins G and J extracted from Schisandrachinensis, as it seems to inhibit Porphyromonasgingivalis(17). Furthermore, the proanthocyanidins (PAC), the most abundant flavonoids extracted from red cranberry fruits, have been reported to possess antimicrobial, antiadhesion, antioxidant, and antiinflammatory properties.

Association between Periodontal Disease and Components of Metabolic Syndrome:

Periodontal disease and insulin resistance /diabetes type 2

Diabetes, a pathology that is extremely widespread, involves an adulterated homeostasis in the glucose metabolism. Diabetes and periodontal diseases are two chronic diseases that have been considered as biologically connected. (18) Type 2 diabetes (T2D) is the most common type and is associated with the recruitment of proin flammatory cytokines that are involved in the onset

of the disease and related complications such as dyslipidemia and atherosclerosis, contributing to the onset of microvascular and macrovascular complications (19,20).A biological relation between diabetes and periodontitis is well documented in many studies, as tested relations exist between glycated hemoglobin, a diabetic marker, and periodontal parameters, and between plasmatic lipid peroxide, an index of oxidative stress, and periodontal markers.(21) 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.(22) AGEs are substances able to promote cytokine production by macrophages such as TNF-α and IL-6, and to stimulate hepatic secretion of acute-phase proteins such as CRP, fibrinogen, plasminogen activator/inhibitor, and serum amyloid A, also correlated with oral infection and cardiovascular diseases, especially in patients suffering from periodontal diseases (AGEs also lead to the rapid expansion of energy in the respiratory polymorphonuclear neutrophils (PMN), and this causes increased damage to periodontal tissues (23) and some changes in bone metabolism, especially on repair, also reducing the production of the extracellular matrix. Additionally both Tumour necrosis factor-α and Interleukin-6 is derived from the fat tissue which mediates inflammation, suggesting that obesity, diabetes and periodontitis are mutually related.

Obesity and periodontal damage

There is a clear relationship between obesity and periodontitis and is well documented in literature. Overweight is one of the important risk factor for the onset of T2D and CVD, as well as for other disorders like respiratory and pressure disorders, osteoarthritis, and some types of cancer (24). Adipocytes of fat tissue show the ability to secrete adipocytokines such as leptin, adiponectin and resistin. Leptin plays a protective role against obesity. (25). Adiponectin remains constant in normal condition but decreases in the presence of diabetes, obesity, insulin resistance, and CVD. Resistin shows a great proinflammatory role, and it seems to be associated with insulin resistance (25,26).However, many researches came up with the conclusion that the most important mediator related with obesity and insulin resistance is TNF-α, expressed plentifully in adipose tissue of obese individuals with severe insulin resistance, and in neoplastic patients that seems to trouble intracellular signaling(27,28).

Various authors have supposed that TNF-α could prevent Tyr phosphorylation of the insulin receptor, inducing hydrogen peroxide formation (29). Recent studies have shown that individuals with normal weight had a lower prevalence of periodontitis, decreased plasma levels of inflammatory markers, and increased insulin sensitivity suggesting the relationship between periodontitis and obesity (30).

The protective role of Leptin, is still a topic of dispute. In periodontal individuals, serum leptin seems increased (31,32). On the contrary, leptin levels in gingival fluid were found to be decreased, especially in the presence of aggressive and advanced periodontitis. No relevant data exists regarding the rate of adiponectin in gingival sulcular fluid, but in vitro it has been shown that they inhibit osteoclast activity induced by LPS resulting in its anti-inflammatory and protective action against the progression of periodontitis and a predictive role for T2D (33).

Hypertension and Periodontitis

Relationship between high blood pressure with periodontitis was first reported in 1977 in animals. Hyperplasia/ hypertrophy in the blood vessel walls from a

chronically irritated gingiva were seen in hypertensive and obese-hypertensive rats (34). Hypertensives suffering from MetS show increased oxidative stress and compromised antioxidant activity in plasma and cells (35,36). Moreover, Obesity and Hyperglycemia are strictly related to hypertension (35,36). The passage of lipoproteins and platelet-derived growth factors is allowed by augmented endothelial permeability, which give rise to the proliferation of muscular smooth cells in the intima, which occludes vessel lumen causing embolia, hypoxia, and consequent cellular death (37).

