A review in the Influence of periodontal treatment in systemic diseases.

Falcao, Artur

Bullon, Pedro

Abstract

The effects and consequences of Periodontal Diseases (PD) might not be confined to the oral cavity, and a great body of evidence has arisen supporting this claim demonstrating an association with several systemic conditions and diseases. With different levels of evidence, an association between PD and Cardiovascular Diseases (CVD), Diabetes, Psoriasis, Rheumatoid Arthritis (RA), Pregnancy outcomes and Respiratory diseases has been established with plausible biological mechanisms proposed to link the two conditions. However the true nature of this association, if it is causal, still remains elusive. For a better understanding of the complex relationships linking different conditions interventional studies now begin to focus on the possible outcomes of periodontal treatment (PT) in relation to the events, symptoms and biomarkers of several systemic conditions, assessing if PT has any impact on them, hopefully reducing their severity or prevalence. Therefore we proceeded to review the recent literature on the subject attempting to present a brief explanation of the systemic condition or disease, what proposed mechanisms might give biological plausibility to its association with PD and finally and more importantly, what data is currently available pertaining to the effects of PT on that systemic condition or disease. Raising awareness and discussing the possible benefits of PT on overall systemic health is important, in order to change the perception that PD is only limited to the oral cavity, and ultimately provide better and comprehensive care to our patients.

Keywords: Periodontal Disease, Systemic Diseases, Periodontal Treatment, Cardiovascular Diseases, Diabetes, Psoriasis, Rheumatoid Arthritis, Pregnancy outcomes, and Respiratory diseases

Introduction

Accounts emphasizing the importance of oral health and its influence in systemic health date back to ancient history and have accompanied the evolution of science and medicine throughout time (93). Therefore the idea of a link between oral health and systemic health is not new, however our understanding (or lack of understanding) of this complex relationship has had great influence on patient treatment protocols. The frequently cited article by Miller in 1891 (88) was perhaps the first step in the construction of what was later to be known as the focal infection theory, and his work was followed by several other authors giving way to the idea that oral infections also referred to as oral sepsis) were solely responsible for a wide range of systemic symptoms and conditions, thus resulting, at the time, in a standardized practice of complete teeth extraction, thought as, a treatment, or as prophylaxis, for almost all the patients. Soon after with the publication of several articles reporting worsening of symptoms and ineffectiveness of teeth extraction the focal infection theory as a pathogenic mechanism and scientific theory was abandoned and dentistry refocused on teeth treatment and maintenance. A more detailed and exhaustive review of the evolution, historical significance and impact of the focal infection theory is available in several other articles (11, 64, 93, 134).

Nonetheless in the past decades there has been a renewed interest in the fundamental principle of the focal infection theory in that the oral microbiota might play an important role in systemic health, specifically that the presence of an oral infection such as Periodontal Disease (PD) may be a cause or exacerbating factor of some systemic conditions (109, 114, 135). The question then is if PD and systemic diseases are merely coincidental, occurring simultaneously perhaps due to sharing same risk factors or have a causal association, in which PD can result in an increased risk of systemic diseases, aggravating or even initiating them (3, 12, 71). Several review articles have been published in the recent years addressing this question, comprehensively reviewing the available data, most noteworthy is the April 2013, jointly published, Journal of Periodontology and Journal of Clinical Periodontology Special issue: Periodontitis and Systemic Diseases - Proceedings of a workshop jointly held by the European Federation of Periodontology (EFP) and American Academy of Periodontology (AAP) (17, 26, 29, 35, 37, 49, 71, 72, 80, 86, 103, 106, 112, 124, 130, 132).

As proposed by Thoden van Velzen et al (1984) (128) three pathways or mechanisms might exist involved in the systemic manifestation of oral diseases: metastatic infection, metastatic immunological injury, and metastatic toxic injury. A simplified description of these pathways, in line with that of Van dyke & Winkelhoff (2013) (132) is that the link, between PD and systemic conditions or diseases can be perceived through two possible major pathways, infectious and inflammatory, that in the majority of situations can occur simultaneously and therefore are not independent. The first, infectious, and perhaps the remnant of the Focal Infection Theory, refers to the oral cavity as a natural reservoir of microorganisms with the associated presence of potential systemic pathogens, presence of whom, when in a diseased condition by the existence of periodontal pockets, can be exacerbated, and the concept is that these oral bacteria and their bacterial products (antigens, endotoxins, among others) can enter the blood stream or respiratory tract resulting in what can be a typically transient bacteremia that can however result in complications for immunocompromised and otherwise susceptible

individuals. The second, inflammatory, refers to the bacterial inflammatory products and diseased periodontium inflammatory molecules that have the potential to trigger systemic inflammation through several pathways and consequently exacerbating, or acting as a risk factor, of inflammatory associated systemic diseases in susceptible patients. Inflammation, in its core, is a highly complex mechanism that acts upon an aggression with the purpose of attempting to identify, control and eliminate that aggression, even at the risk of collateral damage, with the sole purpose of the survival of the organism (104). The inflammatory response presents several pathways dependent on physiological cellular processes that allow a continuously state of readiness for an immediate response and its posterior resolution. However in cases where these processes are thought to be malfunctioning, an aggression might result in a pathological process that can trigger or worsen a systemic disease or condition (22). Thus the proposition is that the control of PD, via adequate treatment, can improve the overall health of our patients by reducing the burden of aggression on the organism.

Considering that this subject is an ever-growing, highly complex relationship, and that the extent of its complexity and of the proposed biological mechanisms, epidemiological data and literature available, would require, for each systemic disease (or condition) and their possible relations with PD, its own review article in order to allow a detailed, exhaustive, discussion of the subject, we will, in this article, summarily review the literature in the subject of PD and systemic diseases with greater focus on some of the published data relating to the effects, or influence, of Periodontal Treatment (PT) in otherwise known to be associated systemic diseases, attempting to present a brief and broad explanation of the proposed biological mechanisms that relate the conditions while attempting to go through systematic reviews and meta-analysis whenever these are available, with the purpose of raising awareness for the importance and relevance of PD and PT and its impact on systemic health.

Assessing the global impact of periodontal treatment in systemic health.

A new trend in health related epidemiologic studies is the use of health insurance databases, which allows access to the data collected on a very large number of subjects, theoretically overcoming the often criticized small sample size of classical clinical studies, in order to access possible relationships between different systemic diseases, their epidemiology, and assessing the outcome of treatments (4, 52, 58). The problem arises when we consider that these databases, and others alike, were not created or designed for the purpose of clinical research and therefore often do not contain critical information such as patient variables and disease confounding factors, forcing that any conclusion, deriving from these database analysis, has to be drawn with a high level of caution (12, 34).

Within this line of work, an interesting approach to establish a possible beneficial relation between PT and systemic diseases was attempted by Jeffcoat et al (52) by analyzing insurance claims data from a large number of individuals (338,891) who had medical and dental insurance, and simultaneously PD and one of five systemic medical conditions - type 2 Diabetes Mellitus (T2DM); Coronary Artery Disease (CAD); Cerebral Vascular Disease (CvD); Rheumatoid Arthritis (RA); and pregnancy. The individuals were grouped into cohorts according to their systemic condition and from the resulting database two outcomes were measured, the total annual covered medical costs and the annual number of hospitalizations, comparing the results obtained from the control and treated groups. Their results showed evidence of lower medical costs and hospitalizations for all systemic medical conditions, with exception of RA, for individuals who were, by their definition, treated for periodontal disease. Results stated a cost reduction of 40.2%, 40.9%, 10.7% and 72.7% respectively for T2DM, CvD, CAD and pregnancy. Despite the apparent promising results and conclusions, this study presents several limitations and sparked justified criticism (33, 116) due to, among several other things, the applied criteria of inclusion in the periodontal treated group, the definition of the control group, the lack of overall information regarding periodontal status and treatment, and the resulting very small treated group accounting for 1% of the total sample. Timothy DeRouen in his letter to the editor (33), and his 2015 article (34) further elaborates on the shortcomings of this study and inherent limitations of such studies, however it is our opinion that, although no strongly based evidence conclusion may be drawn from this particular study, it has nonetheless some merits by first of all attempting to analyze a very large sample and approaching the PD and systemic disease relationship from an economic point of view, possibly raising awareness and encouraging insurance companies and health care providers to promote oral health care for their clients and patients.

Cardiovascular diseases

One of the first, and often cited, articles on the matter of PD and Cardiovascular Diseases (CVD) was published by Mattila et al (1989) (81) where the authors reported a strong association between poor oral health and acute myocardial infarction independent of the classical CVD risk factors, and at the time renewed the scientific community interest in the possible associations between PD and systemic diseases which resulted in hundreds of journal articles being published ever since (73). The term CVD refers to various possible clinical events, manifestations and symptoms ranging from cardiomyopathy, hypertension to myocardial infarction (MI) or cerebrovascular accident (stroke) (47). Atherosclerotic Vascular Disease (ASVD) is the main cause of CVD and the possible association of Atherosclerosis and PD has been the target of several longitudinal and cross-sectional studies, evidencing that patients with cardiovascular problems have a tendency to have a worse periodontal status and vice versa (7, 40, 78). The vast body of evidence has ultimately resulted in the 2009 Consensus by the editors of the American Journal of Cardiology and Journal of Periodontology (43) and the 2012 Statement by the American Heart Association (73), in which, overall, both consider that there is a sufficient level of evidence to support an association between ASVD and PD that cannot however be classified as causal. Supporting this association we can mention, as example, three meta-analysis by: Janket et al (2003), Humphrey et al (2008) and Blaizot et al (2009) (15, 48, 51) that assessed the risk of cardiovascular events in periodontal patients and reported a Risk Ratio (RR) of 1.19 (95% CI: 1.08; 1.32); 1.24 (95% CI: 1.01; 1.51) to 1.34 (95% CI: 1.10; 1.63); and 1.34 (95% CI: 1.27; 1.42) respectively.

