Comorbidity of periodontal disease

two sides of the same coin? An introduction for the clinician

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Comorbidity of periodontal disease: two sides of the same coin? An introduction for the clinician

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ABSTRACT

Increasing evidence has suggested an independent association between periodontitis and a range of comorbidities, for example cardiovascular disease, type 2 diabetes, rheumatoid arthritis, osteoporosis, Parkinson’s disease, Alzheimer’s disease, psoriasis, and respiratory infections. Shared inflammatory pathways are likely to contribute to this association, but distinct causal mechanisms remain to be defined. Some of these comorbid conditions may improve by periodontal treatment, and a bidirectional relationship may exist, where, for example, treatment of diabetes can improve periodontal status. The present article presents an overview of the evidence linking periodontitis with selected systemic diseases and calls for increased cooperation between dentists and medical doctors to provide optimal screening, treatment, and prevention of both periodontitis and its comorbidities.

Introduction

Periodontitis (PDIS) is a common oral disease, the manifestations of which accumulate with increasing age. Often, one gets the impression that PDIS is generally regarded as a natural, almost inevitable physiological consequence of the aging process. It is important to change this outdated perception. The population and the overall health sector should understand that PDIS is an inflammatory disease linked to the individual’s oral microbiota and immune system [1], and that the patients with PDIS, independent of age, benefit from periodontal treatment [2]. As outlined below, a number of other common medical disorders have inflammatory backgrounds too, which may, at least in part, explain their comorbidity with PDIS.

The oral cavity harbors a large amount of bacteria. By using molecular methods, it is now possible to identify precisely and rapidly >700 bacterial species that comprise the oral microbiome, and over the past 15 years, 68% of oral bacterial species in the mouth have been cultured [3]. Of further interest is that the oral microbiome appears to be individualized, implying that it can vary quantitatively and qualitatively between individuals, although there are significant overlaps.

Moreover, there is significant variation in the microbiota at different sites of the oral cavity in one person [3,4]. It is also clear that the oral microbiota changes in relation to different diseases such as PDIS, caries, root canal infections, and mucositis [5].

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limited by treatment blinding issues and ethical reservations by leaving PDIS untreated in the placebo group. Therefore, health authorities must rely on an assessment of the accumulated plausibility of a causal relationship between PDIS and its comorbidities, which will probably forever remain based on a sum of indirect evidence.

PDIS and CVD

Atherosclerosis, the major cause of CVD, is an inflammatory disease that develops in the large arteries, and is responsible for ischemic heart disease, stroke, and peripheral artery disease. Atheromatous plaques are usually asymptomatic until they become unstable with plaque rupture/erosion and thrombosis that are associated with increased inflammatory activity in both the arterial wall and systemically in the body [8]. As indicated above, the question of whether the relationship between PDIS and atherothrombosis is causal is difficult to answer definitively. The present review will focus on clinical studies addressing this issue while results of numerous exciting experimental studies supporting the relationship are beyond the scope of the review.

In the recent Swedish ‘PAROKRANK’ study including 805 patients <75 years of age with first-time acute myocardial infarction (AMI) and 805 matched controls without AMI, clinical dental examination and panoramic X-rays were conducted on all participants [9]. PDIS, verified by radiographically rated bone loss, was more common in patients with AMI than it was in controls. There was an increased (+49%) risk of AMI among the PDIS patients. The risk remained significantly increased (+28%) after adjustment for co-variates (smoking, DM, socioeconomic factors). These findings from the largest and most well-conducted case-control study to date emphasize that there can be an independent association between PDIS and AMI [9], which was supported by another recent study from Scandinavia [10].

Explanatory models

Numerous other population studies, including different ethnicities, have shown a connection between PDIS and CVD, and there is increasing evidence for this connection [11]. This link may be explained by several, not mutually exclusive, mechanisms (see Table 1).

Significance of periodontal treatment

As indicated above, there are several options for PDIS to affect the development of atherosclerosis and its clinical manifestations. The question is whether periodontal treatment can influence this process. A recent systematic review with meta-analysis concluded that periodontal treatment improves a number of surrogate measures for atherosclerosis, including endothelial dysfunction and lipid parameters, glycated hemoglobin (HbA1c), and biomarkers such as high sensitive C-reactive protein and interleukin (IL)-6, especially among those who already suffer from coronary heart disease and DM [21]. A longitudinal study from the United States has also shown that improvement of the periodontal status with reduced clinical probing depth and diminished subgingival presence of bacteria associated with PDIS among 420 participants resulted in a reduced progression of carotid intima-media thickness (IMT) over 3 years, and the average progression of carotid IMT was

| Table 1. Explanatory models for association of PDIS and CVD |
|-------------------------------------------------------------|
| Transfer of periodontal bacteria to atheromatous plaques     |
| Spillover of cytokines from periodontal tissues to the bloodstream |
| Systemic production of cytokines                             |
| Change of lipid metabolism as a result of PDIS               |
| Endothelial dysfunction                                     |
| Shared genetic risk factors                                 |

PDIS, periodontitis; CVD, cardiovascular disease; AMI, acute myocardial infarction.
inversely correlated with the improvement of periodontal status [31]. According to the authors, the study emphasized the significance of periodontal treatment as a possible preventive health effort. As mentioned above, endothelial dysfunction and carotid IMT are surrogate measures for atherosclerosis. While the importance of periodontal treatment for reduction of clinical cardiovascular endpoints has been suggested in epidemiological studies, for ethical reasons, randomized trials are unlikely to be performed in this area of research.

A comprehensive longitudinal study in Taiwan with an average follow-up period of 7 years was based on a random sample of one million people [32]. It was attended by 10,887 people, who had received dental treatment during the study period. A total of 10,989 age-, sex-, and comorbidity-matched subjects who had not received dental treatment were also included. In the scaling group, a significantly lower incidence of AMI (1.6% vs. 2.2%; \( p < 0.001 \)) and stroke (8.9% vs. 10%; \( p = 0.03 \)) was seen. A multivariate analysis showed that scaling was independently associated with significantly reduced risk of AMI (hazard ratio [HR] = 0.69) and stroke (HR = 0.85). Furthermore, there was a dose-dependent correlation with increased frequency of scaling leading to greater reduction in the risk of AMI and stroke. A weakness of this study was, however, that correction for all known risk factors such as smoking was not performed [32]. In a recent longitudinal study, also from Taiwan, 13,573 patients were treated for mild PDIS in the period 2001–2010, and an equal number of matched patients were treated for severe PDIS [33]. Among the latter patients, those who were >60 years of age had more frequent cardiovascular events, suggesting that the severity of PDIS plays a role in these events.

