ARTÍCULO DE REVISIÓN

oral 2017

sep-dic 2017; 18(58): 1530-1536.

Association between periodontal disease, diabetes mellitus and cardiovascular disease

Asociación entre enfermedad periodontal, diabetes mellitus y enfermedad cardiovascular

Mario Alberto Maldonado-Ramírez,* Jorge Issac Cabrera-Cortina.**

***Pediatric Dentistry Departament. **Physician Master in Human Physiology.**

Universidad Autónoma de Tamaulipas. Tampico, Tamaulipas, México.

Resumen

La enfermedad periodontal es una de las enfermedades orales de mayor prevalencia en el mundo y puede ejercer un sinergismo con la diabetes mellitus. El objetivo de éste artículo de revisión es dar a conocer los diferentes estudios que las relacionan y dar una explicación de cómo se lleva a cabo su simbiosis. Enfatizamos en la comunicación para que éstas dos enfermedades sean atendida por un equipo de especialistas y por último una serie de parámetros son enlistados como una guía para el profesional de la salud oral.

Palabras clave: diabetes mellitus, simbiosis, periodontitis, obesidad.

Abstract

Periodontal disease is the second oral disease of higher prevalence worldwide, at the same time diabetes mellitus is a chronic degenerative disease of greater impact on health, and it is often accompanied by vascular disease, mainly arteriosclerosis. Currently, information is being gathered on the existence of a symbiotic relationship between the three diseases, further tightening the relationship between oral health and general health. This time we will try to give an explanation of how these pathologies, periodontal disease, diabetes mellitus and cardiovascular disease interact.

Key words: *periodontal disease, diabetes mellitus, cardiovascular disease.*

BACKGROUND

The maintenance of oral hygiene in any person is crucial to preserve the oral tissues in good health. This is critical when health is diminished by a systemic ill.

When the habits or oral hygiene techniques are not effective, food particles are trapped between the teeth, which eventually are calcified by minerals present in the saliva that precipitate on the detritus stucked to the surfaces of the teeth; this condition can lead to an alteration in the supporting tissues of the teeth, becoming slowly but progressively to periodontal disease (PD). This disease starts the progressive destruction of the supporting tissues of the teeth, to the formation of gingival recessions or periodontal bags or both, causing extensive destruction of the alveolar bone.

It has been documented that PD is considered to be one of the main reasons for tooth loss when it coexists in individuals with Diabetes Mellitus (DM), however this is the latest oral manifestation, between this episode and the onset of the disease, there is a long period of time where changes occur, and not only at the local level. This oral disease can complicate the systemic alterations provoked by the DM and other diseases[1-5] In this paper we give an explanation of how the periodontal disease, diabetes mellitus and cardiovascular disease can interact.

ASSOCIATED PATHOLOGIES AND THEIR COMPLICATIONS

Boland *et al.* (2014), associated with certain medical conditions with periodontitis: Type I Diabetes Mellitus and Type 2 Diabetes Mellitus (T1-T2DM), hypertension, hypercholesterolemia, hyperlipidemia, pregnancy, childbirth and benign prostatic hyperplasia.[6]

Correspondencia: Dr. Mario Alberto Maldonado Ramírez
Correo-e: mmaldon@docentes.uat.edu.mx

Recibido: *marzo 14, 2017* ***Aceptado:*** *septiembre 7, 2017*

One of the most common complication in diabetics with xerostomia is burning mouth syndrome, which is considered a orofacial neuropathy, characterized by bilateral in the oral mucosa burning usually in the absence of clinical findings and laboratory[7] can be accompanied by sensory dysfunction of taste (another oral neuropathy), and both, they may interfere with the determination to maintain proper diet and this situation can lead to a lack of glycemic control.[8]

One of the most alarming reports on the matter and that they are exposed to light PD/DM relationship was exposed by Albert *et al.* (2011), they unveiled and explained in their documents the findings found by Saremi A *et al.* (2005), in a longitudinal study of a population of Indians Pima, where adjusted percentage of natural deaths by age and gender. In people with diabetes but without periodontitis or slight periodontitis, the report of total deaths per 1000 in habitants per year, was 3.7; among people who reported moderate periodontitis was 19.6 and in people with severe periodontitis was 28.4, this behavior shows an upward relationship with the severity of periodontitis.[9,10]

STUDIES THAT CONDITION BIDIRECTIONAL RELATIONSHIP

The second disease of highest prevalence in oral cavity around the world is periodontitis and basically comes in two ways: chronic periodontitis (PC) and the aggressive or severe periodontitis (AP), which is characterized by a fast loss of support tissues of the teeth.