Several proposed biological pathways of association between PD and ASVD exist, they may be direct and indirect (32, 73). Indirect pathways include a fundamentally Inflammatory pathway based upon the knowledge that Atherogenic processes and endothelial dysfunction (which can lead to CVD) have been established to result from elevated inflammatory activity, and considering that, PD triggers a systemic inflammatory response which leads to high levels of various cytokines, also associated with ASVD, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (Il-8) Tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1) among others, some of which can in turn promote a rapid hepatic synthesis and secretion of intravascular plasma proteins such as C-reactive protein (CRP) and fibrinogen (23, 43, 73, 123, 139). Proposed direct pathways consider an Infectious role of PD in ASVD derived from the knowledge that the oral microbiota and the potential pathogens there harbored can gain access to the circulatory system, resulting in a state of typical transient bacteremia, from common daily actions such as chewing, tooth brushing, flossing or clinical dental procedures as root scaling and teeth extraction (103, 107). The resulting bacteremia from this bacterial invasion is more severe in patients with gingivitis or PD, and some of these bacteria can either directly influence CVD mediators such as hypercoagulability or contribute to the atherosclerotic processes (32). Special interest has been given to the presence and the study of some periodontal pathogens such as *P.gingivalis* that presents the ability to invade host cells, induce monocyte migration, induce production of inflammatory cytokines and pro-coagulant molecules, as well as other bacterial species such as *A. actinomycetemcomitans* and *P. intermedia,* among others (18, 103).

In their vast majority the studies relating to periodontal treatment and its relation to CVD have focused on the evaluation and quantification of systemic inflammatory biomarkers and endothelial function as these atherosclerotic risk factors allow a shorter term evaluation of treatment outcomes whereas the study of PT effects on CVD events would require longer term results due to the chronic nature of CVD (126).Considering the vast amount of Randomized Clinical Trials (RCTs) published in recent years with sometimes mixed or conflicting results, it is obvious that a greater level of evidence is obtained by analyzing the available systematic reviews and meta-analysis, however some RCT are worth exploring and reviewing.

In the RCT by Tonetti et al (2007) (129) the authors studied the impact of PT in endothelial function, coagulation and inflammatory biomarkers, over a 6 months period, in 120 patients with diagnosed severe periodontitis without any other systemic disease or recent history of acute or chronic infection. Patients were divided into two groups, a control group that received standard PT consisting of supragingival mechanical scaling and polishing and a test group that received an intensive full-mouth, subgingival plaque removal, treatment course. Data was collected at several time points, baseline and after treatment up to 6 months. Endothelial function was primarily assessed by the vasodilatation of the brachial artery (flow-mediated dilatation - FMD) and inflammatory and coagulation biomarkers by the quantification of CRP, IL-6, von Willebrand factor and soluble E-selectin (a cell adhesion molecule expressed only on endothelial cells activated by cytokines). Results showed, at 24 hours, in the intensive treatment group a significant decrease of FMD, and significant increase, in the levels of CRP, Il-6, and the endothelial-activation markers, soluble E-selectin and von Willebrand factor. At 6 months however, intensive treatment patients presented greater FMD and lower E-selectin levels than the control group. The remaining parameters and biomarkers showed no statistical difference at 6 months. The authors concluded that despite the significant short term inflammation resulting from intensive periodontal treatment, over time the benefits in oral health are also translated in improvement of endothelial function.

Vidal et al (2009) (133) evaluated the outcome of PT on plasma levels of IL-6, CRP and fibrinogen. The population of this study were 22 patients with severe non-responsive arterial hypertension, diagnosed PD without other systemic relevant conditions or previous PT, divided randomly in 2 groups, a control group for whom PT was delayed for 3 months and a test group that received non-surgical PT. Their results showed statistically significant reduction in plasma levels of Il-6, CRP and Fibrinogen in the 3 months reevaluation after PT. At the time it was the first RCT to show simultaneous reductions of these biomarkers at a same time point, however this study does present several limitations (small sample size, short observation period) and raises the question of how much of an influence might the existing severe non-responsive arterial hypertension have on the results obtained.

Several systematic reviews with meta-analysis have also been published in the recent years. Freitas et al (2012) (42) focused in the influence of PT on the systemic CRP levels. Their search strategy and inclusion criteria resulted in 11 studies from which only 4 had randomized samples and therefore were included in the meta-analysis. They reported a statistically mean difference of -0.231 mg/L in CRP levels as a result of non-surgical PT at around 2 months. A more comprehensive systematic review was done by D'Aiuto et al (2013) (29) with an exhaustive review of literature assessing the effects of PT in CVD associated risk factors including lipids (Triglycerides (TGs), serum total cholesterol (TC), high/low density lipoprotein cholesterol (HDL/LDL-C)), blood pressure and inflammatory markers (white blood cell count, CRP, Cytokines, fibrinogen, TNF-α, Serum amyloid A, circulating cell adhesion molecules); and CVD surrogate and

hard endpoints such as endothelial function (FMD), carotid intima-media thickness (c-IMT) and cardiovascular events. For each CVD biomarker the pertinent literature was reviewed, summarized and the level of evidence graded. They reported: "(a) no evidence on the effects of periodontal therapy on subclinical atherosclerosis, serum levels of CD40 ligand, serum amyloid A and monocyte chemoattractant protein-1, (b) limited evidence on the effects of periodontal therapy on arterial blood pressure, leucocyte counts, fibrinogen, tissue necrosis factor-α, sE-selectin, von Willebrand factors, d-dimers, matrix metalloproteinases, oxidative stress and CVD events, and (c) moderate evidence suggesting a negligible effect of periodontal therapy in reducing interleukin-6 and lipids levels, whilst a positive effect in reducing serum C-reactive protein levels and improving endothelial function.". The authors concluded, in line with previous works, that PT short term results include an acute local and systemic inflammatory response, with disruption of the haemostatic system and endothelial function, an event that grants further investigation to properly assess the possible negative systemic implications in high risk populations (patients with co-morbidities). These short term results are followed by up to a 6 month progressive reduction in some CVD risk biomarkers such as lipids, CRP, fibrinogen and E-selectin with different levels of evidence and an improvement of endothelial function. Such an extensive review also highlights the several limitations of the existing body of evidence as pointed out by the authors due to the overall heterogeneity of the study's methodology, small sample sizes, short term study length and lack of studies assessing CVD events rather than just surrogate biomarkers of CVD.

Following this systematic review, Teeuw et al (2014) (126) conducted a meta-analysis on this subject. The body of evidence obtained related to the effects of PT on biomarkers of systemic inflammation, glucose and lipid metabolism, as well of vascular function, and was graded at a moderate level of evidence. The clinical trials (randomized and controlled) presented a test group (PT) compared to a non-PT control group, with or without co-morbidities and with an overall prevalent heterogeneity in the studied population characteristics, disease definition, study design and type of PT. The available data allowed for a meta-analysis to be performed for the systemic inflammation biomarkers CRP, Il-6, TNF-α and fibrinogen; glucose and lipid metabolism included triglycerides, TC, HDL-C, LDL-C and glycated haemoglobin (HbA1c); and for vascular function, the systolic and diastolic blood pressure.

The results as reported by the authors, shown in Table 1, present a weighted mean difference (WMD), between the PT groups and non PT, from baseline to end point, in favor of PT with significant results in the reduction of the majority of biomarkers analyzed, with exception of LDL-C, systolic and diastolic blood pressure which presented no statistical significant difference. Also, and importantly, a sub analysis of the data was also performed comparing PT outcomes only for patients presenting co-morbidities, evidencing even better results as showed in Table 1. These results clearly show that PT is beneficial at reducing these CVD risk factors especially for patients with associated co-morbidities such as CVD and Diabetes Mellitus, nonetheless the conclusions of this meta-analysis must be interpreted with caution due to several factors including the heterogeneity of the sample sizes, periodontal patients, types of PT among others (75) .

Table 1

	WMD	Confidence Interval (CI)	WMD (patients with co-morbidities)	Confidence Interval (CI)
CRP	-0.50 mg/l	-0.78; -0.22, p = 0.0005	-0.71 mg/l	-1.05; -0.36, p < 0.0001
IL-6	-0.48 ng/l	-0.90; -0.06, p = 0.03	-0.87 ng/l	-0.97; -0.78, p < 0.00001
TNF- α	-0.75 pg/ml	-1.34; -0.17, p = 0.01		
Fibrinogen	-0.47 g/l	-0.76; -0.17, p = 0.002		
TC	-0.11 mmol/l	-0.21; -0.01, p = 0.02	-0.15 mmol/l	-0.29; -0.01, p = 0.03
HDL-C	0.04 mmol/l	0.03; 0.06, p < 0.00001	0.05 mmol/l	0.03; 0.06, p < 0.00001
Triglycerides			-0.24 mmol/l	-0.26; -0.22, p < 0.00001
HbA1c			-0.43%	-0.60; -0.25, p < 0.00001

Table 1 – Results from Teeuw et al (2014) (126) presenting the weighted mean difference (WMD) from baseline to end, between PT and non-PT groups, and WMD within a sub group pf patients with co-morbidities for CRP, IL-6, TNF- α, Fibrinogen TC, HDL-C, Triglycerides and HbA1c.