Hypertension

Hypertension is associated with PDIS [34,35], and these conditions occur frequently in patients with greater attachment loss [36]. Since hypertension is a treatable risk factor for CVD, it is important to identify patients with hypertension. Therefore, it should be considered whether dentists can contribute to such screening, since patients usually visit dentists more frequently than they visit medical doctors for preventive healthcare measures in the absence of known disease. Sublingual varices are associated with hypertension [37], and this oral manifestation may be used as indicator for screening and referral of patients to their general physician. Moreover, for the dentist, it is also important to know if the patient has hypertension, which may contribute to increased bleeding during oral surgery. In addition, many patients with hypertension are treated with calcium antagonists that occasionally can cause gingival hyperplasia, which again may result in increased progression of PDIS [38]. Obviously, it is up to the dentist to disrupt this potentially vicious circle.

PDIS and type 2 diabetes

It is well known that there is a relationship between DM and PDIS. As a result of the obesity epidemic, there has been a significant growth in the number of patients with type 2 diabetes (T2D) [39], and it is expected that dentists will receive increasing numbers of such patients for diagnosis and treatment in the future. The relationship is bidirectional in that DM predisposes for PDIS [40], and PDIS can worsen the course of DM, as recently reviewed [41].

Explanatory models

There are several ways by which PDIS and T2D may interfere with each other. DM can affect the development of PDIS through a change in the oral microbiota, although it is still uncertain whether such a change actually takes place [42]. The main factor for the increased propensity to develop PDIS among diabetics is probably the formation of advanced glycation end products (AGE) by glycation of proteins and lipids [43]. At high blood-sugar levels, characteristic of poorly controlled DM, the formation of AGE is increased, and the receptors for AGE (RAGE) are also upregulated, which leads to increased production of proinflammatory cytokines and increased tissue degradation, including increased bone resorption and decreased bone formation [44,45]. In addition, there are studies suggesting that DM patients display altered function of neutrophils, which play a major role in the pathogenesis of PDIS [46]. It is important to emphasize that well-controlled DM patients are not at increased risk of PDIS. It is thus important for the dentist to have information about blood-sugar control in the individual DM patient. On the other hand, epidemiological studies have linked PDIS to insulin resistance, and PDIS appears to be an independent risk factor for T2D [47,48].

Undiagnosed diabetes

Not all patients with T2D are aware that they have the disease because the initial symptoms are mild, and probably almost half of these patients are undiagnosed. Because it is critical for prevention of DM complications, including eye disease, kidney disease, neuropathy, and CVD, DM must be diagnosed as early as possible, and from an individual as well as societal and economic perspective, it is very unfortunate if diagnosis is delayed. It is also disadvantageous for dental treatment that the diabetic state is unknown. In the above-mentioned Swedish PAROKRANK study
in which patients with a first AMI were compared to controls without ischemic heart disease, glucose metabolism was examined by oral glucose tolerance test, and 9.3% of patients with AMI and 5.2% of the control group had undiagnosed DM. Another recent study revealed that 3.1% of 291 patients without diagnosed T2D who sought dental treatment at the Department of Odontology at the University of Copenhagen had HbA1c above the threshold for T2D, and similarly 27.1% had HbA1c above the threshold for pre-diabetes [49]. Pre-diabetes is a condition where blood-glucose levels are above the normal, but still do not qualify for the T2D diagnosis. This condition, which is a precursor of manifest T2D, is also known as impaired glucose tolerance. Patients with PDIS more frequently had elevated HbA1c than the control group without PDIS did. It is easy and cheap to implement screening for elevated HbA1c, and since many patients visit the dentist more regularly than they do the medical doctor, irrespective of whether they feel healthy, there is a golden opportunity to implement HbA1c screening in selected risk patients in dental clinics, with referral to their general physician in the case of elevated values.

Significance of periodontal treatment

Studies on the significance of periodontal treatment for the course of T2D often carry considerable methodological limitations, for example missing sufficient confounder control and with incomplete information on the efficacy of the periodontal treatment. However, several meta-analyses have shown that non-surgical periodontal treatment reduces HbA1c levels significantly in the range of 0.31–0.65% [50,51]. Even such small reductions in HbA1c can be clinically important. Thus, a large British study demonstrated that every percentage point decrease in HbA1c may result in as much as 35% reduction of microvascular complications, and an average reduction in HbA1c of 0.2% was related to a 10% lower mortality rate [52]. Therefore, the reduction by 0.31–0.65%, which can be achieved by periodontal treatment, can have a great impact in terms of systemic health and societal economy.

PDIS and rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease affecting 0.5–1% of the population in the Western world. The disease involves inflammation of the joints, with cartilage degradation and joint deformity, swelling, and pain [53]. Like PDIS, RA is a chronic inflammatory condition, which leads to tissue degradation, and an association between the two diseases has been demonstrated, as recently reviewed [54]. Despite a limited number of participants, the available studies suggest that both younger and older patients with RA have an increased predisposition to attachment loss [55–58]. This might argue for establishing periodontal prevention programs as part of routine treatment of patients with RA [55–58].

Explanatory models

PDIS and RA may associate bidirectionally. Both diseases display elevated circulating and target tissue levels of markers of inflammation and cytokine profiles of ‘tissue degrading’ nature, including increased production of IL-1 and tumor necrosis factor alpha (TNF-α) [55–59]. RA is furthermore characterized by the formation of autoantibodies, including rheumatoid factors recognizing immunoglobulin G (IgG) and antibodies to citrullinated proteins (ACPAs) [60]. The latter are found in approximately three-quarters of RA patients, which also have a characteristic expression of major histocompatibility complex molecules capable of binding citrullinated peptides [61]. Indeed, the subgroups of RA patients who show immune responses to citrullinated proteins and those who do not are considered by many investigators to be two distinct disease entities. Post-translational conversion of the amino acid arginine to citrulline is catalyzed by enzymes of the peptidylarginine deiminase (PAD) family, and these are considered important in disease progression, at least in ACPA-positive RA [60].