Benjamin W. *et al.* (2010), published the results of a meta-analysis of the association between two common diseases in the world's population: periodontal disease and obesity, they suggest that exist a strong association between both biological diseases, although at that time they didn't establish ways of association nor the temporal order of events to clarify if obesity is a risk factor for periodontal disease or if periodontitis may increase the risk of weight gain.[11]

The relationship between the DM and the oral cavity has been documented and is now well known that people with DM tend to have one higher risk to lose their teeth because of complications related to periodontal disease (PD), also when an infection occurs elsewhere in the body in a chronic and intermittent manner such as PD, it can also lead to a lack of control of the DM, so it is important to understand that there is a bidirectional relationship between both diseases.[3]

Hyperglycemia in diabetes is a major risk factor for vascular complications and these originate 5 classic complications associated with Diabetes Mellitus and include: retinopathy, neuropathy, nephropathy, cardiovascular complications (coronary artery disease, attack, fulminant, stroke and peripheral vascular disease) and delayed healing of wounds. Periodontal disease has been recently recognized as the "sixth complication" of DM, which is considered to be a metabolic disorder with oral manifestations that impact on dental care and those oral manifestations profoundly affect the glycemic control in the DM, which in turn complicates the oral pathologies in those patients, these include but are not limited to: candidiasis, cavities, loss of teeth, gingivitis, Lichen Planus, neurosensory disorder (burning mouth syndrome), periodontitis, salivary dysfunction, xerostomia and taste disorders. These manifestations may occur alone or accompanied, which tends to provoke a change in the diet of these individuals. Physicians working to optimize the metabolic control of these patients should recognize the impact of periodontal disease on glycemic metabolism.[12]

Desvarieux M. *et al.* (2003), carried out an epidemiological study of vascular disease and oral infections in people with an average of 66 years age, finding a strong association between the loss of teeth due to periodontal causes and the presence of plaques in carotid arteries, 46% of the participants in the study who had an average of 9 missing teeth had developed plaques in carotid arteries and those who lost 10 teeth or more the prevalence increased to 60%. They concluded that the loss of teeth is a marker of the past history of periodontal disease and is associated with subclinical atherosclerosis.[13,14]

Other research showed that those older than 18 years with DM have twice as much risk of developing PD, compared with people without DM.[15,16]

In longitudinal epidemiological studies it has been observed an association between progressive PD and the development of T2DM in the following two decades after the diagnosis of the PD, in individuals who were initially free of DM. These studies suggest a strong reciprocal interaction between oral infections and systemic inflammatory response, apparently, the mechanism that triggers the development of T2DM is the presence of bacteria in the blood stream, which shoots the occurrence of prolonged form of white cells in the blood, which can produce and activate pro-inflammatory cytokines such as Tumoral Necrosis Factor-alpha (TNFα), reactive oxygen species (ROS) and markers such as C-protein reactive ultrasensitive (PCRu), as well as elevated levels of glycosylated hemoglobin (GH) and increased resistance to insulin.[17,20]

PRODUCTION OF PRO-INFLAMMATORY MOLECULES AND THEIR EFFECTS

Lalla *et al.* (2006), and Roth *et al.* (2007), found in the vascular endothelium of the human aorta cells infected with *Porphyromona Gingivalis (PG),* a bacterium commonly found in the CP, this finding was associated with the significant increase of molecules involved in cell adhesion as: VCAM-1, ICAM-1 and E-selectin, and IL-6, IL-8 and MCP-1, all associated with a pro-atherogenic response[21,22] and have a direct relationship with myocardial infarction.[23] The loss of alveolar bone due tochronic periodontitis (CP) and calcification of the carotid artery is related to the degree of severity of CP.[24,25]

It has also been shown that *PG* and *Fusobacterium Nucleatum (FN)* have a molecular effect on the genes of the oral epithelium cells, activating receptors Factor Nuclear kapa B (NF-κB), which is a precursor of the Tumoral Necrosis Factor-alpha (TNFα) and nitric oxide (NO) among other mediators of inflammation,[26,27] which can be activated by osteoclastic cells and macrophages by inducing the destruction of tissues. Concerning the studies of Kramer *et al.* (2013), show role played by bacteria in the PD of the CP as the aggressive peri-

odontitis (AP), particularly when it comes to AP; following the path of the dendritic cells, inducing the production of receptor activating cytotoxic cells factor (CRACC) in Natural killer cells (NKc) which are a sub-group of lymphocytes which play an important role in the response capacity of the immune system, innate and commonly related to the destruction of tissue in presence of periodontitis.[28]

Studies of Papapanou *et al.* (2007), demonstrated that periodontal therapy in patients with severe periodontitis has a direct effect on gene expression of peripheral blood monocytes, with effect anti-inflammatory and anti-atherogenic.[29]

