—————— REVIEW ARTICLE ——————

Periodontal disease and overall health: An update

Prashanth Balakesavan, Sneha R. Gokhale¹, Vijay Deshmukh, Ray C. Williams²

Department of Periodontology and Oral Implantology, Dr. D.Y. Patil Dental College and Hospital, ¹Periodontology and Implantology, M.A. Rangoonwala College of Dental Sciences and Research Centre, Pune, Maharashtra, India, ²Periodontology, Dean of Dental Medicine, Stony Brook University and School of Dental Medicine, Stony Brook, NY 11794, USA

Address for correspondence:
Dr. Sneha R. Gokhale,
Department of Periodontology and
Implantology, M. A. Rangoonwala College
of Dental Sciences and Research Centre,
Pune - 411 001, Maharashtra, India.
E-mail: drsnehagaikwad@gmail.com

ABSTRACT

Periodontitis is a chronic inflammatory disease caused by a mixed microbial infection. The disease is a result of a complex interaction between the bacteria and the susceptible host. The host reaction to the microbial flora leads to a release of pro-inflammatory cytokines and a low grade inflammatory response that has an effect on the overall health status of the patient. Periodontitis has been associated with several systemic conditions such as cardiovascular disease, diabetes, adverse pregnancy outcomes and respiratory infections. In recent years, the relationship of periodontitis to overall health has been explored by numerous researchers who have expanded our understanding of periodontal disease as it affects the overall health of human subjects. This article further examines the relationship of periodontitis to overall health and throws a light on recent associations.

Key words
Anemia, infertility, neoplasms, periodontitis, periodontitis-systemic disease interactions

INTRODUCTION

Periodontal disease is one of the most common diseases of humans and is one of the main causes of tooth loss in adults. Well conducted studies have shown that periodontal disease is significantly associated with certain systemic diseases such as cardiovascular disease,[1,2] diabetes,[3-5] adverse pregnancy outcomes[6] and respiratory infections.[7] The periodontal disease - systemic disease relationship is supported by over 20 years of studies. The association of periodontal disease with several systemic conditions such as diabetes and atherosclerotic disease is reported to be related to the inflammatory response of periodontal disease. C-reactive protein is an important marker of the inflammatory response and is elevated in subjects with periodontal disease; its levels in peripheral blood are reduced when periodontal disease is treated. Another indication of the systemic inflammatory response associated with periodontal disease is the presence of cytokines, including tumor necrosis factor alpha and interleukins 1 and 6, often found in the circulation of patients with

periodontal disease.[8] There are other conditions that also contribute to a systemic inflammatory response including obesity, psoriasis and rheumatoid arthritis along with periodontal disease.[9-11]

This two way relationship of periodontitis and chronic systemic diseases in turn increase the systemic inflammatory load. This report further examines evidence for the relationship between periodontal disease and overall health.

PERIODONTITIS AND INFERTILITY

Infertility, which affects 15% of all couples worldwide, is defined as the failure of a couple to conceive after one year of unprotected intercourse (WHO 1999). In about half of all cases, infertility is attributed to the male partner (male factor) and results from poor sperm quality. Male factor includes one or more of the following: Low sperm production (oligozoospermia), poor sperm motility (asthenozoospermia) or abnormal sperm morphology (teratozoospermia) Guzick *et al.*,[12] In many cases, infertility of the male partner can be traced to overt infections, immunologic problems, hormonal imbalance, anatomic defects, ejaculatory failures and environmental exposure. In about half of the cases, however, the aetiology of male infertility remains unexplained.

Bieniek and Riedel (1993) published a case series suggesting a direct causal relationship between dental bacterial infections (foci) and therapy-resistant

bacteriospermia, perhaps leading to sub-fertility.[13] They implied that bacteriospermia might be initiated from oral foci of infection spreading through the circulation. Presence of various cytokines, namely tumour necrosis factor alpha (TNF-a), interferon gamma (IFN-g) and interleukin 1 beta (IL-1b) were shown, in seminal plasma of fertile, infertile and immunoinfertile men using specific immunoradiometric assays. Presence of IL-6 may be associated with infertility and may be of importance in the specific diagnosis and treatment of male[14-17] or female[18] infertility.