Although there is lack of statistical evidence, a clinical relation between high blood pressure and aggressive periodontitis has been deduced, as patients with poor oral hygiene have higher blood pressure problems than do healthy subjects with good oral hygiene condition (38). Considering the biological mechanism of this relationship, a recent study evaluated endothelial function in patients with periodontitis. The levels of CRP and IL-6 were significantly higher in the periodontitis subjects with hypertension, than in the control group and periodontal therapy seems to reduce serum concentrations of CRP and IL-6 (39).

Periodontal disease and hyperlipidemia

Hyperlipidemia has a deregulating effect on the immune-system cells and tissue healing, thereby increasing the susceptibility to infections, such as periodontitis. (40) Higher serum levels of total cholesterol, low density lipoprotein cholesterol and triglycerides was seen in individuals with periodontal disease, when compared with periodontally healthy individuals. (41)(42) The variation in the phenotype of immune cells because of the lipids and the serum elevation of proinflammatory cytokines such as Tumour necrosis factor-α and Interleukin-lL6 from chronic periodontitis evidenced the bidirectional relationship between the two conditions. (43)

Metabolic syndrome and periodontitis

Periodontal disease and metabolic syndrome has bidirectional association. Not only systemic diseases have impact on oral health but oral diseases like periodontal diseases have wide ranging systemic effects. Increased serum rates of oxidative stress markers are seen in both MetS and periodontitis (44). The pathogenic bacteria alone is not sufficient to create an disease rather the disease initiation and progression also depends on susceptibility of host .Periodontitis is an chronic inflammatory disease caused by periodontal pathogens in presence of various local factors which is significantly associated with the frequency of tooth brushing,regular dental visits, smoking and drinking habits.(45)The consequence of chronic periodontal infection is the synthesis of inflammatory cytokines and chemokines by local periodontal tissue or circulating inflammatory cells. The inflammatory cytokines such as interleukin-6, Tumour necrosis factor-α, elevated C-reactive protein levels(46)(47). evokes systemic inflammation which contributes to insulin resistance and causes hyperglycemia, which in turn induces the expression of proinflammatory mediators and increases the risk of oral infection and cardiovascular disease among patients with periodontitis. Thus a triangular vicious circle among periodontitis, systemic inflammation and hyperglycemia is perpetuated. (48) However the reverse possibility that periodontitis disturbs glucose handling is also reasonable and worthy of consideration.The periodontitis can also be associated with dyslipidemia via systemic inflammation. Many cytokines including Interleukin6,Interleukin-1,Tumour necrosis factor-α, stimulate hepatic free fatty acid synthesis resulting in increased synthesis of low density protein and hypertriglyceridemia.(49)

In synthesis, metabolic alterations related to MetS component diseases cause an augmented response to

bacterial plaque, which favors periodontitis insurgence. It has been pointed in many studies out how periodontal treatment can reduce inflammatory mediators related to endothelial and cardio-circulatory dysfunctions (50). A very recent work reported a real relationship between periodontitis and MetS, especially in women, while abdominal obesity was the largest contributory factor in both genders . On the contrary, another new work about MetS and periodontal diseases and caries did not find a strong association between MetS and periodontal infections (51).

Odontologic management of metabolic patients

Dentists play a key role in the precocious diagnosis of MetS and its local complications such as periodontitis.

Diet

The capability of an aliment to raise the level of insulin in the blood, compared with a reference food such as glucose or with bread, is known as the glycemic index (GI) (52). Several studies have demonstrated the relationship between the intake of foods with high GI and MetS(53).Intake of food with higher GI will increase the risk of developing insulin resistance, endothelial dysfunction, and CVD. . It is ideal to consume nutrient-rich, high-fiber food such as fruits and vegetables to maintain good health (54).

Good oral health

Maintaining good oral health is fundamental for individuals who are suffering from MetS and have a tendency to develop CVD. Progressive loss of teeth results in variation of diet, with an increased intake of soft foods with great caloric rate, saturated fats, trans fatty acids, and cholesterol.

The use of partial or total removable prosthesis does not seem to cover the masticatory efficacy of natural teeth, but fixed dental prosthetic devices and prosthetic overimplants seem to improve dietary practices (55). Drugs used in patients suffering from MetS may give rise to oral collateral effects and could interact with drugs prescribed in dentistry (56).