Overall the current data suggests that PT might result in a reduction of CVD risk achieved by the control of biomarkers associated with CVD events (inflammatory and thrombotic markers, adhesion molecules and vascular function) (105). Nonetheless there is still a need for further long term interventional studies, preferably, with more homogeneous methodologies, assessing CVD events, thus elucidating if the stated benefits of PT translate in a reduction of CVD events.

Diabetes Mellitus

PD and Diabetes Mellitus (DM) present a highly complex relationship often characterized as bidirectional (119) that has been extensively studied over the last decades with several epidemiological and experimental studies demonstrating that DM is a risk factor for PD, that PD is more prevalent and severe in diabetic patients and also that the inflammatory mechanisms of PD can adversely affect metabolic control of diabetes also playing a role in the pathogenesis of diabetes and of its complications (65, 82, 91). The recent systematic review of epidemiologic observational evidence by Borgnakke et al (2013) (17) supports these claims. From the vast body of evidence supporting an association between the two diseases it is worth mentioning the often cited findings from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States (119) (2001), that reported a 2-fold difference in the prevalence of DM in PD patients (12.5% n=1293) against the prevalence of DM in non PD patients (6.3% n=12178) as well as a higher prevalence of PD in DM patients (17.3% n=928) against only 9% prevalence of PD in non-DM patients.

DM is characterized by hyperglycemia that may result from deficient insulin action, deficient insulin secretion or both and typically, the symptoms associated with hyperglycemia, are polydipsia, polyuria and polyphagia. This state of hyperglycemia results in long-term chronic systemic damage, acting as a risk factor for retinopathy, neuropathy, CVD, delayed wound healing and PD (68, 74). DM is classified in four main types: Type 1 DM (T1DM), Type 2 DM (T2DM), Gestational Diabetes and Other Specific types of diabetes that might occur, in example, as drug or chemical induced, pancreatic disease associated, or diabetes associated with genetic syndromes (5). T1DM accounts for 5 - 10% of all cases where the patients can become insulin dependent as it results from autoimmune destruction of the pancreatic β-cells leading to insufficient insulin secretion and high risk of ketoacidosis. T1DM has multiple genetic predispositions and poorly defined environmental factors (5). Gestational Diabetes occurs in previously non-diabetic pregnant women, that also, after their pregnancy can eventually develop T2DM (22). T2DM accounts for the majority of patients (90 to 95%) and results from a combination of a predominately insulin resistance with associated compensatory insulin secretion deficiency (61). T2DM patients might not be insulin dependent, at least not initially, and can go undiagnosed for several years, also T2DM presents a strong association with obesity.

There are several proposed pathogenic mechanisms linking PD and DM in a bidirectional manner, and the available evidence on these mechanisms was recently, exhaustively, reviewed by Taylor et al (2013) (124) where pro-inflammatory mediators play a key role in this complex relationship. Nevertheless we must also consider the fact that both diseases present possible genetic underlying mechanisms, evidenced by the strong familial inheritance of both diseases, while also possibly sharing immunological mechanisms of exaggerated immune response to environmental factors (68, 119). Insulin resistance (more typical of T2DM) may result from oxidative stress (22) or a chronic inflammatory state possibly associated with obesity (which acts also as a risk factor for T2DM and PD) or untreated PD (61). In turn insulin resistance can manifest as hyperglycemia that can lead to the production of advanced glycation endproducts (AGEs) that have the potential to bind to specific high-affinity cell surface receptors (RAGE) resulting in the production of pro-inflammatory cytokines by macrophages such as IL-1, Il-6 and TNF-α (119). The excessive formation and accumulation of AGEs in tissues results in diabetic complications, interferes with collagen turn-over in fibroblasts (impaired wound healing) and also amplifies neutrophil response to periodontal pathogens (13).

Considering the role of inflammation in T2DM it is thought that PT might have a beneficial effect in reducing insulin resistance, therefore improving glycemic control. HbA1c is used to assess average blood glucose levels over a period of 8 to 12 weeks representing an overall indicator that integrates fasting, preprandial as well as postprandial hyperglycemia. It is used as a biomarker for monitoring a patients glycemic control and as clinical surrogate endpoint in diabetes as it can be correlated to the increased risk of diabetes complications (62).

With regard to the effects of PT in T2DM patients Engebretson & Kocher (2013) (37) in their systematic review and meta-analysis conducted an update to the systematic review of Teewu et al (2010) (125) and Simpson et al (2010) (117), adding five more RCT's, resulting in a total of 9 RCT's that were included in their analysis, while maintaining the same inclusion criteria, for a total 719 subjects (398 in the treated groups). Follow-up data analyzed was of 3 to 4 months and they reported a, consistent with previous works (27), modest reduction of HbA1c in T2DM with PD patients that underwent nonsurgical PT, of -0.36% HbA1c (CI: -0.54; -0.19 $p < 0.0001$). Despite the consistency of this modest reduction of HbA1c the authors warn to the fact that these results are based in several small sample studies and thus the results cannot yet be

generalized, calling for researchers to pool resources in order to conduct larger clinical trials rather that isolated small clinical trials.

Therefore the subject of PT possibly improving glycemic control is not without controversy as Engebretson et al (2013) (38) reported the results from The Diabetes and Periodontal Therapy Trial, a 6-month, single-masked, multicenter randomized clinical trial involving 476 T2DM patients that completed the study and found no improvement of glycemic control resulting from PT in these patients with moderate to advanced PD. The majority of these patients were taking diabetes medication (oral hypoglycemic agents, insulin or both) and presented at baseline a mean HbA1c % of 7.84 (treatment group) and 7.77 (control group). Well controlled T2DM patients are defined as having < 7% HbA1c (6) Given this, a small sample intervention study by Soorya et al (2014) (54) divided 45 T2DM patients into three 15 patients groups according to their glycemic control at baseline (well, moderately and poorly controlled diabetes, 6-7%, 7-8% and >8% HbA1c respectively) and reevaluated them three months after non-surgical PT. The reported improvement in HbA1c and gingival crevicular level of TNF-α was somewhat related to the baseline levels of HbA1c. Thus it is tempting to conclude that baseline levels of glycemic control might be an influencing factor in the results of studies reporting no statistical significance of PT effect on levels of HbA1c alongside with other several possible cofounding factors. However a previous large, multi-centered, clinical trial by Jones et al (2007) (53) that recruited 193 patients, of which 132 completed the study also found no statistical difference in HbA1c at 4 months between the PT group and untreated group, yet these patients had a mean baseline HbA1c of 10%. As with the previously cited study (38) patients were also medicated, and more importantly, the medication was properly assessed leading the authors to state that the PT patients were less likely to receive increases in insulin, although the authors also reported an unsatisfactory resolution of the PD (presence of increased probing depth in several treated patients).

The discussion on whether PT results in beneficial improvement in HbA1c remains very much alive and the analysis of the available evidence must be pondered with caution and with special consideration to some of the studies characteristics, namely diabetes medication and its management, effectiveness of the PT strategy employed and baseline HbA1c values. HbA1c management and control is important since it has been reported that a reduction of 1% HbA1c can be associated with a 27% risk reduction for diabetes end point complications or 37% for microvascular complications (122), also a reduction of approximately 0,4% HbA1c is clinically similar to the addition of a second drug to a pharmacological regime for the management of DM (26). The vast majority of current studies do not account for patient's medication and their management of DM, and considering that these type of medications are often changed and adjusted, possibly together with changes in lifestyle during the studies evaluation period, might account for results reporting similar improvements of HbA1c in Periodontal treated and untreated patients. The periodontal clinical results obtained by PT must also be considered, as its ineffectiveness has been considered to be a possible confounding factor in studies results reporting no changes in HbA1c, this is to say, patients that after PT still present multiple sites with significantly increased probing depth and bleeding on probing are more likely to still have active infectious periodontal processes and therefore the treatment modality employed might not have been adequate. Finally it is also assumed that patients with higher baseline values of HbA1c have a bigger margin of improvement and thus should present better and significant results when adequate PT is conducted. With relation to the significance of DM patient HbA1c management, recently Kowall et al (2015) (63) reported results from the Study of Health in

Pomerania, (SHIP-Trend Study) concluding that PD and tooth loss were associated with poorly controlled T2DM but not with well controlled T2DM or pre-diabetic patients.