In this study it is could substantiate that at least three genes can be activated by the presence of bacteria from periodontal infections and that invade the blood stream. One of these is the gene that encodes with platelet glycoprotein 4 that serving as receiver for thrombospondin, which has an effect anti-angiogenic and can act as a molecule of cell adhesion to collagen, phospholipids and oxidized low-density lipids, the expression of this glycoprotein was recently linked to accelerated atherosclerosis in diabetes type 2 and has been proposed as a marker of metabolic syndrome and potential marker for atherosclerosis.[30] Another expressed gene was related to the proteoglycan chondroitin sulfate wrapped in oxidative stress which leads to cell apoptosis,[31] also related the gene that encodes for TLR 8, 2, 1 and 4. The TLRs are a series of proteins that play a key role in the recognition of pathogen-associated molecules and mediate the production of cytokines necessary for the development of innate immunity,[32] TLR 4 is expressed by macrophages in the presence of lipid-rich atherosclerotic plaques and over-regulated by the oxidation of low-density lipids.[33]

The DM is related to complications of the microvasculature when glycosylated hemoglobin (HbA1c) is increased, and their control to normal levels can decrease the risk of death related to T2DM.[34]

MECHANISM OF ACTION

Several mechanisms have been proposed to explain the increase of susceptibility to uncontrolled PD in patients with DM, including: alterations of the immune response, alterations of collagen metabolism and alterations of the vasculature. Individuals with uncontrolled T2DM have an exaggerated inflammatory response, coupled with the delay in the repair and healing increase the inflammatory response and destruction of periodontal tissues in those patients.[35,36]

The inflammatory response that is altered by the immune system, in individuals with T2DM, appears to be a determining factor critical to the severity of the PD on systemically compromised individuals[37,38] and this can in turn increase the risk of a poor glycemic control.[39,40]

The evidence suggests that the PD would cause bacteremia, causing elevation of pro-inflammatory cytokines in serum and reactive species of oxygen leading to the pathogenesis of the metabolic syndrome and insulin resistance.

The chronic inflammatory state induced by periodontitis may contribute to resistance to insulin, altering the glycemic control[41] and inducing the development of T2DM.[42-44]

Lalla and Papapanou (2011), studies indicate that the DM leads to a hyper-inflammatory in presence of the microbiota periodontal response and also an inadequate resolution of inflammation and repair, which lead to rapid periodontal destruction. Cell surface receptors for advanced glycation end products and their ligands are expressed in the periodontium of individuals with DM. The association between both diseases is bidirectional, periodontitis has been reported to adversely affect the glycemic control in patients with DM and to contribute to the development of complications in diabetic patients. A meta-analysis concluded that periodontal therapy in individuals with DM may result in a modest improvement of glycemic control. The effects of periodontal infections in the DM are potentially explained by the increase in the levels of systemic pro-inflammatory mediators, which may exacerbate insulin resistance.[36]

The presence of pro-inflammatory cytokines into the blood stream in intermittent form can cause cell damage by oxidative stress.

Oxidative stress can act as a potential connection between the relationship of each component of the metabolic syndrome and periodontitis. Both conditions show increases in serum of products derived from oxidative damage with a state pro-inflammatory influencing each directionally. The cytokines can modulate the oxidant/antioxidant balance in this relationship.[45]

Recent studies have shown that diabetic individuals with periodontitis may present increased HbA1c levels[46] and that the reduction of periodontitis leads to a reduction in HbA1c levels.[47,48]

Other studies have linked high levels of HbA1c with reduction of salivary flow, arising in these individuals xerostomia and this, in turn, is related to: fibroids, fissured tongue, ulcers traumatic, Lichen Planus, recurrent aphthous stomatitis as well as infections like candidiasis.[49-58]

One possible explanation for this could be found in the Roth report *et al.* (2007), which found that the *PG,* can originate the death of endothelial cells that line arteries, activating mechanisms of apoptosis.[59] It has also been proven that these bacteria have a direct action on the cells of smooth muscle of the aortic arteries, causing effects pro-thrombotic in them.[60]

Part of the explanation of how the bacteria present in the PD (*PG*) and CP act causing the formation of lipid plaques and hardening of the arteries (atherosclerosis), is the modification that induced intracellular function on the receiver end-products of the advanced glycation, regulating the response to vascular inflammation and atherogenesis in the cells of the vascular endothelium.[61-63]

This information serves as support for these patients to be attended by a team of specialists simultaneously without their treatments antagonistic as it may come to happen, both the internist, geriatrician or intensivist as the dentist himself should understand that both seek the same benefit for their patient so the communication between them will be paramount, only valuing the risk to develop these diseases can be successful in its prevention and treatment.