Klinger A *et al.,* studied a possible relationship between infertility and the presence of periodontal disease.[19] They conducted a study to examine the association between fertility parameters and the periodontal status of men attending a fertility and *in vitro* fertilization (IVF) clinic. The investigators found a positive correlation between deep periodontal pockets and sperm sub-motility. It can be postulated that bacteriospermia and cytokine production due to periodontal disease which acts as a foci of infection can increase the risk for male infertility.[18] However, it might also be plausible that periodontal disease is merely a risk indicator for infertility, arising from common exposures such as environmental, nutritional, stress-related, behavior oriented or genetic. This may point to a possible association between male infertility, diminished semen quality and periodontal infection in men attending fertility and IVF clinics. However, due to the small sample size and less than ideal statistical methods used, these findings need to be interpreted with caution within the context of the study.

Hart reported that the negative effect of periodontal disease on conception was of the same order of magnitude as the effect of obesity.[20] This was the first report to suggest that periodontal disease might be one of several factors that could be modified to improve the chances of pregnancy. The researchers followed a group 3737 pregnant women who were taking part in a Western Australian study, the SMILE study,[20] and analyzed information on pregnancy planning and pregnancy outcomes for 3416 of them. The information about time of conception was available for 1,956 women and of these 146 women took longer than 12 months to conceive. Periodontal disease was found to be a modifiable risk factor for impaired fertility in women.

Collectively, the evidence suggests that periodontal disease gives rise to foci of infection which leads to the increase in pro-inflammatory cytokines. This leads to increased risk of infertility in male patients and adverse pregnancy outcomes in female patients.

ANEMIA AND PERIODONTITIS

Anemia is one of the most common global public health problems in developed as well as developing countries.

Worldwide, anemia affects 1.62 billion people, representing 24.8% of the total population.[21] Anemia of Chronic Disease (ACD) is the most common form of anemia observed in clinical medicine.[22,23] ACD is defined as the anemia occurring in chronic infections, inflammatory conditions or a neoplastic disorder that is not due to marrow deficiencies or other diseases, and occurring despite the presence of adequate iron stores and vitamins.[24,25]

The possible explanation for ACD was postulated by Cartwright in 1966.[26] He reported that at least three pathologic processes are involved in ACD: Shortened erythrocyte survival, failure of the bone marrow to increase red blood cell (RBC) production to compensate for this increased demand, and impaired release of iron from the reticuloendothelial system. The pro-inflammatory cytokines such as interleukin 1 (IL- 1), IL- 6, and tumor necrosis factor–alpha (TNF α) are thought to act as mediators in suppressing erythropoiesis from the bone marrow leading to anemia.

The association of anemia and periodontitis has been explored since the early 20th century. Early reports suggested that anemia was a cause of destructive periodontitis and not a consequence of it. Lainson *et al.,* implicated anemia as a systemic cause of periodontitis.[27] Chawla *et al.,* suggested that anemia is an important factor in the etiology or pathogenesis of periodontal disease.[28] On the other side, Siegel *et al.,* reported a depression in the number of erythrocytes apparently secondary to the presence of periodontal disease.[29] Hutter *et al.,* evaluated the blood parameters in patients with chronic periodontitis and concluded that these patients show signs of anemia.[30] Gokhale *et al.*, performed a cross sectional study which included a total of 60 systemically healthy male patients.[31] Red blood cell parameters were evaluated from the peripheral blood samples. They concluded that patients suffering from chronic periodontitis have a statistically significant lower number of erythrocytes and lower hemoglobin as compared to healthy controls.

A recent interventional trial by Pradeep *et al.* supports the earlier findings regarding signs of anemia in patients with chronic periodontitis.[32] They treated 60 chronic periodontitis patients, who had lower hemoglobin levels, with non-surgical periodontal therapy. After a follow up of 6 m, they found a statistically significant improvement in the red blood cell parameters. This finding presents early clues that treating periodontal disease may be beneficial in the management of anemia and suggest a role for periodontal disease in ACD.