Considering the relevant role of inflammation in insulin resistance Correa et al (2010) (28) assessed the effects of PT on 23 T2DM patients evaluating not only circulating concentration of HbA1c, but also, CRP, Fibrinogen, IL-4, Il-6, Il-8, Il-10 and TNF-α. Patients were on average obese, and also medicated for DM but reported no changes in their medication regime or lifestyle in the duration of the study. 3 months after the end of the non-surgical PT the reevaluation of the patients resulted in a significant reduction in Fibrinogen and TNF-α, and a trend for the reduction of the remaining biomarkers that however did not achieve statistical significance. Focusing only in inflammatory biomarkers in T2DM patients, Artese et al (2015) (9) performed a systematic review and meta-analysis that included 9 studies reporting a statistically significant mean difference in favor of PT for TNF- α -1.33 pg/ml, (95% CI: -2.10; -0.56, $p < 0.001$) and CRP -1.28 mg/l (95% CI: -2.07; - 0.48, $p < 0.001$).

Despite the mixed results and controversy one must consider the conclusions of the Joint EFP / AAP Workshop as reported by Chapple & Genco (2013) (26) stating that the current evidence allows to conclude that PD has dose-dependent negative impact on glycemic control in diabetic patients, with adverse outcomes in diabetes complications and emerging evidence of increased risk of diabetes onset in periodontal patients. That also considering the consistent RCT's results of reduction in HbA1C, guidelines for PT and care of diabetes patients are granted and were presented.

Pregnancy outcomes

From the information previously acquired in experimental animal studies Offenbacher et al (1996) (94) conducted a pilot case-control study of 124 pregnant or postpartum women to assess the influence of PD on adverse pregnancy outcomes defined by preterm birth (< 37 weeks) and low birth weight (< 2,500g). Their results showed PD as a statistical significant risk factor for these adverse outcomes. Adverse pregnancy outcomes have several identified contributing factors such as smoking, alcohol consumption, maternal age, poor maternal nutrition and stress among several others (16). Despite some contradictory data, inflammation triggered by bacterial infections is thought to play a central role in this association (142). Other pathways consider direct infection by oral bacteria in the fetal-placental unit (47). A thorough review of the possible pathogenic mechanisms and the evidence that support them has been published by Madianos et al (2013) (80). Several systematic reviews and meta-analysis have also been published in recent years attaining to the subject of how PT might impact pregnancy

outcomes, some of which resorted to the same RCT's as was reviewed by other authors, and presented contradicting results (76, 86). Kim et al (2012) (60) in their meta-analysis of 11 RCT's concluded that PT was only statistically beneficial for reducing risk of pre term birth in high risk groups, while others such as Uppal et al (2010) (131), concluded to be no beneficial effects from PT in pre term birth or low birth weight. In light of the conflicting existing data, Lopez et al (2015) (76) conducted a systematic review of six meta-analysis and arrived to some very important conclusions: that several of the RCT's available, and used in these meta-analysis, present several methodological flaws resulting in a lack of control of the many cofounding factors; imprecise definition of PD and ineffectiveness of PT strategies employed to control the PD; and hence, as the authors conclude, these meta-analysis are not based on consistent scientific data. The authors also state that, in trials that do not present these flaws, PT demonstrated a reduction of pre term birth rate. A study analyzing insurance data of 23441 women was performed by Albert et al (2011) (4) and within the several limitations associated with these types of studies, they reported that preventive dental treatment, or post-delivery PT or prophylaxis, was statistically associated with lower odds of adverse pregnancy outcomes. While the overall data on the possible effects of PT in reducing the risks of adverse pregnancy outcomes can be conflicting (79), or at a minimum doubtful, studies continue to emerge presenting results showing CRP (59) and inflammatory cytokines (98) reduction in pregnant women undergoing non-surgical PT. At present, there is still no compelling evidence indicating that PT can improve pregnancy outcomes (85), despite the biological plausibility and promising initial results, the improvement of pregnancy outcomes will require the search and treatment of other etiological agents (121), nonetheless the current lack of evidence does not exclude the need for adequate PT in pregnant women with the propose of controlling infection and inflammation (142).

Psoriasis

In recent years several articles analyzing a possible association between PD and Psoriasis have been published (39, 45, 58, 66, 90, 102, 115, 118). With a renewed interest in the research of possible links between PD and other systemic inflammatory diseases, this hypothesis is specifically interesting due to the fact that an exaggerated immune response in epithelial surfaces with a dysregulation of the host inflammatory response, is present in both PD and Psoriasis (90). Psoriasis is characterized as a chronic, immune-mediated inflammatory systemic disease with predominantly skin and joint manifestations, with a prevalence of 1-3% in the world population that is subject to great variability between populations and ethnicities (46, 113). It has a strong hereditary, and hence genetic, component and can be triggered or worsened by multiple environmental factors, sharing with PD some risk factors such as smoking, alcohol consumption, stress, immune depression among others (115). Psoriasis is also reported to be associated with other systemic and inflammatory diseases such as CVD, metabolic syndrome and RA (102). The true etiology of Psoriasis is still not fully understood, being proposed that it

might be an autoimmune disease, or triggered by the bacterial microbiota of the skin, with some recent questions raised about the autoimmune theory (44).

Preus et al (2010) (102) performed a pilot cross-sectional clinical study investigating the prevalence of PD in psoriasis patients compared to an age and gender matched non-psoriasis control group. Trough bitewing x-ray measurements they evaluated radiographic alveolar bone loss and number of absent teeth in 155 psoriasis patients and in 155 matched control patients. They reported that psoriasis patients presented significantly higher mean bone loss ($p < 0.001$) and higher number of missing teeth ($p < 0.001$) compared to their matched controls. No confounding factors were registered and the population consisted of regular dental attendees. A similar study by Lazaridou et al (2012) (66) compared 100 Psoriasis patients to 100 matched controls while also recording the presence of metabolic syndrome. Their results showed that patients with PD were 3-times more likely to be in the Psoriasis group (OR: 3.329, 95% CI: 1.513; 7.324, $P = 0.003$) while also reporting a positive association between metabolic syndrome and Psoriasis and a positive correlation between the severity of Psoriasis, PD and metabolic syndrome. Even after performing a multivariate analysis model to account for the presence of metabolic syndrome, the association between PD and Psoriasis subsisted (OR: 2.486, 95% CI: 1.002; 5.842, $p = 0.049$). Other small sample clinical studies reported similar conclusions about an apparent association between PD and Psoriasis also influenced by the severity of the Psoriasis (45, 115, 118).

A epidemiological study by Keller et al (2013) (58) used data from the Longitudinal Health Insurance Database (LHID2000) released by the Taiwan National Health Research Institute to assess the impact of PD and PT on the risk of psoriasis. Based upon a reported diagnosis of PD they tracked a total of 230730 patients (115,365 with PD and 115,365 without PD as a control group matched for age, gender and geographical area) for a period of 5 years. Based on the insurance claims data, upon adequate statistical analysis, they reported an increased incidence of Psoriasis during the 5-year follow up period of 1.88 (95% CI: 1.77; 1.99) per 1000 person-years in patients with diagnosed with PD when compared to an incidence of 1.22 (95% CI: 1.14; 1.32) per 1000 person-years for the control group. Further they estimated a hazard ratio of Psoriasis in PD patients of 1.52 (95% CI: 1.38; 1.70). The effect of periodontal treatment on the risk of Psoriasis was also analyzed by comparing subjects that had undergone a gingivectomy or flap surgery to the control group achieving a lower hazard risk of 1.26. As the authors claim, PT attenuated but did not nullify the risk for subsequent psoriasis. Such studies do have the advantage of access to a very large sample size, however also present several inherent limitations as previously discussed (34), most importantly in this case, relating to the authors conclusion on the effect of periodontal treatment, is the lack of information about the PD severity and having compared only patients who were submitted to surgical treatment with no reference about non-surgical periodontal treatment, that is the most frequent treatment modality for periodontal patients. Regarding the effect of periodontal treatment, to the best of our knowledge, only a few case reports are available all describing overall improvement of Psoriasis symptoms and manifestations in patients suffering from Pustulosis palmaris et plantaris (PPP), a form of Psoriasis, upon undergoing comprehensive periodontal treatment (2, 50, 89).

The current hypothesis of common etiopathogenesis pathways between PD and Psoriasis are mainly speculative but involve several possible mechanisms such as an abnormal response to the microbiota inhabiting the oral cavity and skin, triggered by a common genetic defect, resulting in a genetic dysbiosis (44, 92) possibly affecting components of the innate

immune system such as dendritic cells (DC) with an upregulation of Toll-like receptors (TLR)-2 that results in an amplified inflammatory reaction and T-cell activation (102). The production of the associated T-cells cytokines TNF, IL-17, IL-22, leptin and interferon-gamma are associated with both diseases and contribute to an increased inflammatory response (115). A lower concentration of salivary IgA and lysozyme has been found in Psoriasis patients and thus possibly results in a higher risk of bacterial infection (45). Other hypothesis consider a more direct influence of the oral microbiota through bacterial heat shock proteins that result in higher levels of IgG (50), or the presence of *P. gingivalis*, a frequently associated periodontal pathogen bacteria, that possibly increases expression of Il-17 and that can produce peptidylarginine deiminase (PAD), an enzyme suggested to be associated with autoantigen presentation and autoantibody expression (58). Also considering that Psoriasis and PD are linked to metabolic syndrome and atherosclerotic plaques they may share similar pathways (66).