TIPS

However, not all is lost, Behel *et al.* published in 2010, encourage to try to carry out preventive measures, since the results of his research showed that people receiving successful periodontal treatment, had a reduction in biomarkers of systemic inflammation in the plasma.[64] The benefits can also be long lasting, 3-year longitudinal studies have shown that when individuals with PD received successful treatment in the long term, improves their clinical and microbiological periodontal condition having an important impact on the decrease in the rate of progression of the thickness of the layer intima-media of artery carotid 3 years of follow-up in average.[65]

A good oral health maintenance plan must focus not only on dental hygiene, their objectives should go beyond a good tooth brushing, so it is necessary to identify the tissues where it may negatively impact the diabetes not controlled: teeth, gums, periodontium, salivary glands, oral mucosa and finally alveolar bone.

We must therefore start with a complete oral diagnosis, this includes: index of caries, periodontal status, detection of plaque, saliva flow, capacity buffer of the saliva, bacteria in saliva counting and detection of lesions in the oral mucosa.

If we find dental caries lesions, these must be eliminated and restored teeth, the presence of active carious lesions are indicative of: a) a significant number of bacteria, b) diet, cariogenic and c) hygienic habits likely to be improved. We must remember that untreated cavities can lead to infections and end with the loss of teeth, and in more ways than one, these conditions can affect glycemic control. On the other hand the diet cariogenic is a diet rich in carbohydrates, which associates it with the DM, and this is another factor that points to a bi-directional relationship between both diseases.

- Periodontal status is an indication of how so far it has been performing oral maintenance, healthy gums with form, normal size, color and consistency, indicate a healthy periodontium and probably all we should do is reaffirm what already has been done; but the presence of bleeding, gingival recession, and formation of periodontal pockets, are unmistakable signs of a, possibly aggressive periodontitis, urging to set up a treatment to avoid advance and intensification of the disease and with this possible complications of glycemic control, in such periodontal therapy combined with the use of antibiotics may be justified.

- A good brushing technique should be trained and supervised by qualified dentist, it is well known that the public in general knows how to brush your teeth, but almost always does it quickly and without confirming if it was good, we tend to fall into this bad habit, so knowing does not mean "do" and brushing should be supervised more than once in different time periods, it is the only way to be sure that the good habit is taken, at the same time is to be instructing the patient to be able to check at home brushing is fulfilling its function: the cleaning of food remains from the surfaces of the teeth even where these make contact with gums, since there is where begins the periodontium and that's where usually starts the periodontal disease; the way to verify the success of brushing is to make use of tablets or revealing plaque fluids. If you are elderly people where there is a motor dysfunction the use of electric brushes can help.

- Flow salivary, this is an important measure because a dehydrated mouth may exacerbate the sensitivity of lesions in the oral mucosa (traumatic ulcers, Lichen Planus, aphthous ulcers), since the tissues aren't lubricating it enough and therefore instead of sliding, these make friction causing one higher sensitivity, this dehydration also tends to be associated with the "Burning mouth syndrome", disabling condition, who suffers from it has a heightened sensitivity that generates them nutritional problems because it supports nothing touch his tongue and mucous membranes, also less salivary flow represents a decrease in the ability to wrap the food bowl and form a mass steeped in mucin that facilitates the patient to swallow their food. Another factor to consider is that saliva's immunoglobulin (IgG and IgA) inside and lactoferrins which form part of the defense system. There are two ways of measuring salivary flow: 1) passively, the patient is sat with the head slightly tilted forward and down with the mouth open so that saliva slips up to the vessel that holds in the hands below the mouth, the milliliters per minute will tell if there is xerostomia or not; 2) another way of measuring, is the active one where the patient is previously provided with rinses or tablets of wax to chew, aiming to stimulate salivation and thus obtaining a greater production of saliva.

- The capacity buffer of the saliva is the time that it takes saliva in reverse changes in the salivary pH after eating some food with sugars (bread, potatoes, fruits, etc.), the way to do this is to first measure the salivary pH after a professional cleaning, this gives us a value which from, subsequently asked to 15 to 30 minutes before going to consultation to eat foods and that you do not brush the teeth to get readings with the variation of the salivary pH, this way we can have the normal values of the salivary pH, the variation with food intake and the time that saliva needs to return to the normal value, between more variation we find and the greater the clearance time, the greater the risk.

- Bacterial count, there are products on the market (Dentocult® or CRT® bacteria Ivoclar Vivadent AG-Schaan/ Liechtenstein) that help us to make the bacteria count in the doctor's office, or else we can order it at a specialized laboratory that will help us with this point, a result of 1 x 10^6 bacteria per mL or greater of *Streptococcus Mutans* increases the risk that patient develop tooth decay.