PERIODONTITIS AND CHRONIC KIDNEY DISEASE

The number of patients with chronic kidney disease (CKD) is growing and is projected to rise in the future. With this

in mind, it is important to understand the relationship of CKD and periodontal disease. CKD is associated with many physiologic changes that might contribute to the development of periodontal disease [Figure 1]. These include xerostomia, decreased salivary pH levels and decreased mineralization of enamel.[33] Additionally, some of the medications commonly prescribed to CKD patients may increase the risk of developing periodontal disease. Periodontal disease may represent a modifiable contributor to the already high inflammatory burden in patients with CKD, especially in those with diabetes. Treatment of periodontal disease in these patients could decrease the overall chronic inflammatory burden and its squeal.

Borawski *et al.* compared the periodontal status of three groups of adult CKD patients: (i) undergoing maintenance hemodialysis (HD), (ii) treated with continuous ambulatory peritoneal dialysis (CAPD) and (iii) pre-dialysis CKD patients.[34] The results were related to those obtained in generally healthy individuals

with advanced periodontitis requiring specialized treatment and in general population subjects. This study showed a marked level of periodontitis in adult CKD patients compared with the general population. The disease is particularly severe in maintenance HD patients and comparable to its full-symptomatic form in subjects requiring specialized treatment. The results also indicate that periodontal disease is less severe in CAPD patients and moderate in pre-dialysis CKD subjects. In summary, periodontal disease is prevalent, severe and under recognized in CKD patients.

Fischer *et al.,* assessed the potential bidirectional relationship between CKD and periodontal disease and potential mediators of this relationship using structural equation models.[35] The direct effect of one factor (periodontal disease) on the outcome (CKD) while simultaneously controlling for direct effects of many other factors (diabetes, hypertension, socio-economic status etc.) were studied.
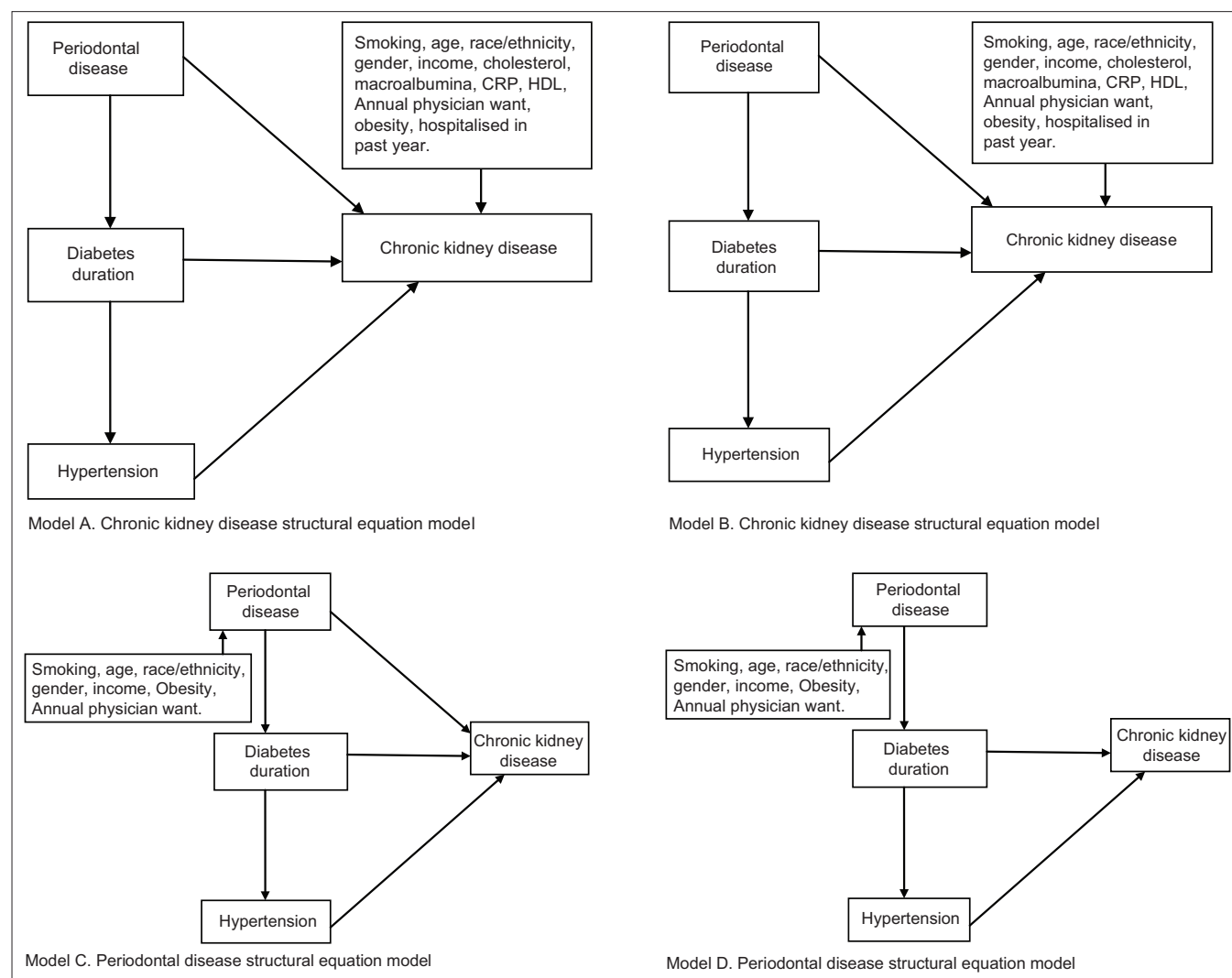