While there is growing evidence suggesting an association further studies are still required. Despite de biological plausibility of the proposed etiopathogenic pathways both diseases share several risk factors and that can act as cofounding factors in the available studies, potentially leading to misinterpretations.

Rheumatoid Arthritis

RA is characterized by chronic synovial inflammation with destruction of cartilage and bone. It is considered as an autoimmune disease and presents several similarities to PD due to the inflammatory pathogenic mechanisms present that relate both diseases, and also the bone reabsorption phenomena (56, 67, 83, 100). Some emphasis has been given to the periodontal pathogen *P. gingivalis* and its specific role in the production of anti-citrullinated protein antibodies (ACPA) that may lead to RA (77, 136, 137). Some of the evidence of the association between Rheumatoid Arthirtis (RA) and PD (8, 101) has been questioned on methodological grounds despite the biological plausibility, some findings are inconsistent mainly due to a possible selection bias in small sample case-control studies and PD diagnosis criteria (31, 71, 72).

The systematic review by Kaur et al (2013) (56) assessed the available evidence on an association between RA and PD attempting to establish its nature and specifically clarify if, the diseases have an negative impact on each other, also assessing the inflammatory biomarkers present and if PT had an effect on RA clinical parameters. Their inclusion criteria included well diagnosed PD and RA patients, as a primary RA outcome they considered measures such as erythrocyte sedimentation rate (ESR), CRP, ACPA and rheumatoid factor (RF). For PD the primary outcomes were tooth loss and clinical attachment loss, secondary outcomes included antibodies for *P. gingivalis* and ESR levels after PT. Their search criteria resulted in a total of 19 studies reviewed, 16 case-control and 3 experimental studies. Within the limitations of the available data, the authors concluded that RA patients presented a higher incidence of PD, that in RA patients with PD, ESR and CRP may be elevated and that evidence exists indicating the presence of serum antibodies for periodontal pathogenic bacteria in the synovium. Three studies included with evaluation of the effect of PT, reported some potential for a beneficial effect in reducing RA severity. Overall these findings support the existence of an association, albite not causal, and give strength to the proposed mechanisms of association related to inflammatory mediators and role of periodontal pathogens in auto-immunity. Following this work, and the promising effects of PT, Kaur et al (2014) (55), conducted a systematic review and meta-analysis focused on PT outcomes in RA patients as measured by clinical and biochemical measures. Five studies met their inclusion criteria, but only four were included in the meta-analysis and within these, aside from small sample sizes and short time periods, heterogeneity in the methodology of measures undertaken were found, resulting that in the meta-analysis the results for some biomarkers did not include all four studies. Comparing PT to non-PT groups they reported a standardized mean difference (SMD) of -0.479 (95% CI: -0.924; -0.034) for ESR suggesting a reduction following non-surgical PT. A trend for reduction of TNF, yet not significant, -1.352 (95% CI: -3.072; 0.369). No statistical significant difference was found for CRP levels, -0.072 (95% CI: -0.497; 0.352). For ACPA, RT and Il-6 meta-analysis was not possible and the studies reporting on these markers showed no statistical significant differences.

Recently Payne et al (2015) (97) reviewed the shortcomings of these results as well, critically appraising other recent publications and their own previous work (87) concluding that there is evidence of an association between the diseases and that PT has the potential of reducing RA disease activity, however further longitudinal and RCT with larger sample sizes, longer term follow up, are required to further elucidate this relationship.

Respiratory Diseases

Poor oral health (PD and caries) has been associated with respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD) and Bacterial Pneumonia which includes several subtypes such as nosocomial (hospital acquired) pneumonia (HAP), nursing home-associated pneumonia (NHAP), aspiration pneumonia and ventilator-associated pneumonia (VAP) (107). Several mechanisms have been proposed linking oral bacteria to these respiratory diseases, these include the aspiration of oral pathogens and respiratory pathogens that can colonize oral tissues, and inflammatory cytokines originating from periodontal tissues that can have an effect on respiratory epithelium promoting infection(108). Scannapieco and Ho (2001) (111) reviewing the data from the National Health and Nutrition Examination Survey III (NHANES III) from 13,792 subjects concluded that PD was associated with COPD, in that greater attachment loss resulted

in increased risk of COPD and there was a trend for diminished lung function with increased attachment loss. Two systematic reviews from 2003 (110) and 2006 (10) have however deemed the available evidence on the association between COPD and PD as firstly preliminary, and secondly as poor evidence of a weak association. Nonetheless several authors have reported this association (99), including diminished quality of life in COPD patients associated with the severity of the PD (141) and a Meta-analysis by Zeng et al (2012) (140) concluded that PD is a risk factor for COPD with an OR of 2.08 (95% CI: 1.48; 2.91; $p < 0.001$). The association between PD and the several forms of Pneumonia present overall a strong level of evidence as pointed out in the previously cited systematic reviews of 2003 (110) and 2006 (10). In the 2003 review, Scannapieco et al (110) concluded that poor oral hygiene and PD were associated with the colonization of oral tissues by respiratory pathogens and that diverse oral treatment methods and interventions that promoted better plaque control, resulted on an average 40 % reduction in the incidence of HAP. Azarpazhooh et al (2006) (10) reviewed ten studies aimed at the effects of improved oral health on progression and occurrence of VAP with a wide range of protocols ranging from professional dental care to chlorhexidine gel and rinse. Their results provided a good level of evidence that, improved oral health, results in reduced occurrence of Pneumonia, with a relative risk reduction of 34% to 83%. In line with these conclusions, a review by Pace and McCullough (2010) (95) further elaborates on the association between Pneumonia and poor oral health and issues recommendations for the oral management of elderly patients.

Other systemic diseases and conditions.

Associations between PD and other systemic conditions have also been pursued. A systematic review by Chambrone et al (2013) (24) concluded that there is sufficient evidence to positively associate Chronic Kidney Disease and PD, furthermore, they also concluded that PT results in positive outcomes. Also several studies proposing a possible association between PD and cancer have been reported in the recent years, on the basis that changes in the oral microbiota and/or the increase of inflammatory molecules with systemic effect might be an etiopathogenic link to the two conditions. Reviews on this subject show some level of evidence of association between poor oral hygiene, and possibly PD, to primarily oral cancer, followed by

pancreatic cancer and upper gastrointestinal cancer (1, 41, 84). Tezal et al (2009) (127) and Eliot et al (2013) (36) assessed the incidence of PD in patients with Head and Neck Squamous Cell Carcinoma (HNSCC) based on the mounting evidence of a growing association between chronic inflammation and cancer. While further larger studies with well controlled variables and cofounding factors for HNSCC such as smoking, alcohol consumption, and human papillomavirus, are still required, both studies reported a statistically significant association between HNSCC and PD, suggesting that PD can be an independent risk factor, and therefore this presents practical implications within prevention, early diagnosis and treatment within the search of a possible improvement in this disease's prognosis. In a similar line of reasoning, identical conclusions were drawn from results reported by Dar et al (2013) (30) describing an inverse association between oral hygiene and esophageal squamous cell carcinoma.

PD has also been proposed and hypothesized to have a role in several other systemic diseases and conditions such as Metabolic Syndrome (20, 21, 69), Obesity (57, 96), Osteoporosis (19, 25, 70), Alzheimer's (120), Depression (14) and Non-alcoholic fatty liver disease (138). Further research in needed to clarify the validity and nature of these proposed associations and if PT presents any beneficial results for these systemic conditions.

Conclusion

Overall the available systematic reviews and meta-analysis call out for further methodologically well-structured studies to further elucidate the validity and true nature of the associations between PD and systemic conditions, as well into the effects of PT on those systemic conditions. However, overviewing the available data on these several conditions, some considerations must be made, first of all, PT in the vast majority of cases is non-surgical, and therefore it is a relatively inexpensive, noninvasive procedure with undoubting beneficial

results, improving oral health. Secondly no study presented any adverse effects in periodontal or systemic health resulting from PT, so in a worst case scenario PT results in no change for the systemic condition, while maintaining its benefits for periodontal health. Thus we consider it is important to raise awareness within the medical and dental communities, promoting inter disciplinary teamwork that will allow patients suffering from targeted systemic conditions to be referred to dental professionals for periodontal diagnosis and treatment if required, as well for dental professionals to be alert regarding the possible systemic implications that might be present in their periodontal patients and thus by conducting a comprehensive medical history, an adequate referral might allow an early detection and adequate treatment or management of a systemic condition.