Patients with antibodies against citrullinated proteins more frequently appear to have PDIS than patients with osteoarthritis do [62]. In addition, RA patients more frequently have antibodies against Porphyromonas gingivalis than healthy controls do [63]. In search for a mechanistic link between PDIS and RA, special attention has been drawn to P. gingivalis, which is the only bacterium with capacity to produce a PAD (PPAD). Like the corresponding human enzyme, PPAD is capable of converting arginine to citrulline [64]. In theory, PPAD may therefore convert harmless host proteins into citrullinated autoantigens that become the target for autoantibodies and pathogenic T cells that drive RA. Smoking, which increases the risk of PDIS, is also the strongest lifestyle factor linked to the development of RA. Smoking is also believed to promote the secretion of PAD from leukocytes in the lungs and thus initiate citrullination [65].

Significance of periodontal treatment

Several studies have evaluated the effect of periodontal treatment on RA and biomarkers of the disease [58]. The available studies, however, are small and with limited follow-up, but they suggest that non-surgical periodontal treatment may reduce clinical
symptoms and biomarkers of active RA. Major intervention studies in RA patients with PDIS are needed in order to draw firm conclusions on this matter.

**PDIS and osteoporosis**

A possible association between PDIS and osteoporosis was described already in 1968 [66]. Osteoporosis is a systemic skeletal disease characterized by reduced bone density. Clinically, osteoporosis is divided into (1) an idiopathic form that appears early in life and affects men and women with equal frequency, and (2) an involutional form, which is subdivided into two types, the first of which includes postmenopausal women, and the other being age-related and including both elderly men and women [67]. The most prevalent form is postmenopausal osteoporosis, the possible association of which with PDIS has been examined in several clinical studies. The majority of these studies have been cross-sectional and with few participants, all postmenopausal women [68–75]. A recent cross-sectional study from Taiwan including 35,127 osteoporosis patients and 50,498 healthy controls showed that PDIS was associated with an increased risk of osteoporosis (odds ratio [OR] = 1.29) after adjustment for sex, age, and comorbidity, and that the risk increased with increased degree of periodontal inflammation [76]. Furthermore, osteoporosis was associated with a sixfold increased risk of concurrent PDIS. These results are supported by a second cross-sectional study from South Korea, which showed a positive correlation between PDIS and osteoporosis (OR = 1.21) after adjustment for age [77]. However, longitudinal studies are missing to substantiate a causal relationship between PDIS and osteoporosis.

**Explanatory models**

Various systemic risk factors, such as genetics, age, sex, vitamin D deficiency, medical hormone therapy, diet, smoking, obesity, and physical activity, affects the development of osteoporosis [78,79], but several of these are also risk factors for PDIS [80]. Bone density changes throughout life, but after the menopause a decrease in estrogen production occurs, which seems to be associated with an increased risk of osteoporosis. Decreased bone density in the jaw bone in subjects with osteoporosis is obviously compatible with this condition, leading to attachment loss in individuals with PDIS [72,73,81,82]. Besides being associated with decreased bone density, estrogen deficiency also affects the other periodontal tissues and the immune response against the periodontal biofilm in a proinflammatory direction [81].

**Significance of periodontal treatment**

As yet, no studies have evaluated the effect of periodontal treatment on osteoporosis. Furthermore, it remains unclear whether bisphosphonate treatment of postmenopausal patients with osteoporosis worsens or improves periodontal parameters. One study, however, showed that bisphosphonate therapy did not reduce alveolar bone loss in osteoporosis patients with PDIS [82].

**PDIS and Alzheimer’s disease**

Alzheimer’s disease (AD) is a neurodegenerative disease and the most common example of a group of diseases causing dementia. It is a progressive disease, with susceptibility genes working with little-understood environmental and behavioral influences [83]. AD is characterized by atrophy and neuronal death, especially in the hippocampal region of the brain [84]. There are two main categories of AD: the familial, early-onset form that targets individuals <65 years of age and accounts for about 2% of all cases of AD; and the late-onset form of AD that affects older (>65 years) subjects and accounts for approximately 98% of the cases. Late-onset AD has several genetic susceptibility traits. Among these, the apolipoprotein APOE ε4 allele is considered to be the most important [85]. The disease is already a great economic burden for society, and there is currently no treatment. Late AD probably has several causes, while a genetic component is more essential for the early form. Characteristically, late AD includes inflammatory changes in the brain, which may be initiated by local or systemic infection [86].

Among the microorganisms most frequently associated with AD are bacteria such as spirochetes, *P. gingivalis*, *Prevotella*, fusobacteria, *Actinomyces*, and *Chlamydophila pneumoniae*. Also, herpes virus (Epstein–Barr virus and cytomegalovirus) and yeasts of the genus *Candida* have been connected with AD [83]. With the exception of *C. pneumoniae*, all these microorganisms can be present in the periodontal pockets.

There is emerging evidence of a link between PDIS and AD. The relationship has been shown in cross-sectional and longitudinal studies by examining the association of AD with clinical signs of PDIS and circulating levels of antibodies against bacteria associated with PDIS, respectively [84].

**Explanatory models**

**Association of AD with periodontal bacteria**

In addition to the red complex bacteria, *Fusobacterium nucleatum* and *Prevotella intermedia*, both known to be associated with PDIS, also associate with AD.
Indeed, in the National Health and Nutrition Examination Survey (NHANES), antibody levels to these organisms were significantly increased in serum from patients with AD compared to controls [87]. This result was significant after controlling for each subject’s age, Mini-Mental State Examination score, and APOE ε4 allele status. Unexpectedly, Noble et al. found that a high (>640 ng/mL) anti-Actinomyces naeslundii titer was present in 10% of subjects with increased risk of AD, suggesting that AD pathogenesis may involve a spectrum of bacteria [88].

In 14 studies, oral spirochetes that are neurotrophic were demonstrated in the brain of AD patients. Seven different spirochetes were identified in 14/16 AD brains [89,90]. Spirochetes induced biological and pathological characteristics of AD (plaque accumulations of beta-amyloid and neurofibrillary tangles) after exposure of neuronal and glial cells in organ cultures. Lipopolysaccharide (LPS) from P. gingivalis was also detected in human brains with AD but not in control brains [91]. In a study based on 2,355 people >60 years of age, a positive correlation between PDIS and cognitive impairment was found, and a negative correlation was observed between antibody titers to P. gingivalis and scores in cognitive tests [87,92].

The original inflammatory hypothesis of AD suggested that AD hallmark proteins, for example beta-amyloid, were the main contributors to central nervous system inflammation. This hypothesis has been expanded to include involvement of infections, and life-style, genetic, and environmental factors in AD pathogenesis. PDIS is a prototypical oral condition that encompasses all these factors, including pathogenic bacteria [93].