Model A. Chronic kidney disease structural equation model

Model B. Chronic kidney disease structural equation model

Model C. Periodontal disease structural equation model

Model D. Periodontal disease structural equation model

Figure 1: Hypothetical structural equation models outlining 4 possible relationships between CKD and periodontal disease. Not shown are relevant potential risk factors of diabetes e.g., obesity, hypertension and race/ethnicity

Models A, C and D appear to be the most plausible models. Each model suggests that a bidirectional relationship may exist between CKD and periodontal disease. Periodontal disease impacts CKD directly; CKD impacts periodontal disease directly; and periodontal disease indirectly affects CKD through diabetes duration and hypertension.

Results from models A, C and D also suggest a bidirectional relationship between periodontal disease and diabetes duration. These findings support direct relationship of diabetes and CKD (Model D) and that diabetes impacts CKD indirectly through periodontal disease (Model B) and hypertension.

Fisher *et al.* investigated the association between chronic kidney disease and clinical measures and serologic markers of periodontal infection in 4,053 patients.[36] Nine percent of the study population had chronic kidney disease, 22% had high *A. actinomycetemcomitans* antibody titer, 24% had high *P. gingivalis* antibody titer, 9% had periodontal disease and 17% were edentulous. After simultaneously adjusting for recognized risk factors, adults with a high *A. actinomycetemcomitans* titer were less likely to have chronic kidney disease, suggesting a composite systemic antibody response to clusters of periodontal pathogens which may be important. The authors concluded that the results support considering edentulism and low serum titer to *A. actinomycetemcomitans* as risk indicators for chronic kidney disease. The rationale for including edentulism in the analysis was based on the observation that periodontal disease is the major cause of edentulism among 40-to 69-year-olds, with 60.5% of teeth extracted due to periodontal disease,[37] tooth loss was a marker of past periodontal disease among adults over 55 years of age,[38] and non-surgical periodontal therapy was associated with a reduction in the rate of tooth loss.

In a cross sectional study Fisher *et al.* identified 12,947 adults 18 years or older with information for kidney function and at least one risk factor in the Third National Health and Nutrition Examination Survey (NHANES III).[39] The main predictor was periodontal status. The prevalence of Chronic kidney disease and periodontal disease was 3.6% and 6.0% respectively; and the prevalence of edentulism was 10.5%. Adults with periodontal disease and edentulous adults were twice as likely to have chronic kidney disease. In summary, the findings support the conclusion that periodontal disease is a potential nontraditional risk factor associated with CKD.

Thus, the evidence suggests that periodontitis and CKD share a bidirectional relationship with direct and indirect effects on each other.[35] Both the diseases lead to an increase in the systemic inflammatory load.

PERIODONTITIS AND CANCER

With increasing attention being focused on oral/systemic interactions, studies have suggested that periodontal disease may be associated with increased cancer risk.[40] Current understanding would indicate that tooth loss in older individuals may often be a result of periodontal disease.