- Detection of lesions in mucous, the repetitive appearance of lesions in the mucous located on the same site, can be due to:
  a) Poorly fitting prosthesis
  b) Defective restorations or
  c) Teeth fractured with sharp and irregular edges

  When lesions are dispersed may be due to a nutritional deficiency or recurrent infections, so we will have to watch

and be in constant communication with the treating physician of the patient to assess the possibility of testing the immune system, the lesions may have a bacterial, viral or fungal origin.

- Finally, the image of a panoramic x-ray will give us an idea about the state of the alveolar bone, if there is loss of the same is indicative of periodontal disease, the evolution of this bone loss, can say us if it is aggressive periodontitis or chronic periodontitis.

  Summarized, the diabetic patient must keep a neat mouth, use tooth brushes that are able to eliminate the remains of food attached to the surfaces of the teeth without causing injury to the same tooth and periodontium, complement the hygiene with use of attachments as the thread of floss in the spaces where the contact between teeth is narrow and interproximal brushes on more open spaces and where there are fixed prostheses as well as thread floss to clean underneath the prostheses, oral rinses should be limited to those containing fluorine and are free from alcohol, in cases where chronic oral dehydration is observed, it will be stated a saliva substitute, control the high intake of coffee and alcohol, since these beverages can cause dryness, as well as the consume of medications such as antihypertensive, sedatives or tranquilizers due to the fact that their side effects may lead to decreased salivary flow.

- Visits to the dentist every 6 months in a healthy patient free of caries and PD who has good control of plaque may be, but ill patients must undergo treatment until they have controlled the disease: in the case of PD, treatment depends on the severity of the disease, but generally consists of scaling (removal of supragingival Tartar and infragingival and root planning) control of plaque and control bacterial plaque; in patients at risk of developing conditions such as periodontitis and caries, the visits shall be within a shorter period, as much as the patient requires it, until the patient achieves control by itself, emphasis on the control of PB and bacteria count should be present.