Microorganisms and inflammatory mediators may reach the brain

Oral microorganisms and inflammatory mediators can be transported from inflamed periodontal tissues to the brain via the bloodstream. An increased amount of cytokines, particularly the macrophage-secreted TNF-α, has been detected in the plasma of AD subjects [94]. Also, elderly people harbored a higher titer of circulating IgG against several periodontal pathogens [87]. Cestari et al. [95] found an association between circulating IL-6 and TNF-α levels in patients with AD and PDIS, implicating these proinflammatory cytokines in the overlapping pathogenic mechanisms between oral infections and AD [95].

As mentioned above, daily episodes of bacteraemia follow from dental procedures, including toothbrushing and flossing, and from chewing, particularly in patients with PDIS. The bacteria involved can disseminate into the brain by closely related anatomical pathways, that is, trigeminal and olfactorial nerves [93]. The long-term effect of inflammatory mediators and pathogens and/or their virulence factors reaching the brain may over time prime the brain’s own microglia in individuals having inherent susceptibility traits. According to Singhrao et al., such susceptibilities could contribute to inadequate neutralization of invading agents reaching the brain and result in loss of cytoarchitectural integrity and vital neurons with subsequent deterioration of cognitive function [93].

Blood–brain barrier

The permeability of the blood–brain barrier (BBB) increases with age. Prolonged exposure to high concentrations of TNF-α tends to weaken the protective role of the BBB, making it more permeable to bacteria or endotoxins [96]. The APOE ε4 gene is also associated with increased BBB permeability, allowing microorganisms, their products, and inflammatory mediators such as TNF-α to penetrate into the brain [97]. These microorganisms and substances can also pass through circumventricular tissues and perivascular spaces of the brain because these regions lack a BBB [98]. The olfactory nerve and the trigeminal nerve also circumvent the BBB [99]. Indeed, olfactory cells may act as Trojan horses by which microorganisms can reach the brain [100].

Bacteria in the brain

Biofilm has been demonstrated in the brain of AD patients and was probably created by dental and Lyme spirochetes with accompanying local tissue activation of the innate immune system [101]. Riviere et al. also demonstrated the presence of seven different Treponema species in 14/16 specimens from AD brains [102]. Microorganisms and their toxic products as well as microbial DNA have been reported in the brain tissue of AD patients and animal models [83]. Spirochetes induce a latent and slowly progressive infection by circumventing host defense, and are able to induce beta-amyloid plaque formation in the brain [87,92]. Periodontal bacteria, especially T. denticola, may contribute to AD pathology using a range of inflammatory mechanisms by which neurons would be attacked. This occurs despite the fact that these bacteria inhibit inflammasome activity [103,104]. Spirochetes possibly promote their own survival and proliferation by blocking the complement cascade [105]. Moreover, P. gingivalis has LPS with various lipid A structures and is capable of modifying the latter components, which may provide the bacteria with the capacity to disguise itself from recognition by the immune system via TLR4 [106].

Genetics, environmental factors, nutrition, and other factors

A very important risk factor for AD is the APOE ε4 gene, which is associated with susceptibility for
infections and increases the expression of inflammatory mediators [107]. In total, 20 different genetic loci have been estimated to increase the susceptibility to AD, including APOE ε4. These include the genes for IL-1β and TNF-α, which are also linked to the development of PDIS [108]. The pathogenesis of AD probably includes an interaction between genes, microorganisms/toxins, and environmental factors. Inadequate nutrient intake is common in the elderly and in people with dementia, and this can contribute to gradual loss of nerve synapses. In addition, neglect of or an inability to maintain oral hygiene in the elderly promotes inflammation in the periodontium, which may favor the transport of microorganisms and their products, as well as inflammatory mediators, to the brain. Loss of teeth, which is often the result of PDIS, has been connected to a poor memory [109].

**PDIS and Parkinson’s disease**

Parkinson’s disease is another chronic neurodegenerative disease that results in selective loss of dopaminergic neurons in the substantia nigra of the brain. During the progression of Parkinson’s disease, there is a gradual degeneration of the nigrostriatal compounds, leading to cognitive, motor, and psychiatric symptoms. There is still no solid evidence that PDIS influences the pathogenesis of Parkinson’s disease [110]. However, there are studies indicating that PDIS is more common in patients with Parkinson’s disease, although large longitudinal studies and randomized case-control or case-cohort studies are lacking to substantiate this association [111,112].

**Explanatory models**

Parkinson’s disease causes motor disability, which complicates the provision of simple daily oral procedures such as brushing the tooth, which will inevitably lead to the accumulation of plaque. In addition, the cognitive changes in patients with Parkinson’s disease may have an impact on the quality and frequency of the home dental-care habits (as well as the dentists’ willingness to perform periodontal treatment), which contributes to increased plaque accumulation and risk of PDIS. A number of studies also indicate that systemic low-grade inflammation induced by PDIS [17,19,22] contributes to neural dysfunction at early stages of Parkinson’s disease [110]. Much evidence suggests that the pathogenesis of Parkinson’s disease has an inflammatory component, for example elevated plasma IL-6 appears to increase the risk of the disease [113,114]. There are no published studies on the effect of periodontal treatment of patients with Parkinson’s disease.

**PDIS and psoriasis**

Psoriasis is a chronic inflammatory disease with a prevalence of up to 8.5% of the population in the Nordic countries. The disease is also characterized by extensive comorbidity in the form of, for example, CVD and T2D, probably on the basis of shared inflammatory mechanisms [115–117]. An association between psoriasis and chronic PDIS has been shown, and increased concentrations of proinflammatory cytokines such as TNF-α and IL-1β have been found in saliva from patients with psoriasis [118–120]. The results from a large epidemiological study from Taiwan also suggest that intensive treatment of chronic PDIS can reduce the risk of psoriasis [121]. Activated T-helper (Th)-17 cells producing IL-17 are key pathogenic players in psoriasis, and bacterial infection, including infection with *P. gingivalis*, can promote the polarization of naïve T-helper cells into Th-17 cells. Also, activated Th-17 cells have been found in periodontal lesions, and increased IL-17 levels have been demonstrated in crevicular fluid from patients with MP [122–124].