The oral complications of diabetes are candidiasis, xerostomia, burning mouth syndrome, gingivitis, oral acute infections, and, clearly, periodontal diseases – all diseases treated with dentistry. So, the role of dentists in the diagnosis, therapy, and management of metabolic patients is important (57), and an improvement of collaboration among dentists, cardiologists, endocrinologists, and dietists is needed to promote the multidisciplinary therapeutic approach to this syndrome.

Conclusions

The review article explains the possible relationships between MetS and periodontitis, in relation to both local and systemic health and disease. Oxidative stress seems to be the chief suspect in ethiopathogenesis of periodontal disease; for this, the use of drugs with antioxidative activity or anti-AGE is the subject of research However, this argument needs more clarity, and the search for answers goes encouraged. As we await more results, we can increase prevention in at-risk individuals by advising lifestyle changes and prescribing a balanced diet so as to control body weight, hyperlipidemia, and hypertension; explaining the adverse effects of smoking and the importance of good oral hygiene also serves the purpose. The role of dentists in the diagnosis, therapy, and management of metabolic patients is fundamental, but an improvement of collaboration among dentists, cardiologists, endocrinologists, dietists, etc., is needed.

References

1. Andriankaja OM, Sreenivasa S, Dunford R, DeNardin E: Association beteen metabolic syndrome and periodontal disease. Aust Dent J 2010, 55:252–259.

2. Zadik Y, Bechor R, Shochat Z, Galor S: Ethnic origin and alveolar bone loss in Israeli adults. RefuatHapehVehashinayim 2008, 25(2):19–22.
3. 1.Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk. A systematic review and meta-analysis. J Am CollCardiol. 2010;56(14):1113–1132.
4. Alexandrina L.Dumitrescu, L.Zetu, Silvia Teslaru, Metabolic syndrome and Periodontal diseases.ROM.J.Intern.Med,46(3) ,2008,207-212.
5. Cameron AJ, Shaw JE, Zimmet PZ (2004). The metabolic syndrome: prevalence in worldwide populations. EndocrinolMetabClin North Am 33:351-375.
6. Kushiyama M, Shimazaki Y, Yamashita Y. Relationship between metabolic syndrome and periodontal disease in Japanese adults. J Periodontol. 2009 Oct;80(10):1610-5.
7. Kuo LC, Polson AM, Kang T (2008). Associations between periodontal diseases and systemic diseases: a review of the inter-relationships and interactions with diabetes, respiratory diseases, cardiovascular diseases and osteoporosis. Public Health 122:417-433.
8. Chapple IL, Matthews JB (2007). The role of reactive oxygen and antioxidant species in periodontal tissue destruction. Periodontol 2000 43:160-232
9. Ceriello A, Motz E: Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. ArterioscIerThrombVascBiol 2004, 24(Suppl5):816–823.
10. Bullon P, Morillo JM, Ramirez-Tortosa MC, Quiles JL, Newman HN, Battino M: Metabolic Syndrome and Periodontitis: Is Oxidative Stress a Common Link? J Dent Res 2009, 88:503–518
11. Armutcu F, Ataymen M, Atmaca H, Gurel A: Oxidative stress markers, C-reactive protein and heat shock protein 70 levels in subjects with metabolic syndrome. ClinChem Lab Med 2008, 46(Suppl 6):785–790.
12. Di Filippo C, Verza M, Coppola L, Rossi F, D'Amico M, Marfella R: Insulin resistance and postprandial hyperglycemia the bad companionsin natural history of diabetes: effects on health of vascular tree. Curr Diabetes Rev 2007, 3:268–273.
13. Tilg H, Moschen AR: Inflammatory mechanisms in the regulation of insulin resistance. Mol Med 2008, 14:222–231.
14. Bruce CR, Carey AL, Hawley JA, Febbraio MA: Intramuscular heat shock protein 72 and heme oxygenase-1 mRNA are reduced in patients with type 2 diabetes: evidence that insulin resistance is associated with a disturbed antioxidant defence mechanism. Diabetes 2003, 52:2338–2345.
15. Koyama H, Shoji T, Yokoyama H, Motoyama K, Mori K, Fukumoto S, et al: Plasma level of endogenous secretory RAGE is associated with components of the metabolic syndrome and atherosclerosis. ArterioscIerThrombVascBiol 2005, 25:2587–2593
16. Soory M: A Role for Non-Antimicrobial Actions of Tetracyclines in Combating Oxidative Stress in Periodontal and Metabolic Diseases: A Literature Review. The Open Dentistry Journal 2008, 2:5–12
17. Ryu EY, Park SY, Kim SG, da Park J, Kang JS, Kim YH, Seetharaman R, Choi YW, Lee SJ: Anti-inflammatory effect of heme oxygenase-1 toward Porphyromonasgingivalis lipopolysaccharide in macrophages exposed to gomisins A, G, and J. J Med Food 2011, 14(12):1519–1526