In the first study in which the periodontium was assessed, Tezal *et al.* used a cross-sectional analysis of data obtained from the (NHANES III; National Center for Health Statistics 1994).[41] Following adjustment for age, gender, race, ethnicity, education, tobacco use, alcohol consumption, and occupational hazard, clinical attachment loss was significantly associated with the presence of oral tumors (OR: 4.6; CI: 2.3-9.3). Additional analyses considering the interactions between clinical attachment levels (CAL) and smoking indicated that CAL was a significant risk for tumor (OR: 21.76; CI: 3.6-131.63) in current smokers, suggesting that it is a risk modifier. This concept is strengthened by the observation that CAL had no effect on tumor risk for former smokers or people who never smoked and hence, is probably not an independent risk factor.

Rosenquist *et al.*, in a case control study of a Swedish population, alcohol consumption, tobacco use, oral hygiene, dental status and dental radiographic status were evaluated for increasing risk for oral cancer.[42] Upon radiographic assessment, a high level of marginal bone was noted to have an increased risk for oral cancer in unadjusted analyses (OR: 3.00; CI: 1.0-8.7); however, this failed to reach significance in adjusted analyses. Regular dental check-ups were noted to be associated with a decreased risk of oral cancer in adjusted analyses (OR: 0.4; CI: 0.2-0.6).

In a subsequent study, Tezal *et al.* carried out a case-control study of pre-existing data for patients.[43] Analyses following adjustments for the confounders of age, smoking habit, and number of missing teeth indicated that for every millimeter of alveolar bone loss, there was a 5.2-fold increase in the risk of tongue cancer (OR: 5.2; CI: 2.6-10.4). Other variables studied, including caries, restorations, and root canal treatment, failed to show any significant association with tongue cancer.

The most recent published study assessing the association between oral hygiene, periodontal disease, and oropharyngeal and oral cancer was a cross-sectional prospective case-control study. In this study Rezende *et al.* reported that advanced periodontal disease was greater in the subjects with oral and oropharyngeal cancer.[44] Up to 76% of the cancer subjects had periodontal probing pockets greater than 6 mm compared to 20% of the patients without cancer. No statistically

significant differences could be found for caries, missing teeth, restorations, or prostheses.

In a well conducted study, Michaud *et al.* analyzed periodontal disease, tooth loss and cancer risk in a male health professional cohort.[45] From this study, the five main cancers experienced by this cohort were colorectal, melanoma of the skin, lung, bladder, and prostate. Following adjustment for known cancer risk factors such as smoking history and diet, compared to individuals with no reported history of periodontal disease, individuals with a self reported history of periodontal disease demonstrated an increased risk for total cancer (HR: 1.14; CI: 1.07-1.22). For specific cancers, a past history of Periodontal disease was associated with increased risk for lung (HR: 1.36; CI: 1.15-1.60), kidney (HR: 1.49; CI: 1.12-1.97), pancreas (HR: 1.54; CI: 1.16-2.04) and hematological cancers (HR: 1.30; CI: 1.11-1.53). These findings for lung and pancreas were in agreement with previously published studies. The findings for kidney and hematological cancers were new and have not been reported previously. In contrast to previous studies, the association for esophageal cancer, while increased, was not significant after adjusting for smoking status.

Overall, the authors concluded that periodontal disease appeared to be associated with a small but nonetheless significant risk for cancer in general. Some influence of smoking was noted in smokers but the associations persisted in people who had never smoked. Whether some of these associations were due to direct effects of periodontal disease on cancer or the result of being more a surrogate marker requires further investigation.

The most widely quoted study is population-based and derived from data obtained from the NHANES I Epidemiologic Follow-up Study.[46] The authors reported that an association between periodontitis and lung cancer, after adjustment for known risk factors, could be demonstrated. However, they cautioned that this periodontitis-cancer association could be spurious. Another published report in which periodontitis and lung cancer was studied does not support a link. In this study,[47] associations between tooth loss and mortality patterns in a cohort from Glasgow were studied. The authors concluded there was no association between external causes of death and tooth loss as a continuous (HR: 0.97; CI: 0.92-1.03) or categorical variable for missing five to eight teeth (HR: 0.74; CI: 0.45-1.21) or missing nine or more teeth (HR: 0.89; CI: 0.42-1.88). In addition, no evidence of an association between lung cancer and tooth loss was found, with or without adjustment for smoking.

While the literature is scant on this topic, to date it does not seem to support any association between periodontal condition and lung cancer.