REFERENCES

1. Loe H. Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care 1993; 16(1): 329-34. [PubMed: 8422804].
2. Al-Shammari KF, Al-Khabbaz AK, Al-Ansari JM, Neiva R, Wang HL. Risk indicators for tooth loss due to periodontal disease. Journal of Periodontology 2005; 76(11): 1910-18. [PubMed: 16274310].
3. Kapp JM, Boren SA, Yun S, LeMaster J. Diabetes and tooth loss in a national sample of dentate adults reporting annual dental visits. Preventing chronic disease 2007; 4(3): A59. [PubMed: 17572963].
4. Oliver RC, Tervonen T. Periodontitis and tooth loss: comparing diabetics with the general population. J Am Dent Assoc 1993; 124(12): 71-76. [PubMed: 8277062].
5. Kaur G, Holtfreter B, Rathmann W, Schwahn C, Wallaschofski H, Schipf S, *et al*. Association between type 1 and type 2 diabetes with periodontal disease and tooth loss. Journal of Clinical Periodontology 2009; 36(9): 765-74. [PubMed: 19622096].
6. Boland MR, Hripcsak G, Albers DJ, Wei Y, Wilcox AB, Wei J, *et al*. Discovering medical conditions associated with periodontitis using linked electronic health records. J Clin Periodontol. Author manuscript; available in PMC 2014 May 01; 40(5): 474-82.
7. Vesterinen M, Ruokonen H, Furuholm J, Honkanen E, Meurman JH. Clinical questionnaire study of oral health care and symptoms in diabetic *vs.* non-diabetic predialysis chronic kidney disease patients. Clinical oral investigations 2012; 16(2): 559-63. [PubMed: 21455747].
8. Stolbova K, Hahn A, Benes B, Andel M, Treslova L. Gustometry of diabetes mellitus patients and obese patients. The International Tinnitus Journal 1999; 5(2): 135-40. [PubMed: 10753433].
9. Albert DA, Ward A, Allweiss P, Graves DT, Knowler WC, Kunzei C, *et al*. Diabetes and Oral Disease: Implication for Health Professionals. Ann N Y Acad Sci. 2012 May; 1255: 1-15.
10. Saremi A, *et al*. Periodontal disease and mortality in type 2 diabetes. Diabetes Care 2005; 28: 27-32. [PubMed: 15616229].
11. Bejamin W. Chafee y Scott J. Weston. Association Between Chronic Periodontal Disease and Obesity: A Systematic Review and Meta-Analysis. J Periodontal 2010; 81(12): 1708-24.
12. Oliver RC, Tervonen T. Periodontitis and tooth loss: comparing diabetics with the general population. J Am Dent Assoc 1993; 124(12): 71-76. [PubMed: 8277062].
13. Desvarieux M, Demmer R, Rundek T, Boden-Albala B y Sacco R. Relationship Between Periodontal Disease, Tooth Loss, and Carotid Artery Plaque. J of the American Heart Association. Stroke 2003; 34: 2120-25.
14. Julie M. Kapp, Suzanne Austin Boren, Shumei Yun, and Joseph LeMaster. Diabetes and Tooth Loss in a National Sample of Dentate Adults Reporting Annual Dental Visits. Centers for Disease Control and Prevention 2007; 4(3): 1-8.
15. Collin HL, Uusitupa M, Niskanen L, Kontturi-Narhi V, Markkanen H, Koivisto AM, *et al*. Periodontal findings in elderly patients with non-insulin dependent diabetes mellitus. Journal of Periodontology 1998; 69(9): 962-66. [PubMed: 9776023].
16. Santos Tunes R, Foss-Freitas M, Nogueira-Filho R. Impact of periodontitis on the diabetes-related inflammatory status. J Can Dent Assoc 2010; 76: a35. [PubMed: 20831852].
17. Lorini R, Scaramuzza A, Vitali L, d'Annunzio G, Avanzini MA, De Giacomo C, *et al*. Clinical aspects of coeliac disease in children with insulin-dependent diabetes mellitus. Journal of Pediatric Endocrinology & Metabolism 1996; 9(Suppl 1): 101-11.
18. Lalla E, Kaplan S, Yang J, Roth GA, Papapanou PN, Greenberg S. Effects of periodontal therapy on serum C-reactive protein, sE-selectin, and tumor necrosis factor-alpha secretion by peripheral blood-derived macrophages in diabetes. A pilot study. J Periodontal Res 2007 Jun; 42(3): 274-82.
19. Bullon P, Morillo JM, Ramirez-Tortosa MC, Quiles JL, Newman HN, Battino M. Metabolic syndrome and periodontitis: is oxidative stress a common link? Journal of Dental Research 2009; 88(6): 503-18.
20. Guggenheimer J, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, *et al*. Insulindependent diabetes mellitus and oral soft tissue pathologies: II. Prevalence and characteristics of Candida and Candidal lesions. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 2000; 89(5): 570-76.
21. Lalla E, Kaplan S, Chang SM, Roth GA, Celenti R, Hinckley K, Greenberg E, Papapanou PN. Periodontal infection profiles in type 1 diabetes. J Clin Periodontol 2006 Dec; 33(12): 855-62.
22. Roth GA, Moser B, Roth-Walter F, Giacona MB, Harja E, Papapanou PN, Schmidt AM, Lalla E. Infection with a periodontal pathogen increases mononuclear cell adhesion to human aortic