**Lung diseases and oral hygiene**

Colonization of the oral cavity with respiratory pathogens related to a lack of oral hygiene and PDIS can be linked to the development of pneumonia. There is strong scientific evidence from randomized clinical trials that interventions aimed at improving oral hygiene may prevent pneumonia and reduce pneumonia-related deaths, particularly in elderly care-dependent patients [125]. A Norwegian study also showed that chronic PDIS occurs more frequently in patients with severe chronic obstructive pulmonary disease, even after adjusting for risk factors such as age, smoking, obesity, corticosteroid use, and decreased bone density [126].

**Conclusion**

There are numerous studies showing a correlation between PDIS and a variety of medical disorders. This is not surprising, since the mouth, of course, is part of the human body. These medical conditions are particularly frequent in the elderly population. Important for the dental clinician, there is evidence to suggest that periodontal treatment may have beneficial effects on some of these conditions (Table 2). It is obvious that cooperation between medical doctors and dentists should be strengthened, and a major prerequisite for this is increased awareness and knowledge about the disease connections mentioned in this article. Importantly, low-grade inflammation is considered to be one of the most prominent
mechanistic links between PDIS and its medical comorbidities.

A considerable amount of knowledge has accumulated about the link between PDIS and CVD, with growing evidence for a causal relationship. There are plausible mechanistic data (including experimental results that are not discussed here), and it appears that periodontal treatment may reduce the risk of atherosclerotic disease.

There is also extensive evidence that poor blood-sugar control in patients with T2D leads to an increased risk of PDIS with increased severity and extension, and that PDIS may lead to increased risk of elevated HbA1c and T2D. The growing prevalence of T2D in the populations will probably result in increased development of PDIS, which in turn can aggravate the course of T2D. Thus, the two diseases have a bidirectional relationship, presumably due to shared immunological reactions. Clinical studies also indicate that non-surgical periodontal treatment can improve metabolic control, which may reduce the development of diabetic complications. There are ample reasons for establishing systematic examination, prevention, and therapy programs for PDIS in diabetic patients.

Evidence suggests that there is also a bidirectional link between PDIS and RA, with increased risk for PDIS in patients with RA, and non-surgical periodontal treatment may reduce clinical symptoms and biomarkers of active RA. The increased propensity for attachment loss in patients with RA can also speak for the establishment of a periodontal prevention program as part of routine treatment of these patients. Moreover, studies of patients with osteoporosis suggest that there is an increased propensity to develop attachment loss.

PDIS is also associated with certain neurological disorders. Parkinson’s disease involves motor impairment and cognitive changes, which may entail deterioration of home dental-care habits. Moreover, low-grade inflammation, for example as a result of PDIS, may contribute to neurological dysfunction in the early stages of Parkinson’s disease. AD has a complex and multifactorial etiology, and periodontal infection may be one of several risk factors for AD. Thus, the presence of periodontal bacteria and their products have been found in the brain of AD patients. Infection can occur decades before AD becomes apparent. Improved oral hygiene can be an important prophylactic measure, but unfortunately can be challenging because AD patients are not always cooperative.

Psoriasis is characterized by widespread comorbidity in the form of, for example, CVD, diabetes, and PDIS, which probably also has a background in shared inflammatory mechanisms. Finally, there is scientific evidence that better oral health has a positive effect in the prevention of pneumonia, especially in elderly care-dependent patients.

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Table 2. Medical disorders with studies indicating that periodontal treatment has beneficial effect on course of disease or surrogate measures of disease

| Disorder    | Reference |
|-------------|-----------|
| CVD         | [21,31–33]|
| T2D         | [50,51]   |
| RA          | [58]      |

T2D, type 2 diabetes; RA, rheumatoid arthritis.
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References

[1] Bartold PM, Van Dyke TE. Periodontitis: a host-mediated disruption of microbial homeostasis. Unlearning learned concepts. Periodontol. 2000 2013;62:203–217.

[2] Pappapanou PN, Lindhe J, Sterrett JD, et al. Considerations on the contribution of ageing to loss of periodontal tissue support. J Clin Periodontol. 1991;18:611–615.

[3] Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. J Bacteriol. 2010;192:5002–5017.

[4] Aas JA, Paster BJ, Stokes LN, et al. Defining the normal bacterial flora of the oral cavity. J Clin Microbiol. 2005;43:5721–5732.

[5] Belstrom D, Paster BJ, Fiehn NE, et al. Salivary bacterial fingerprints of established oral disease revealed by the Human Oral Microbe Identification using Next Generation Sequencing (HOMINGS) technique. J Oral Microbiol. 2016;8:30170.

[6] Kozarov EV, Dorn BR, Shelburne CE, et al. Human atherosclerotic plaque contains viable invasive Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis. Arterioscler Thromb Vasc Biol. 2005;25:e17–e18.

[7] Venkataramani A, Santo-Domingo NE, Main DM. Actinobacillus actinomycetemcomitans pneumonia with possible septic embolization. Chest. 1994;105:645–646.

[8] Libby P, Hansson GK. Inflammation and immunity in diseases of the arterial tree: players and layers. Circ Res. 2015;116:307–311.

[9] Ryden L, Buhlin K, Ekstrand E, et al. Periodontitis increases the risk of a first myocardial infarction: a report from the PAROKRANK study. Circulation. 2016;133:576–583.

[10] Hansen GM, Egeberg A, Holmstrup P, et al. Relation of periodontitis to risk of cardiovascular and all-cause mortality (from a danish nationwide cohort study). Am J Cardiol. 2016;118:489–493.

[11] Stewart R, West M. Increasing evidence for an association between periodontitis and cardiovascular disease. Circulation. 2016;133:549–551.

[12] Forner L, Larsen T, Kilian M, et al. Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. J Clin Periodontol. 2006;33:401–407.

[13] Rosenfeld ME, Campbell LA. Pathogens and atherosclerosis: update on the potential contribution of multiple infectious organisms to the pathogenesis of atherosclerosis. Thromb Haemost. 2011;106:858–867.

[14] Aarabi G, Eberhard J, Reissmann DR, et al. Interaction between periodontal disease and atherosclerotic vascular disease–Fact or fiction? Atherosclerosis. 2015;241:555–560.

[15] Fiehn NE, Larsen T, Christiansen N, et al. Identification of periodontal pathogens in atherosclerotic vessels. J Periodontol. 2005;76:731–736.

[16] Rafferty B, Jonsson D, Kalachikov S, et al. Impact of monocyte cells on recovery of uncultivable bacteria from atherosclerotic lesions. J Intern Med. 2011;270:273–280.