References

1. Ahn J, Chen CY,Hayes RB. Oral microbiome and oral and gastrointestinal cancer risk. Cancer Causes Control 2012: **23:** 399-404
2. Akazawa H, Nishimura F, Maeda H, Takashiba S, Mine A, Maekawa K,Kuboki T. Regression of pustulosis palmaris et plantaris by periodontal treatment in a subject with severe periodontitis. Int J Dermatol 2006: **45:** 1420-1422
3. Akshata KR, Ranganath V,Nichani AS. Thesis, antithesis, and synthesis in periodontal and systemic interlink. J Indian Soc Periodontol 2012: **16:** 168-173
4. Albert DA, Begg MD, Andrews HF, Williams SZ, Ward A, Conicella ML, Rauh V, Thomson JL,Papapanou PN. An examination of periodontal treatment, dental care, and pregnancy outcomes in an insured population in the United States. Am J Public Health 2011: **101:** 151-156
5. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care 2005: **28 Suppl 1:** S37-42
6. American Diabetes A. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2003: **26 Suppl 1:** S33-50
7. Andriankaja O, Trevisan M, Falkner K, Dorn J, Hovey K, Sarikonda S, Mendoza T,Genco R. Association between periodontal pathogens and risk of nonfatal myocardial infarction. Community Dent Oral Epidemiol 2011: **39:** 177-185
8. Arkema EV, Karlson EW,Costenbader KH. A prospective study of periodontal disease and risk of rheumatoid arthritis. J Rheumatol 2010: **37:** 1800-1804
9. Artese HP, Foz AM, Rabelo Mde S, Gomes GH, Orlandi M, Suvan J, D'Aiuto F,Romito GA. Periodontal therapy and systemic inflammation in type 2 diabetes mellitus: a meta-analysis. PLoS One 2015: **10:** e0128344

10. Azarpazhooh A,Leake JL. Systematic review of the association between respiratory diseases and oral health. J Periodontol 2006: **77:** 1465-1482
11. Barnett ML. The oral-systemic disease connection. An update for the practicing dentist. J Am Dent Assoc 2006: **137 Suppl:** 5S-6S
12. Barnett ML,Hyman JJ. Challenges in interpreting study results: the conflict between appearance and reality. J Am Dent Assoc 2006: **137 Suppl:** 32S-36S
13. Bascones-Martinez A, Matesanz-Perez P, Escribano-Bermejo M, Gonzalez-Moles MA, Bascones-Ilundain J,Meurman JH. Periodontal disease and diabetes-Review of the Literature. Med Oral Patol Oral Cir Bucal 2011: **16:** e722-729
14. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML,Maes M. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med 2013: **11:** 200
15. Blaizot A, Vergnes JN, Nuwwareh S, Amar J,Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. Int Dent J 2009: **59:** 197-209
16. Bobetsis YA, Barros SP,Offenbacher S. Exploring the relationship between periodontal disease and pregnancy complications. J Am Dent Assoc 2006: **137 Suppl:** 7S-13S
17. Borgnakke WS, Ylostalo PV, Taylor GW,Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. J Periodontol 2013: **84:** S135-152
18. Bullon P, Cordero MD, Quiles JL, Morillo JM, del Carmen Ramirez-Tortosa M,Battino M. Mitochondrial dysfunction promoted by Porphyromonas gingivalis lipopolysaccharide as a possible link between cardiovascular disease and periodontitis. Free Radic Biol Med 2011: **50:** 1336-1343
19. Bullon P, Goberna B, Guerrero JM, Segura JJ, Perez-Cano R,Martinez-Sahuquillo A. Serum, saliva, and gingival crevicular fluid osteocalcin: their relation to periodontal status and bone mineral density in postmenopausal women. J Periodontol 2005: **76:** 513-519
20. Bullon P, Jaramillo R, Santos-Garcia R, Rios-Santos V, Ramirez M, Fernandez-Palacin A,Fernandez-Riejos P. Relation of periodontitis and metabolic syndrome with gestational glucose metabolism disorder. J Periodontol 2014: **85:** e1-8
21. 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
22. Bullon P, Newman HN,Battino M. Obesity, diabetes mellitus, atherosclerosis and chronic periodontitis: a shared pathology via oxidative stress and mitochondrial dysfunction? Periodontol 2000 2014: **64:** 139-153
23. Caula AL, Lira-Junior R, Tinoco EM,Fischer RG. The effect of periodontal therapy on cardiovascular risk markers: a 6-month randomized clinical trial. J Clin Periodontol 2014: **41:** 875-882
24. Chambrone L, Foz AM, Guglielmetti MR, Pannuti CM, Artese HP, Feres M,Romito GA. Periodontitis and chronic kidney disease: a systematic review of the association of diseases and the effect of periodontal treatment on estimated glomerular filtration rate. J Clin Periodontol 2013: **40:** 443-456
25. Chang WP, Chang WC, Wu MS, Pai JT, Guo YC, Chen KC, Liu ME, Chiu WT,Hung KS. Population-based 5-year follow-up study in Taiwan of osteoporosis and risk of periodontitis. J Periodontol 2014: **85:** e24-30
26. Chapple IL, Genco R,working group 2 of the joint EFPAAPw. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol 2013: **84:** S106-112

27. Corbella S, Francetti L, Taschieri S, De Siena F,Fabbro MD. Effect of periodontal treatment on glycemic control of patients with diabetes: A systematic review and meta-analysis. J Diabetes Investig 2013: **4:** 502-509
28. Correa FO, Goncalves D, Figueredo CM, Bastos AS, Gustafsson A,Orrico SR. Effect of periodontal treatment on metabolic control, systemic inflammation and cytokines in patients with type 2 diabetes. J Clin Periodontol 2010: **37:** 53-58
29. D'Aiuto F, Orlandi M,Gunsolley JC. Evidence that periodontal treatment improves biomarkers and CVD outcomes. J Clin Periodontol 2013: **40 Suppl 14:** S85-105
30. Dar NA, Islami F, Bhat GA, Shah IA, Makhdoomi MA, Iqbal B, Rafiq R, Lone MM, Abnet CC,Boffetta P. Poor oral hygiene and risk of esophageal squamous cell carcinoma in Kashmir. Br J Cancer 2013: **109:** 1367-1372
31. de Pablo P, Chapple IL, Buckley CD,Dietrich T. Periodontitis in systemic rheumatic diseases. Nat Rev Rheumatol 2009: **5:** 218-224
32. Demmer RT,Desvarieux M. Periodontal infections and cardiovascular disease: the heart of the matter. J Am Dent Assoc 2006: **137 Suppl:** 14S-20S; quiz 38S
33. DeRouen TA. Effect of periodontal therapy on systemic diseases. Am J Prev Med 2015: **48:** e4
34. DeRouen TA. Promises and Pitfalls in the Use of "Big Data" for Clinical Research. J Dent Res 2015: **94 (9 Suppl)**: 107S-109S.
35. Dietrich T, Sharma P, Walter C, Weston P,Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. J Periodontol 2013: **84:** S70-84
36. Eliot MN, Michaud DS, Langevin SM, McClean MD,Kelsey KT. Periodontal disease and mouthwash use are risk factors for head and neck squamous cell carcinoma. Cancer Causes Control 2013: **24:** 1315-1322
37. Engebretson S,Kocher T. Evidence that periodontal treatment improves diabetes outcomes: a systematic review and meta-analysis. J Periodontol 2013: **84:** S153-169
38. Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, Seaquist ER, Reddy MS, Lewis CE, Oates TW, Tripathy D, Katancik JA, Orlander PR, Paquette DW, Hanson NQ,Tsai MY. The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. JAMA 2013: **310:** 2523-2532
39. Fadel HT, Flytstrom I, Calander AM, Bergbrant IM, Heijl L,Birkhed D. Profiles of dental caries and periodontal disease in individuals with or without psoriasis. J Periodontol 2013: **84:** 477-485
40. Fisher MA, Borgnakke WS,Taylor GW. Periodontal disease as a risk marker in coronary heart disease and chronic kidney disease. Curr Opin Nephrol Hypertens 2010: **19:** 519-526
41. Fitzpatrick SG,Katz J. The association between periodontal disease and cancer: a review of the literature. J Dent 2010: **38:** 83-95
42. Freitas CO, Gomes-Filho IS, Naves RC, Nogueira Filho Gda R, Cruz SS, Santos CA, Dunningham L, Miranda LF,Barbosa MD. Influence of periodontal therapy on C-reactive protein level: a systematic review and meta-analysis. J Appl Oral Sci 2012: **20:** 1-8
43. Friedewald VE, Kornman KS, Beck JD, Genco R, Goldfine A, Libby P, Offenbacher S, Ridker PM, Van Dyke TE, Roberts WC, American Journal of C,Journal of P. The American Journal of Cardiology and Journal of Periodontology editors' consensus: periodontitis and atherosclerotic cardiovascular disease. J Periodontol 2009: **80:** 1021-1032
44. Fry L, Baker BS, Powles AV,Engstrand L. Psoriasis is not an autoimmune disease? Exp Dermatol 2015: **24:** 241-244
45. Ganzetti G, Campanati A, Santarelli A, Pozzi V, Molinelli E, Minnetti I, Brisigotti V, Procaccini M, Emanuelli M,Offidani A. Periodontal disease: an oral manifestation of psoriasis or an occasional finding? Drug Dev Res 2014: **75 Suppl 1:** S46-49