endothelial cells. Atherosclerosis 2007 Feb; 190(2): 271-81.
23. Renvert S, Ohlsson O, Persson S, Lang NP, Persson GR. Analysis of periodontal risk profiles in adults with or without a history of myocardial infarction. J Clin Periodontol 2004; 31: 19-24.
24. Ravon NA, Hollender LG, McDonald V, Persson GR. Signs of carotid calcification from dental panoramic radiographs are in agreement with Doppler sonography results. J Clin Periodontol 2003; 30: 1084-90.
25. Steven P. Engebretson, Ira B. Lamster, Mitchell S.V. Elkind, Tatjana Rundek, Neill J. Serman, Ryan T. Demmer, Ralph L. Sacco, Panos N. Papapanou and Moïse Desvarieux. Radiographic Measures of Chronic Periodontitis and Carotid Artery Plaque. Stroke 2005; 36: 561-66.
26. MR Milward, ILC Chapple, HJ Wright, JL Millard, JB Matthews and PR Cooper. Differential activation of NF-kB and gene expression in oral epithelial cells by periodontal pathogens. Clinical and Experimental Immunology 2007, 148(2): 307-24.
27. Roth GA, Moser B, Roth-Walter F, Giacona MB, Harja E, Papapanou PN, Schmidt AM, Lalla E. Infection with a periodontal pathogen increases mononuclear cell adhesion to human aortic endothelial cells. Atherosclerosis 2007 Feb; 190(2): 271-81.
28. Benjamin Krämer, Moritz Kebschull, Michael Nowak, Ryan T. Demmer, Manuela Haupt, Christian Körner, SvenPerner, SørenJepsen, Jacob Nattermann, Panos N. Papapanou. Role of the NK Cell-Activating Receptor CRACC in Periodontitis. Infection and Immunity 2013; (18)3: 690-96.
29. Panos N. Papapanou, Michael H. Sedaghatfar, Ryan T. Demmer, Dana L. Wolf, Jun Yang, Georg A. Roth, Romanita Celenti, Paul B. Belusko, Evanthia Lalla, and Paul Pavlidis. Periodontal therapy alters gene expression of peripheral blood monocytes. J Clin Periodontol 2007 September; 34(9): 736-47.
30. Handberg A, Levin K, Hojlund K, Beck-Nielsen H. Identification of the oxidized low-density lipoprotein scavenger receptor CD36 in plasma: a novel marker of insulin resistance. Circulation 2006; 114: 1169-76. [PubMed: 16952981].
31. Wu Y, Wu J, Lee DY, Yee A, Cao L, Zhang Y, Kiani C, Yang BB. Versican protects cells from oxidative stress-induced apoptosis. Matrix Biology 2005; 24: 3-13. [PubMed: 15748997].
32. Morris GE, Parker LC, Ward JR, Jones EC, Whyte MK, Brightling CE, Bradding P, Dower SK, Sabroe I. Cooperative molecular and cellular networks regulate Toll-like receptor-dependent inflammatory responses. FASEB Journal 2006; 20(12): 2153-55. [PubMed: 16935934].
33. Xu XH, Shah PK, Faure E, Equils O, Thomas L, Fishbein MC, Luthringer D, Xu XP, Rajavashisth TB, Yano J, Kaul S, Arditi M. Toll-like receptor-4 is expressed by macrophages in murine and human lipid-rich atherosclerotic plaques and upregulated by oxidized LDL. Circulation 2001; 104(25): 3103-08. [PubMed: 11748108].
34. Renata S. Leite, Nicole M. Marlow and Jyotika K. Fernandes. Oral Health and Type 2 Diabetes. Am J Med Sci 2013 April; 345(4): 271-73.
35. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. Nature reviews Endocrinology 2011; 7(12): 738-48.
36. Lakschevitz F, Aboodi G, Tenenbaum H, Glogauer M. Diabetes and periodontal diseases: interplay and links. Current diabetes reviews 2011; 7(6): 433-39. [PubMed: 22091748].
37. Williams RC, Offenbacher S. Periodontal medicine: the emergence of a new branch of periodontology. Periodontology 2000. 2000; 23: 9-12. [PubMed: 11276770].
38. Takeda M, Ojima M, Yoshioka H, Inaba H, Kogo M, Shizukuishi S, *et al*. Relationship of serum advanced glycation end products with deterioration of periodontitis in type 2 diabetes patients. Journal of Periodontology 2006; 77(1): 15-20. [PubMed: 16579698].
39. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, *et al*. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. Journal of Periodontology 1996; 67(10 Suppl): 1085-93. [PubMed: 8910827].
40. Collin HL, Uusitupa M, Niskanen L, Kontturi-Narhi V, Markkanen H, Koivisto AM, *et al*. Periodontal findings in elderly patients with non-insulin dependent diabetes mellitus. Journal of Periodontology 1998; 69(9): 962-66. [PubMed: 9776023].
41. Santos Tunes R, Foss-Freitas M, Nogueira-Filho R. Impact of periodontitis on the diabetes-related inflammatory status. J Can Dent Assoc. 2010; 76: a35. [PubMed: 20831852].
42. Park K, Steffes M, Lee DH, Himes JH, Jacobs DR Jr. Association of inflammation with worsening HOMA-insulin resistance. Diabetologia 2009; 52: 2337-44.
43. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286: 327-34.
44. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. Diabetes 2004; 53: 693-700.
45. Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, *et al*. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. Journal of Periodontology 1997; 68(8): 713-19. [PubMed: 9287060].
46. Simpson TC, Needleman I, Wild SH, Moles DR, Mills EJ. Treatment of periodontal disease for glycaemic control in people with diabetes. Cochrane Database Syst Rev. 2010; (5): CD004714. [PubMed: 20464734].
47. Teeuw WJ, Gerdes VE, Loos BG. Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis. Diabetes care 2010; 33(2): 421-27. [PubMed: 20103557].
48. Guggenheimer J, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, *et al*. Insulindependent diabetes mellitus and oral soft tissue pathologies. I. Prevalence and characteristics of non-candidal lesions. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics 2000; 89(5): 563-69.
49. Petrou-Amerikanou C, Markopoulos AK, Belazi M, Karamitsos D, Papanayotou P. Prevalence of oral lichen planus in diabetes mellitus according to the type of diabetes. Oral Diseases 1998; 4(1): 37-40. [PubMed: 9655043].
50. Lorini R, Scaramuzza A, Vitali L, d'Annunzio G, Avanzini MA, De Giacomo C, *et al*. Clinical aspects of coeliac disease in children with insulin-dependent diabetes mellitus. Journal of Pediatric Endocrinology & Metabolism 1996; 9(Suppl 1): 101–11.
51. Guggenheimer J, Moore PA, Rossie K, Myers D, Mongelluzzo MB, Block HM, *et al*. Insulindependent diabetes mellitus and oral soft tissue pathologies: II. Prevalence and characteristics of Candida and Candidal lesions. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics 2000; 89(5): 570-76.
52. Kadir T, Pisiriciler R, Akyuz S, Yarat A, Emekli N, Ipbuker A. Mycological and cytological examination of oral candidal carriage in diabetic patients and non-diabetic control subjects: thorough analysis of local aetiologic and systemic factors. Journal of Oral Rehabilitation 2002; 29(5): 452-57. [PubMed: 12028493].
53. Fox PC, van der Ven PF, Sonies BC, Weiffenbach JM, Baum BJ. Xerostomia: evaluation of a symptom with increasing significance. J Am Dent Assoc 1985; 110(4): 519-25. [PubMed: 3858368].
54. Longman LP, Higham SM, Rai K, Edgar WM, Field EA. Salivary gland hypofunction in elderly patients attending a xerostomia clinic. Gerodontology 1995; 12(12): 67-72. [PubMed: 9084292].