[17] Gamonjal J, Acevedo A, Bascones A, et al. Levels of interleukin-1 beta, –8, and –10 and RANTES in gingival crevicular fluid and cell populations in adult periodontitis patients and the effect of periodontal treatment. J Periodontol. 2000;71:1535–1545.

[18] Houcken W, Teeuw WJ, Bizzarro S, et al. Arterial stiffness in periodontitis patients and controls. A case-control and pilot intervention study. J Hum Hypertens. 2016;30:24–29.

[19] Teeuw WJ, Laine ML, Bizzarro S, et al. ANRIL polymorphism is associated with elevated CRP levels in periodontitis: a pilot case-control study. Plos One. 2015;10:e0137335.
[20] Nicu EA, Van der Velden U, Nieuwland R, et al. Elevated platelet and leukocyte response to oral bacteria in periodontitis. J Thromb Haemost. 2009;7:162–170.

[21] Teeuw WJ, Slot DE, Susanto H, et al. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. J Clin Periodontol. 2014;41:70–79.

[22] Forner I, Nielsen CH, Bendtzen K, et al. Increased plasma levels of IL-6 in bacteremic periodontitis patients after scaling. J Clin Periodontol. 2006;33:724–729.

[23] Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. J Clin Periodontol. 2013;40(Suppl 14):S51–S69.

[24] Ridker PM, Rifai N, Stampfer MJ, et al. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation. 2001;101:1767–1772.

[25] Nibali L, D’aiuto F, Griffiths G, et al. Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: a case-control study. J Clin Periodontol. 2007;34:931–937.

[26] Monteiro AM, Jardini MA, Alves S, et al. Cardiovascular disease parameters in periodontitis. J Periodontol. 2009;80:378–388.

[27] Amar S, Gokce N, Morgan S, et al. Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. Arterioscler Thromb Vasc Biol. 2003;23:1245–1249.

[28] Tonetti MS, D’aiuto F, Nibali L, et al. Treatment of periodontitis and endothelial function. N Engl J Med. 2007;356:911–920.

[29] Geismar G, Enevold C, Sorensen LK, et al. Involvement of interleukin-1 genotypes in the association of coronary heart disease with periodontitis. J Periodontol. 2008;79:2322–2330.

[30] Schaefer AS, Bochene G, Jochens A, et al. Genetic evidence for PLASMINOGEN as a shared genetic risk factor of coronary artery disease and periodontitis. Circ Cardiovasc Genet. 2015;8:159–167.

[31] Desvarieux M, Demmer RT, Jacobs DR, et al. Changes in clinical and microbiological periodontal profiles relate to progression of carotid intima-media thickness: the oral infections and vascular disease epidemiology study. J Am Heart Assoc. 2013;2:e000254.

[32] Chen ZY, Chiang CH, Huang CC, et al. The association of tooth scaling and decreased cardiovascular disease: a nationwide population-based study. Am J Med. 2012;125:568–575.

[33] Chou SH, Tung YC, Lin YS, et al. Major adverse cardiovascular events in treated periodontitis: a population-based follow-up study from Taiwan. Plos One. 2015;10:e0130807.

[34] Desvarieux M, Demmer RT, Jacobs DR Jr., et al. Periodontal bacteria and hypertension: the oral infections and vascular disease epidemiology study (INVEST). J Hypertens. 2010;28:1413–1421.

[35] Darnaud C, Thomas F, Pannier B, et al. Oral health and blood pressure: the IPC cohort. Am J Hypertens. 2015;28:1257–1261.

[36] Cortsen B. Sammenhæng mellem oral sundhed og generel sundhed, livsstil, medicinforskrift samt forbrug af tandplejedyelser. Resultater fra Tandundersøgelsen ved KRAM-undersøgelsen. København: Det Nationale Institut for Kommunernes og Regionernes Analyse og Forskning. 2012.

[37] Hedstrom L, Albrektsson M, Bergh H. Is there a connection between sublingual varices and hypertension? BMC Oral Health. 2015;15:78.

[38] Livada R, Shlosh J. Calcium channel blocker-induced gingival enlargement. J Hum Hypertens. 2014;28:10–14.

[39] Carstensen B, Kristensen JK, Ottosen P, et al. Steering group of the national diabetes R. The Danish national diabetes register: trends in incidence, prevalence and mortality. Diabetologia. 2008;51:2187–2196.

[40] Casanova L, Hughes FJ, Preshaw PM. Diabetes and periodontal disease: a two-way relationship. Br Dent J. 2014;217:433–437.

[41] Holmstrup P, Flyvbjerg A. Linkage between periodontal disease and diabetes mellitus. In: Pedersen A, editor. Oral infections and general health. Switzerland: Springer International Publishing; 2016. p. 35–44.

[42] 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–S134.

[43] Chapple IL, Genco R, working group 2 of the joint EFP/AAP Workshop. Diabetes and periodontal diseases: consensus report of the joint EFP/AAP Workshop on periodontitis and systemic diseases. J Periodontol. 2013;84:S106–S112.

[44] Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813–820.

[45] Preshaw PM, Bisset SM. Periodontitis: oral complication of diabetes. Endocrinol Metab Clin North Am. 2013;42:849–867.

[46] Sima C, Rhourida K, Van Dyke TE, et al. Type 1 diabetes predisposes to enhanced gingival leukocyte margination and macromolecule extravasation in vivo. J Periodontal Res. 2010;45:748–756.

[47] Demmer RT, Squillaro A, Papapanou PN, et al. Periodontal infection, systemic inflammation, and insulin resistance: results from the continuous National Health and Nutrition Examination Survey (NHANES) 1999-2004. Diabetes Care. 2012;35:2235–2242.

[48] Demmer RT, Jacobs DR Jr., Desvarieux M. Periodontal disease and incident type 2 diabetes: results from the first national health and nutrition examination survey and its epidemiologic follow-up study. Diabetes Care. 2008;31:1373–1379.

[49] Holm NC, Belstrom D, Ostergaard JA, et al. Identification of individuals with undiagnosed diabetes and pre-diabetes in a danish cohort attending dental treatment. J Periodontol. 2016;87:395–402.

[50] Corbella S, Francetti L, Taschieri S, et al. Effect of periodontal treatment on glycemic control of patients with diabetes: A systematic review and meta-analysis. J Diabetes Investig. 2013;4:502–509.

[51] Sgolastra F, Severino M, Pietropaoli D, et al. Effectiveness of periodontal treatment to improve metabolic control in patients with chronic periodontitis and type 2 diabetes: a meta-analysis of randomized clinical trials. J Periodontol. 2013;84:958–973.