46. Gudjonsson JE,Elder JT. Psoriasis: epidemiology. Clin Dermatol 2007: **25:** 535-546
47. Han YW, Houcken W, Loos BG, Schenkein HA,Tezal M. Periodontal disease, atherosclerosis, adverse pregnancy outcomes, and head-and-neck cancer. Adv Dent Res 2014: **26:** 47-55
48. Humphrey LL, Fu R, Buckley DI, Freeman M,Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med 2008: **23:** 2079-2086
49. Ide M,Papapanou PN. Epidemiology of association between maternal periodontal disease and adverse pregnancy outcomes--systematic review. J Periodontol 2013: **84:** S181-194
50. Ishihara K, Ando T, Kosugi M, Kato T, Morimoto M, Yamane G, Takahashi S, Ogiuchi H,Okuda K. Relationships between the onset of pustulosis palmaris et plantaris, periodontitis and bacterial heat shock proteins. Oral Microbiol Immunol 2000: **15:** 232-237
51. Janket SJ, Baird AE, Chuang SK,Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003: **95:** 559-569
52. Jeffcoat MK, Jeffcoat RL, Gladowski PA, Bramson JB,Blum JJ. Impact of periodontal therapy on general health: evidence from insurance data for five systemic conditions. Am J Prev Med 2014: **47:** 166-174
53. Jones JA, Miller DR, Wehler CJ, Rich SE, Krall-Kaye EA, McCoy LC, Christiansen CL, Rothendler JA,Garcia RI. Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study. J Clin Periodontol 2007: **34:** 46-52
54. K VS, A S, P L, N S, S MA, Bhat D,Mundinamane DB. The Effect of Scaling and Root Planing on Glycaemic Control, Periodontal Status and Gingival Crevicular Fluid TNF-alpha Levels in an Indian Population- To Reveal the Ambivalent Link. J Clin Diagn Res 2014: **8:** ZC22-26
55. Kaur S, Bright R, Proudman SM,Bartold PM. Does periodontal treatment influence clinical and biochemical measures for rheumatoid arthritis? A systematic review and meta-analysis. Semin Arthritis Rheum 2014: **44:** 113-122
56. Kaur S, White S,Bartold PM. Periodontal disease and rheumatoid arthritis: a systematic review. J Dent Res 2013: **92:** 399-408
57. Keller A, Rohde JF, Raymond K,Heitmann BL. Association between periodontal disease and overweight and obesity: a systematic review. J Periodontol 2015: **86:** 766-776
58. Keller JJ,Lin HC. The effects of chronic periodontitis and its treatment on the subsequent risk of psoriasis. Br J Dermatol 2012: **167:** 1338-1344
59. Khairnar MS, Pawar BR, Marawar PP,Khairnar DM. Estimation of changes in C-reactive protein level and pregnancy outcome after nonsurgical supportive periodontal therapy in women affected with periodontitis in a rural set up of India. Contemp Clin Dent 2015: **6:** S5-S11
60. Kim AJ, Lo AJ, Pullin DA, Thornton-Johnson DS,Karimbux NY. Scaling and root planing treatment for periodontitis to reduce preterm birth and low birth weight: a systematic review and meta-analysis of randomized controlled trials. J Periodontol 2012: **83:** 1508-1519
61. King GL. The role of inflammatory cytokines in diabetes and its complications. J Periodontol 2008: **79:** 1527-1534
62. Kohnert KD, Heinke P, Vogt L,Salzsieder E. Utility of different glycemic control metrics for optimizing management of diabetes. World J Diabetes 2015: **6:** 17-29
63. Kowall B, Holtfreter B, Volzke H, Schipf S, Mundt T, Rathmann W,Kocher T. Pre-diabetes and well-controlled diabetes are not associated with periodontal disease: the SHIP Trend Study. J Clin Periodontol 2015: **42:** 422-430

64. Kumar PS. Oral microbiota and systemic disease. Anaerobe 2013: **24:** 90-93
65. Lalla E, Cheng B, Lal S, Tucker S, Greenberg E, Goland R,Lamster IB. Periodontal changes in children and adolescents with diabetes: a case-control study. Diabetes Care 2006: **29:** 295-299
66. Lazaridou E, Tsikrikoni A, Fotiadou C, Kyrmanidou E, Vakirlis E, Giannopoulou C, Apalla Z,Ioannides D. Association of chronic plaque psoriasis and severe periodontitis: a hospital based case-control study. J Eur Acad Dermatol Venereol 2013: **27:** 967-972
67. Leech MT,Bartold PM. 2: The association between rheumatoid arthritis and periodontitis. Best Practice & Research Clinical Rheumatology 2015
68. Leite RS, Marlow NM,Fernandes JK. Oral health and type 2 diabetes. Am J Med Sci 2013: **345:** 271-273
69. Li Y, Lu Z, Zhang X, Yu H, Kirkwood KL, Lopes-Virella MF,Huang Y. Metabolic syndrome exacerbates inflammation and bone loss in periodontitis. J Dent Res 2015: **94:** 362-370
70. Lin TH, Lung CC, Su HP, Huang JY, Ko PC, Jan SR, Sun YH, Nfor ON, Tu HP, Chang CS, Jian ZH, Chiang YC,Liaw YP. Association between periodontal disease and osteoporosis by gender: a nationwide population-based cohort study. Medicine (Baltimore) 2015: **94:** e553
71. Linden GJ, Herzberg MC,working group 4 of the joint EFPAAPw. Periodontitis and systemic diseases: a record of discussions of working group 4 of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol 2013: **84:** S20-23
72. Linden GJ, Lyons A,Scannapieco FA. Periodontal systemic associations: review of the evidence. J Periodontol 2013: **84:** S8-S19
73. Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, Taubert KA, Newburger JW, Gornik HL, Gewitz MH, Wilson WR, Smith SC, Jr., Baddour LM, American Heart Association Rheumatic Fever E, Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young CoE, Prevention CoPVD,Council on Clinical C. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. Circulation 2012: **125:** 2520-2544
74. Loe H. Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care 1993: **16:** 329-334
75. Lopez NJ. Periodontal treatment may reduce levels of systemic inflammation markers associated with atherosclerotic profile. J Evid Based Dent Pract 2014: **14:** 53-55
76. Lopez NJ, Uribe S,Martinez B. Effect of periodontal treatment on preterm birth rate: a systematic review of meta-analyses. Periodontol 2000 2015: **67:** 87-130
77. Lundberg K, Wegner N, Yucel-Lindberg T,Venables PJ. Periodontitis in RA-the citrullinated enolase connection. Nat Rev Rheumatol 2010: **6:** 727-730
78. Machuca G, Segura-Egea JJ, Jimenez-Beato G, Lacalle JR,Bullon P. Clinical indicators of periodontal disease in patients with coronary heart disease: a 10 years longitudinal study. Med Oral Patol Oral Cir Bucal 2012: **17:** e569-574
79. Macones GA, Parry S, Nelson DB, Strauss JF, Ludmir J, Cohen AW, Stamilio DM, Appleby D, Clothier B, Sammel MD,Jeffcoat M. Treatment of localized periodontal disease in pregnancy does not reduce the occurrence of preterm birth: results from the Periodontal Infections and Prematurity Study (PIPS). Am J Obstet Gynecol 2010: **202:** 147 e141-148
80. Madianos PN, Bobetsis YA,Offenbacher S. Adverse pregnancy outcomes (APOs) and periodontal disease: pathogenic mechanisms. J Periodontol 2013: **84:** S170-180
81. Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesaniemi YA, Syrjala SL, Jungell PS, Isoluoma M, Hietaniemi K,Jokinen MJ. Association between dental health and acute myocardial infarction. BMJ 1989: **298:** 779-781
82. Mealey BL. Periodontal disease and diabetes. A two-way street. J Am Dent Assoc 2006: **137 Suppl:** 26S-31S

83. Mercado FB, Marshall RI, Klestov AC,Bartold PM. Relationship between rheumatoid arthritis and periodontitis. J Periodontol 2001: **72:** 779-787
84. Meyer MS, Joshipura K, Giovannucci E,Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. Cancer Causes Control 2008: **19:** 895-907
85. Michalowicz BS,Durand R. Maternal periodontal disease and spontaneous preterm birth. Periodontol 2000 2007: **44:** 103-112
86. Michalowicz BS, Gustafsson A, Thumbigere-Math V,Buhlin K. The effects of periodontal treatment on pregnancy outcomes. J Periodontol 2013: **84:** S195-208
87. Mikuls TR, Payne JB, Yu F, Thiele GM, Reynolds RJ, Cannon GW, Markt J, McGowan D, Kerr GS, Redman RS, Reimold A, Griffiths G, Beatty M, Gonzalez SM, Bergman DA, Hamilton BC, 3rd, Erickson AR, Sokolove J, Robinson WH, Walker C, Chandad F,O'Dell JR. Periodontitis and Porphyromonas gingivalis in patients with rheumatoid arthritis. Arthritis Rheumatol 2014: **66:** 1090-1100
88. Miller WD. THE HUMAN MOUTH AS A FOCUS OF INFECTION. The Lancet: **138:** 340-342
89. Murai O, Sasaki D, Ando Y, Fujimura A, Oikawa H, Suwa N, Watabe D, Maeda F, Endo K, Yaegashi T, Akasaka T,Naruishi K. Improvement of pustulosis palmaris et plantaris by periodontal infection control in a patient with chronic periodontitis. Clin Lab 2012: **58:** 323-327
90. Nakib S, Han J, Li T, Joshipura K,Qureshi AA. Periodontal disease and risk of psoriasis among nurses in the United States. Acta Odontol Scand 2013: **71:** 1423-1429
91. Naruse K. Diabetes and periodontal disease: What should we learn next? J Diabetes Investig 2014: **5:** 249-250
92. Nibali L, Henderson B, Sadiq ST,Donos N. Genetic dysbiosis: the role of microbial insults in chronic inflammatory diseases. J Oral Microbiol 2014: **6:**
93. O'Reilly PG,Claffey NM. A history of oral sepsis as a cause of disease. Periodontol 2000 2000: **23:** 13-18
94. Offenbacher S, Katz V, Fertik G, Collins J, Boyd D, Maynor G, McKaig R,Beck J. Periodontal infection as a possible risk factor for preterm low birth weight. J Periodontol 1996: **67:** 1103-1113
95. Pace CC,McCullough GH. The association between oral microorgansims and aspiration pneumonia in the institutionalized elderly: review and recommendations. Dysphagia 2010: **25:** 307-322
96. Papageorgiou SN, Reichert C, Jager A,Deschner J. Effect of overweight/obesity on response to periodontal treatment: systematic review and a meta-analysis. J Clin Periodontol 2015: **42:** 247-261
97. Payne JB, Golub LM, Thiele GM,Mikuls TR. The Link Between Periodontitis and Rheumatoid Arthritis: A Periodontist's Perspective. Curr Oral Health Rep 2015: **2:** 20-29
98. Penova-Veselinovic B, Keelan JA, Wang CA, Newnham JP,Pennell CE. Changes in inflammatory mediators in gingival crevicular fluid following periodontal disease treatment in pregnancy: relationship to adverse pregnancy outcome. J Reprod Immunol 2015: **112:** 1-10
99. Peter KP, Mute BR, Doiphode SS, Bardapurkar SJ, Borkar MS,Raje DV. Association between periodontal disease and chronic obstructive pulmonary disease: a reality or just a dogma? J Periodontol 2013: **84:** 1717-1723
100. Pinho MdN, Oliveira RDR, Novaes Jr. AB,Voltarelli JC. Relationship between periodontitis and rheumatoid arthritis and the effect of non-surgical periodontal treatment. Brazilian Dental Journal 2009: **20:** 355-364
101. Pischon N, Pischon T, Kroger J, Gulmez E, Kleber BM, Bernimoulin JP, Landau H, Brinkmann PG, Schlattmann P, Zernicke J, Buttgereit F,Detert J. Association among rheumatoid arthritis, oral hygiene, and periodontitis. J Periodontol 2008: **79:** 979-986