18. Nagasawa T, Noda M Katagiri S, Takaichi M, Takahshi 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.
19. Bjelland S, Bray P, Gupta N, et al: Dentists, diabetes and periodontitis. Austr Dent Journ 2002, 47:202–207.
20. Mustapha IZ, Debrey S, Oladubu M, Ugarte R: Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: a systematic review and meta-analysis. J Periodontol 2007, 78(12):2289–2302
21. Iwamoto Y, Nishimura F, Nakagawa M, Sugimoto H, Shikata K, Makino H, et al: The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycatedhemoglobin level in patients with type 2 diabetes. J Periodontol 2001, 72:774–778.
22. Mealey BL, Rose LF. Diabetes mellitus and inflammatory periodontal diseases. CurrOpin Endocrinal Diabetes Obes.2008 Apr;15(2):135-41.
23. Bjelland S, Bray P, Gupta N, et al: Dentists, diabetes and periodontitis. Austr Dent Journ 2002, 47:202–207.
24. Pischon N, Heng JP, et al: Obesity, inflammation and periodontal disease. J Dent Res 2007, 86(suppl. 5):400–409
25. Bullon P, Morillo JM, Ramirez-Tortosa MC, Quiles JL, Newman HN, Battino M: Metabolic Syndrome and Periodontitis: Is Oxidative Stress a Common Link? J Dent Res 2009, 88:503–518.
26. Sgolastra F, Petrucci A, Gatto R, Monaco A: Efficacy of Er:YAG laser in the treatment of chronic periodontitis: systematic review and meta-analysis. Lasers Med Sci 2011, 27(3):661–673.
27. Hotamisligil GS, Amer P, Caro JF, Atkinson RL, Spiegelman BM: Increased adipose tissue expression of tumor necrosis factor-at in human obesity and insulin resistance. J Clin Invest 1995, 95:2409–2415.
28. Lundholm K, Holm G, Schersten T: Insulin resistance in patients with cancer. Cancer Res 1997, 38:4665–4670
29. Hansen LL, Ikeda Y, Olsen GS, Busch AK, Mosthaaf L: Insulin signaling is inhibited by micromolar concentrations of H202. Evidence for a role of H202 in tumor necrosis factor a-mediated insulin resistance. J BiolChem 1999, 274:25078–25084
30. Bawadi HA, Khader YS, Haroun TF, Al-Omari M, Tayyem RF: The association between periodontal disease, physical activity and healthy diet among adults in Jordan. J Periodontal Res 2011, 46(1):74–81.
31. 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 ClinPeriodontol 2008, 43:556–562.
32. Saito T, Yamaguchi N, Shimazaki Y, Hayashida H, Yonemoto K, Doi Y, et al: Serum levels of resistin and adiponectin in women with periodontitis: the Hisayama study. J Dent Res 2008, 87:319–322.
33. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Rimm EB: Leisure-time physical activity and reduced plasma levels of obesityrelated inflammatory markers. Obes Res 2003, 11:1055–1064.
34. Perlstein MI, Bissada NF (1977). Influence of obesity and hypertension on the severity of periodontitis in rats. Oral Surg Oral Med Oral Pathol 43:707-719
35. Abdilla N, Tormo MC, Fabia MJ, Chaves FJ, Saez G, Redon J: Impact of the components of metabolic syndrome on oxidative stress and enzymatic

antioxidant activity in essential hypertension. J Hum Hypertens 2007, 21(suppl.1):68–75.