[52] Anonymous. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective
Diabetes Study (UKPDS) Group. Lancet. 1998;352:837–853.

[53] Scott DL, Wolfe F, Huizenga TW. Rheumatoid arthritis. Lancet. 2010;376:1094–1108.

[54] Holmstrup P, Nielsen CH. Linkage between periodontal disease and rheumatoid arthritis. In: Pedersen A, editor. Oral infections and general health. Switzerland: Springer International Publishing; 2016. p. 45–51.

[55] Havemose-Poulsen A, Westergaard J, Stoltze K, et al. Periodontal and hematological characteristics associated with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. J Periodontol. 2006;77:280–288.

[56] Kasser UR, Gleissner C, Dehne F, et al. Risk for periodontal disease in patients with longstanding rheumatoid arthritis. Arthritis Rheum. 1997;40:2248–2251.

[57] Fuggle NR, Smith TO, Kaul A, et al. Hand to mouth: a systematic review and meta-analysis of the association between rheumatoid arthritis and periodontitis. Front Immunol. 2016;7:80.

[58] Kaur S, Bright R, Proudman SM, et al. Does periodontal treatment influence clinical and biochemical measures for rheumatoid arthritis? A systematic review and meta-analysis. Semin Arthritis Rheum. 2014;44:113–122.

[59] Kaur S, White S, Bartold PM. Periodontal disease and rheumatoid arthritis: a systematic review. J Dent Res. 2013;92:399–408.

[60] Schellekens GA, de Jong BA, van den Hoogen FH, et al. Citrulline is an essential constituent of anti- genic determinants recognized by rheumatoid arthritis-specific autoantibodies. J Clin Invest. 1998;101:273–281.

[61] Hill JA, Southwood S, Sette A, et al. Cutting edge: the conversion of arginine to citrulline allows for a high-affinity peptide interaction with the rheumatoid arthritis-associated HLA-DRB1*0401 MHC class II molecule. J Immunol. 2003;171:538–541.

[62] Mikuls TR, Payne JB, Yu F, et al. Periodontitis and Porphyromonas gingivalis in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66:1090–1100.

[63] Mikuls TR, Payne JB, Reinhardt RA, et al. Antibody responses to Porphyromonas gingivalis (P. gingivalis) in subjects with rheumatoid arthritis and periodontitis. Int Immunopharmacol. 2009;9:38–42.

[64] McGraw WT, Potempa J, Farley D, et al. Purification, characterization, and sequence analysis of a potential virulence factor from Porphyromonas gingivalis, peptidylarginine deiminase. Infect Immun. 1999;67:3248–3256.

[65] Catrina AI, Joshua V, Klaresekog L, et al. Mechanisms involved in triggering rheumatoid arthritis. Immunol Rev. 2016;269:162–174.

[66] Groen JJ, Menczel J, Shapiro S. Chronic destructive periodontal disease in patients with presenile osteoporosis. J Periodontol. 1968;39:19–23.

[67] Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. Endocr Rev. 2010;31:266–300.

[68] Von Wowern N, Klausen B, Kollerup G. Osteoporosis: a risk factor in periodontal disease. J Periodontol. 1994;65:1134–1138.

[69] Mohammad AR, Brunsvold M, Bauer R. The strength of association between systemic postmenopausal osteoporosis and periodontal disease. Int J Prosthodont. 1996;9:479–483.

[70] Mohammad AR, Bauer RL, Yeh CK. Spinal bone density and tooth loss in a cohort of postmenopausal women. Int J Prosthodont. 1997;10:381–385.

[71] Tezal M, Wactawski-Wende J, Grossi SG, et al. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol. 2000;71:1492–1498.

[72] Singh A, Sharma RK, Siwach RC, et al. Association of bone mineral density with periodontal status in postmenopausal women. J Investig Clin Dent. 2014;5:275–282.

[73] Hernandez-Vigueras S, Martinez-Garriga B, Sanchez MC, et al. Oral microbiota, periodontal status, and osteoporosis in postmenopausal females. J Periodontol. 2016;87:124–133.

[74] Alves RC, Felix SA, Rodriguez-Archilla A, et al. Relationship between menopause and periodontal disease: a cross-sectional study in a Portuguese population. Int J Clin Exp Med. 2015;8:11412–11419.

[75] Passos JS, Vianna MI, Gomes-Filho IS, et al. Osteoporosis/osteopenia as an independent factor associated with periodontitis in postmenopausal women: a case-control study. Osteoporos Int. 2013;24:1273–1283.

[76] Huang YF, Chang CT, Liu SP, et al. The impact of oral hygiene maintenance on the association between periodontitis and osteoporosis: a nationwide population-based cross sectional study. Medicine (Baltimore). 2016;95:e2348.

[77] Lee JH, Lee JS, Park JY, et al. Association of lifestyle-related comorbidities with periodontitis: a nationwide cohort study in Korea. Medicine (Baltimore). 2015;94:e1567.

[78] Penoni DC, Torres SR, Farias ML, et al. Association of osteoporosis and bone medication with the periodontal condition in elderly women. Osteoporos Int. 2016;27:1887–1896.

[79] Cosman F, de Beur SJ, LeBoff MS, et al. Clinician’s guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25:2359–2381.

[80] Reynolds MA. Modifiable risk factors in periodontitis: at the intersection of aging and disease. Periodontol. 2000;2014;64:7–19.

[81] Wactawski-Wende J. Periodontal diseases and osteoporosis: association and mechanisms. Ann Periodontol. 2001;6:197–208.

[82] Grgic O, Kovačev-Zavisic B, Veljovic T, et al. The influence of bone mineral density and bisphosphonate therapy on the determinants of oral health and changes on dental panoramic radiographs in postmenopausal women. Clin Oral Investig. 2016;21:151–157.

[83] Olsen I, Singhrao SK. Can oral infection be a risk factor for Alzheimer’s disease? J Oral Microbiol. 2015;7:29143.

[84] Balin BJ, Hudson AP. Etiology and pathogenesis of late-onset Alzheimer’s disease. Curr Allergy Asthma Rep. 2014;14:417.

[85] Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer’s disease in late onset families. Science. 1993;261:921–923.
[86] Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer’s disease. Lancet Neurol. 2015;14:388–405.

[87] Sparks Steen P, Steffen MJ, Smith C, et al. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer’s disease. Alzheimers Dement. 2012;8:196–203.