55. Chavez EM, Borrell LN, Taylor GW, Ship JA. A longitudinal analysis of salivary flow in control subjects and older adults with type 2 diabetes. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics 2001; 91(2):166-73.
56. Loesche WJ, Abrams J, Terpenning MS, Bretz WA, Dominguez BL, Grossman NS, *et al.* Dental findings in geriatric populations with diverse medical backgrounds. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics1995; 80(1): 43-54.
57. Napenas JJ, Brennan MT, Fox PC. Diagnosis and treatment of xerostomia (dry mouth). Odontology 2009; 97(2): 76-83. [PubMed: 19639449].
58. Bullon P, Morillo JM, Ramirez-Tortosa MC, Quiles JL, Newman HN, Battino M. Journal Dental Research Metabolic syndrome and periodontitis: is oxidative stress a common link? Journal of Dental Research 2009, 88(6): 503-18.
59. Georg A. Roth, Hendrik J. Ankersmit, Vinette B. Brown, Panos N. Papapanou, Ann Marie Schmidt & Evanthia Lalla. *Porphyromonas gingivalis* infection and cell death in human aortic endothelial cells. FEMS Microbiol Lett 2007; 272(1): 106-13.
60. Georg A. Rotha, Klaus Aumayrc, Mary Beth Giaconac, Panos N. Papapanou, Ann Marie Schmidta, and Evanthia Lallac. *Porphyromonas gingivalis* infection and prothrombotic effects in human aortic smooth muscle cells. Thromb Res 2009 March; 123(5): 780-84.
61. Andreas Pollreisz, Barry I. Hudson, Jong S. Chang, Wu Qu, Bin Cheng, Panos N. Papapanou, Ann Marie Schmidt and Evanthia Lalla. Receptor for advanced glycation endproducts mediates proatherogenic responses to periodontal infection in vascular endothelial cells. Atherosclerosis 2010 October; 212(2): 451-56.
62. Roth GA, Moser B, Roth-Walter F, Giacona MB, Harja E, Papapanou PN, Schmidt AM, Lalla E. Infection with a periodontal pathogen increases mononuclear cell adhesion to human aortic endothelial cells. Atherosclerosis 2007 Feb; 190(2): 271-81.
63. Roth GA, Moser B, Roth-Walter F, Giacona MB, Harja E, Papapanou PN, Schmidt AM, Lalla E. Infection with a periodontal pathogen increases mononuclear cell adhesion to human aortic endothelial cells. Atherosclerosis 2007 Feb; 190(2): 271-81.
64. Behle JH, Sedaghatfar MH, Demmer RT, Wolf DL, Celenti R, Kebschull M, *et al*. Heterogeneity of Systemic Inflammatory Responses to Periodontal Therapy. J Clin Periodontol. Author manuscript; available in PMC 2010 April 1.
65. Moïse Desvarieux, Ryan T. Demmer, David R. Jacobs, Jr; Panos N. Papapanou, Ralph L. Sacco, Tatjana Rundek. Changes in Clinical and Microbiological Periodontal Profiles Relate to Progression of Carotid Intima-Media Thickness: The Oral Infections and Vascular Disease Epidemiology Study. J Am Heart Assoc. 2013; 2:e000254.