Pancreatic cancer is the fourth leading cause of cancer death in the U.S. It is an extremely difficult cancer to treat and little is known about what causes it. One established risk factor in pancreatic cancer is cigarette smoking; other links have been made to obesity, diabetes type 2 and insulin resistance. The oral cavity provides a gateway between the external environment and the gastrointestinal tract, and it facilitates both food ingestion and digestion. Oral hygiene and tooth loss can potentially affect gastrointestinal flora and nutritional status, and thus they have implications for the development of chronic diseases. The consequences of poor oral hygiene are dental plaque, periodontal disease, and tooth loss.[48]

Stolzenberg-Solomon *et al.*, hypothesized that tooth loss may be associated with pancreatic cancer.[49] This study suggests a positive association between tooth loss and the development of pancreatic cancer but further studies were needed to fully evaluate the association between tooth loss and pancreatic cancer. Tooth loss that occurs through poor dental hygiene may be a marker for more deleterious gastrointestinal flora and, consequently, greater endogenous nitrosation.[50] It has been estimated that 45%-75% of nitrosamine formation comes from endogenous formation by salivary and gastrointestinal bacteria converting nitrate to nitrite and nitrosamines,[51-55] with the rest coming from immunostimulation and macrophage response *via* intermediate production of nitric oxide.[56] Endogenous formation of nitrosamines in the oral cavity in persons with poor oral hygiene is 8-fold that in persons with good oral hygiene.[50]

Hujoel *et al.*, in their study utilizing the NHANES I data to investigate the association between periodontitis and various cancers found no association for pancreatic cancer.[46]

A subsequent study by Michaud *et al.*, investigated the association of periodontitis in 216 males diagnosed with pancreatic cancer from a larger cohort of 48,375 men.[57] This study provides the first strong evidence that periodontal disease may increase the risk of pancreatic cancer. The results showed that, after adjusting for age, smoking, diabetes, body mass index and a number of other factors, men with periodontal disease had a 63% higher risk of developing pancreatic cancer compared to those reporting no periodontal disease. The most convincing finding was that never-smokers (in subjects with periodontitis) had a two-fold increase in risk of pancreatic cancer.

A possible explanation for the results is that inflammation from periodontal disease may promote cancer of the pancreas.

Another explanation, according to Michaud, is that periodontal disease could lead to increased pancreatic

carcinogenesis because individuals with periodontal disease have higher levels of oral bacteria and higher levels of nitrosamines, which are carcinogens, in their oral cavity. More research is needed to confirm and explore the role of inflammation in cancer.

PERIODONTITIS AND MORTALITY

Further prospects for a relationship between oral health and increased risk of total death and death from cancer have been made from a cohort study on rural Chinese.[58] It was concluded that tooth loss (which occurs through poor dental hygiene) was significantly associated with increased risk for total death from cancer and from upper GI cancer.

Tramini *et al.,* investigated tooth loss and associated factors in elderly patients in France who had been institutionalized long term.[59] This was a cross-sectional study. The authors concluded that poor oral conditions can affect the general health of the patient which in turn can lead to increased risk of premature death.

Söder *et al.,* published the results from a 16-year longitudinal study investigating periodontitis and premature death.[60] It was concluded that young periodontitis patients with missing molars were at higher risk for premature death by life threatening diseases such as neoplasms than were their more healthy counterparts.

Ajwani *et al.,* conducted a prospective study in 364 individuals in the age group above 75 years.[61] They followed the patients for 5 years and found that after controlling for the common risk factors, periodontitis doubled the risk of cardiovascular related mortality.

SUMMARY

In recent years periodontitis has been linked to a number of systemic conditions. Substantial research indicates that oral health is an important component of general health, and individuals with periodontitis may be at risk for other diseases as well. The search for molecular mechanisms linking periodontitis to changes in systemic health has resulted in the evolution of a new era of multidisciplinary biomedical literature. However, an understanding about the effect of treatment of periodontal disease on systemic health is unclear. Well conducted intervention studies are required to substantiate the benefit of periodontal therapy in preventing or in reducing the risk of systemic disease. There is a need for a coherent approach by the dentists and the physicians to substantiate the two way relationship between oral and systemic disease. In this era of evidence based approach, further studies are required to close the gap between medicine and dentistry.

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