36. Chaves FJ, Mansego ML, Blesa S, Gonzalez-Albert V, Jimenez J, Tormos MC, Espinosa O, Giner V, Iradi A, Saez G, Redon J: Inadequate cytoplasmic antioxidant enzymes response contributes to the oxidative stress in human hypertension. Am J Hypertens 2007, 20(supp 1):62–69.
37. Arthur H, Friedlander DMD, JaneWeinreb MD: Metabolic syndrome: pathogenesis, medical care and dental implications. Clinical pactice 2007, 138:179–187
38. Rivas-Tumanyan S, Spiegelman D, Curhan GC, Forman JP, Joshipura KJ: Periodontal disease and Incidence of Hypertension in the Health Professionals Follow-Up Study. Am J Hypertens 2012, 25(7):770–776
39. Higashi Y, Goto C, Jitsuiki D, Umemura T, Nishioka K, Hidaka T, Takemoto H, Nakamura S, Soga J, Chayama K, Yoshizumi M, Taguchi A: Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. Hypertension 2008, 51(2):446–453.
40. Fentoglu O, Bozkurt FY, The bidirectional relationship between periodontal disease and hyperlipidemiaEur J Dent 2(2), 2008 Apr,142-6.
41. Fentoglu O, Koroglu BK Hicyilmaz H, Sert T, Oxdem M. Sutcu R et al Pro inflammatory cytokine levels in association between periodontal disease and hyperlipidemia J ClinPeriodontol 38(1), 2011 Jan,8-16.
42. 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 periodontal Implant Dent 2(1), 2010, 29-32.
43. Fentoglu O, Bozkurt FY. The bi-directional relationship between periodontal disease dandhyperlipidemiaEUr J Dent;2(2), 2008 Apr,142-146
44. Brock GR, Matthews JB, Butterworth CJ, Chapple ILC: Local and systemic antioxidant capacity in periodontitis and health. J ClinPeriodontol 2004, 31:515–521
45. Y.Shimazaki,T.Saito,K.Yonemoto,Y.kiyohara,M.Lida and Y.Yamashita.Relationship of Metabolic syndrome to Periodontal Disease inJapaneseWomen: TheHisayamastudy.JDent Res 86(3):271-275,2007.
46. Chen LP,ChaingCK,Chan CP et al.Does periodontitis reflect inflammation and malnutrition status in hemodialysispatients?Am J Kidney Dis;47; 2006,s815-822.
47. FentogluO, KorogluBK, Hicyilmaz H et al.Pro inflammatory cytokine levels ion association between periodontal disease and hyperlipidaemia. JClinPeriodontol 38,8-16
48. Kirk EP,KlienS. Pathogenesis and pathophysiology of thecardiometabolicsyndrome.JClinHpertens(Greenwich)11,2009,761- 765.
49. KhovidhunkitW,MemonRA,Feingold KR et al.Infection and inflammation-induced proatherogenic changes of lipoproteins.J Infect Dis 2000;181(Suppl 3):S462-S472.
50. Chaffee BW, Wetson SJ: Association between chronic periodontal disease and obesity: a systematic review and meta-analysis. J Periodontol 2010, 81:1708–1724.
51. Jenkins DJ, Wolever TM, Taylor RH, et al: Glycemix index of foods:a physiological basis for carbohydrate exachange. Am J ClinNutr 1981, 34:362–366.

52. Ludvig DS: The glycemic index: physiological mechanisms relating to obesity, diabetes and cardiovascular disease. JAMA 2002, 287:2414–2423
53. Liu S, Manson JE: Dietary carbohydrates, physical inactivity, obesity, and the 'metabolic syndrome' as predictors of coronary heart disease. CurrOpinLipidol 2001, 12:395–404.
54. Nowjack-Raymer RE, Sheiham A: Association of edentulism and diet and nutrition in US adults. J Dent Res 2003, 82:123–126
55. Morais JA, Heydecke G, Pawliuk J, Lund JP, Feine JS: The effects of mandibular two-implant overdentures on nutrition in elderly edentulous individuals. J Dent Res 2003, 82:53–58.
56. Wynn RL, Meiller TF, Crossley HL: Drug information for dentistry: Oral medicine for medically-compromised patients and specific oral conditions. 9th edition. Hudson, Ohio: Lexi-Comp; 2003.
57. Vernillo AT: Dental considerations for the treatment of patients with diabetes mellitus. JADA 2003, 134:24s–33s.