102. Preus HR, Khanifam P, Kolltveit K, Mork C,Gjermo P. Periodontitis in psoriasis patients: a blinded, case-controlled study. Acta Odontol Scand 2010: **68:** 165-170
103. Reyes L, Herrera D, Kozarov E, Rolda S,Progulske-Fox A. Periodontal bacterial invasion and infection: contribution to atherosclerotic pathology. J Periodontol 2013: **84:** S30-50
104. Rock KL,Kono H. The inflammatory response to cell death. Annu Rev Pathol 2008: **3:** 99-126
105. Saffi MA, Furtado MV, Polanczyk CA, Montenegro MM, Ribeiro IW, Kampits C, Haas AN, Rosing CK,Rabelo-Silva ER. Relationship between vascular endothelium and periodontal disease in atherosclerotic lesions: Review article. World J Cardiol 2015: **7:** 26-30
106. Sanz M, Kornman K,working group 3 of the joint EFPAAPw. Periodontitis and adverse pregnancy outcomes: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol 2013: **84:** S164-169
107. Scannapieco FA. The oral microbiome: Its role in health and in oral and systemic infections. Clinical Microbiology Newsletter 2013: **35:** 163-169
108. Scannapieco FA. Role of oral bacteria in respiratory infection. J Periodontol 1999: **70:** 793-802
109. Scannapieco FA. Systemic effects of periodontal diseases. Dent Clin North Am 2005: **49:** 533-550, vi
110. Scannapieco FA, Bush RB,Paju S. Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. Ann Periodontol 2003: **8:** 54-69
111. Scannapieco FA,Ho AW. Potential associations between chronic respiratory disease and periodontal disease: analysis of National Health and Nutrition Examination Survey III. J Periodontol 2001: **72:** 50-56
112. Schenkein HA,Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. J Periodontol 2013: **84:** S51-69
113. Schon MP,Boehncke WH. Psoriasis. N Engl J Med 2005: **352:** 1899-1912
114. Seymour RA. Is gum disease killing your patient? Br Dent J 2009: **206:** 551-552
115. Sharma A, Raman A,Pradeep AR. Association of chronic periodontitis and psoriasis: periodontal status with severity of psoriasis. Oral Dis 2015: **21:** 314-319
116. Sheiham A. Claims that periodontal treatment reduces costs of treating five systemic conditions are questionable. J Evid Based Dent Pract 2015: **15:** 35-36
117. 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 CD004714
118. Skudutyte-Rysstad R, Slevolden EM, Hansen BF, Sandvik L,Preus HR. Association between moderate to severe psoriasis and periodontitis in a Scandinavian population. BMC Oral Health 2014: **14:** 139
119. Soskolne WA,Klinger A. The relationship between periodontal diseases and diabetes: an overview. Ann Periodontol 2001: **6:** 91-98
120. Sparks Stein P, Steffen MJ, Smith C, Jicha G, Ebersole JL, Abner E,Dawson D, 3rd. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. Alzheimers Dement 2012: **8:** 196-203
121. Srinivas SK,Parry S. Periodontal disease and pregnancy outcomes: time to move on? J Womens Health (Larchmt) 2012: **21:** 121-125
122. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC,Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000: **321:** 405-412
123. Tabeta K, Yoshie H,Yamazaki K. Current evidence and biological plausibility linking periodontitis to atherosclerotic cardiovascular disease. Japanese Dental Science Review 2014: **50:** 55-62

124. Taylor JJ, Preshaw PM,Lalla E. A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. J Clin Periodontol 2013: **40 Suppl 14:** S113-134
125. 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:** 421-427
126. Teeuw WJ, Slot DE, Susanto H, Gerdes VE, Abbas F, D'Aiuto F, Kastelein JJ,Loos BG. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. J Clin Periodontol 2014: **41:** 70-79
127. Tezal M, Sullivan MA, Hyland A, Marshall JR, Stoler D, Reid ME, Loree TR, Rigual NR, Merzianu M, Hauck L, Lillis C, Wactawski-Wende J,Scannapieco FA. Chronic periodontitis and the incidence of head and neck squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2009: **18:** 2406-2412
128. Thoden van Velzen SK, Abraham-Inpijn L,Moorer WR. Plaque and systemic disease: a reappraisal of the focal infection concept. J Clin Periodontol 1984: **11:** 209-220
129. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P,Deanfield J. Treatment of periodontitis and endothelial function. N Engl J Med 2007: **356:** 911-920
130. Tonetti MS, Van Dyke TE,working group 1 of the joint EFPAAPw. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Periodontol 2013: **84:** S24-29
131. Uppal A, Uppal S, Pinto A, Dutta M, Shrivatsa S, Dandolu V,Mupparapu M. The effectiveness of periodontal disease treatment during pregnancy in reducing the risk of experiencing preterm birth and low birth weight: a meta-analysis. J Am Dent Assoc 2010: **141:** 1423-1434
132. Van Dyke TE,van Winkelhoff AJ. Infection and inflammatory mechanisms. J Periodontol 2013: **84:** S1-7
133. Vidal F, Figueredo CM, Cordovil I,Fischer RG. Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension. J Periodontol 2009: **80:** 786-791
134. Vieira CL,Caramelli B. The history of dentistry and medicine relationship: could the mouth finally return to the body? Oral Dis 2009: **15:** 538-546
135. Wade WG. The oral microbiome in health and disease. Pharmacol Res 2013: **69:** 137-143
136. Wegner N, Lundberg K, Kinloch A, Fisher B, Malmstrom V, Feldmann M,Venables PJ. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunol Rev 2010: **233:** 34-54
137. Wegner N, Wait R, Sroka A, Eick S, Nguyen KA, Lundberg K, Kinloch A, Culshaw S, Potempa J,Venables PJ. Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and alpha-enolase: implications for autoimmunity in rheumatoid arthritis. Arthritis Rheum 2010: **62:** 2662-2672
138. Yoneda M, Naka S, Nakano K, Wada K, Endo H, Mawatari H, Imajo K, Nomura R, Hokamura K, Ono M, Murata S, Tohnai I, Sumida Y, Shima T, Kuboniwa M, Umemura K, Kamisaki Y, Amano A, Okanoue T, Ooshima T,Nakajima A. Involvement of a periodontal pathogen, Porphyromonas gingivalis on the pathogenesis of non-alcoholic fatty liver disease. BMC Gastroenterol 2012: **12:** 16
139. Zeigler CC, Wondimu B, Marcus C,Modeer T. Pathological periodontal pockets are associated with raised diastolic blood pressure in obese adolescents. BMC Oral Health 2015: **15:** 41
140. Zeng XT, Tu ML, Liu DY, Zheng D, Zhang J,Leng W. Periodontal disease and risk of chronic obstructive pulmonary disease: a meta-analysis of observational studies. PLoS One 2012: **7:** e46508

141. Zhou X, Wang Z, Song Y, Zhang J,Wang C. Periodontal health and quality of life in patients with chronic obstructive pulmonary disease. Respir Med 2011: **105:** 67-73
142. Zi MY, Longo PL, Bueno-Silva B,Mayer MP. Mechanisms Involved in the Association between Periodontitis and Complications in Pregnancy. Front Public Health 2014: **2:** 290