[88] Noble JM, Scarmea N, Celenti RS, et al. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. Plos One. 2014;9:e114959.

[89] Miklossy J. Emerging roles of pathogens in Alzheimer disease. Expert Rev Mol Med. 2011;13:e30.

[90] Miklossy J. Alzheimer’s disease - a neuroinfectious disease. Analysis of the evidence following Koch’s and Hill’s criteria. J Neuroinflammation. 2011;8:90.

[91] Poole S, Singhrao SK, Kesavalu L, et al. Determining the presence of periodontopathic virulence factors in short-term postmortem Alzheimer’s disease brain tissue. J Alzheimers Dis. 2013;36:665–677.

[92] Noble JM, Borrell LN, Papapanou PN, et al. Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III. J Neurol Neurosurg Psychiatry. 2009;80:1206–1211.

[93] Singhrao SK, Harding A, Simmons T, et al. Oral inflammation, tooth loss, risk factors, and association with progression of Alzheimer’s disease. J Alzheimers Dis. 2014;42:723–737.

[94] Kamer AR, Craig RG, Pirraglia E, et al. TNF-alpha and antibodies to periodontal bacteria discriminate between Alzheimer’s disease patients and normal subjects. J Neuroimmunol. 2009;216:92–97.

[95] Cestari JA, Fabri GM, Kalil J, et al. Oral infections and cytokine levels in patients with Alzheimer’s disease and mild cognitive impairment compared with controls. J Alzheimers Dis. 2016;54:845.

[96] Dickstein JB, Moldofsky H, Hay JB. Brain-blood permeability: TNF-alpha promotes escape of protein tracer from CSF to blood. Am J Physiol Regul Integr Comp Physiol. 2000;279:R148–R151.

[97] Bell RD, Winkler EA, Singh I, et al. Apolipoprotein E controls cerebrovascular integrity via cyclophilin A. Nature. 2012;485:512–516.

[98] Fry M, Ferguson AV. The sensory circumventricular organs: brain targets for circulating signals controlling ingestive behavior. Physiol Behav. 2007;91:413–423.

[99] Danielyan L, Schafer R, von Ameln-Mayerhofer A, et al. Intranasal delivery of cells to the brain. Eur J Cell Biol. 2009;88:315–324.

[100] Leung JY, Chapman JA, Harris JA, et al. Olfactory ensheathing cells are attracted to, and can endocytose, bacteria. Cell Mol Life Sci. 2008;65:2732–2739.

[101] Allen HB, Morales D, Jones K, et al. Alzheimer’s disease: a novel hypothesis for the development and the subsequent role of beta amyloid. J Neuroinfectious Dis. 2016;7:211.

[102] Riviere GR, Riviere KH, Smith KS. Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer’s disease. Oral Microbiol Immunol. 2002;17:113–118.

[103] Olsen I, Yilmaz O. Modulation of inflammasome activity by Porphyromonas gingivalis in periodontitis and associated systemic diseases. J Oral Microbiol. 2016;8:30385.

[104] Olsen I, Singhrao SK. Inflammasome involvement in Alzheimer’s disease. J Alzheimers Dis. 2016;54:45–53.

[105] Embers ME, Ramamoorthy R, Philipp MT. Survival strategies of Borrelia burgdorferi, the etiologic agent of Lyme disease. Microbes Infect. 2004;6:312–318.

[106] Coats SR, Jones JW, Do CT, et al. Human Toll-like receptor 4 responses to P. gingivalis are regulated by lipid A 1- and 4'-phosphatase activities. Cell Microbiol. 2009;11:1587–1599.

[107] Sando SB, Melquist S, Cannon A, et al. APOE epsilon 4 lowers age at onset and is a high risk factor for Alzheimer’s disease; a case control study from central Norway. BMC Neuro. 2008;8:9.

[108] Rosenberg RN, Lambrecht-Washington D, Yu G, et al. Genomics of Alzheimer disease: a review. JAMA Neurol. 2016;73:867–874.

[109] Stein PS, Kryscio RJ, Desrosiers M, et al. Tooth loss, apolipoprotein E, and decline in delayed word recall. J Dent Res. 2010;89:473–477.

[110] Kaur T, Uppoor A, Naik D. Parkinson’s disease and periodontitis - the missing link? A review. Gerodontology. 2016;33:434–438.

[111] Hanaoka K, Kashiwara K. Increased frequencies of caries, periodontal disease and tooth loss in patients with Parkinson’s disease. J Clin Neurosci. 2009;16:1279–1282.

[112] Einarsdottir ER, Gunnstedsdottir H, Hallsdottir MH, et al. Dental health of patients with Parkinson’s disease in Iceland. Spec Care Dentist. 2009;29:123–127.

[113] Chao Y, Wong SC, Tan EK. Evidence of inflammatory system involvement in Parkinson’s disease. Biomed Res Int. 2014;2014:308654.

[114] Chen H, O’Reilly EJ, Schwarzschild MA, et al. Peripheral inflammatory biomarkers and risk of Parkinson’s disease. Am J Epidemiol. 2008;167:90–95.

[115] Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013;133:377–385.

[116] Ahlehoff O, Gislason GH, Lindhardsen J, et al. Prognosis following first-time myocardial infarction in patients with psoriasis: a Danish nationwide cohort study. J Intern Med. 2011;270:237–244.

[117] Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. J Eur Acad Dermatol Venerol. 2012;26(Suppl 2):3–11.

[118] Preus HR, Khanifam P, Kolltveit K, et al. Periodontitis in psoriasis patients: a blinded, case-controlled study. Acta Odontol Scand. 2010;68:165–170.

[119] Skudutyte-Rysstad R, Slevolden EM, Hansen BF, et al. Association between moderate to severe psoriasis and periodontitis in a Scandinavian population. BMC Oral Health. 2014;14:139.

[120] Ganzetti G, Campanati A, Santarelli A, et al. Involvement of the oral cavity in psoriasis: results of a clinical study. Br J Dermatol. 2015;172:282–285.

[121] 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.

[122] Moutsopoulos NM, Kligfeld HM, Angelov N, et al. Porphyromonas gingivalis promotes Th17 inducing pathways in chronic periodontitis. J Autoimmun. 2012;39:294–303.
[123] Adibrad M, Deyhimi P, Ganjalikhani Hakemi M, et al. Signs of the presence of Th17 cells in chronic periodontal disease. J Periodontal Res. 2012;47:525–531.

[124] Shaker OG, Ghallab NA. IL-17 and IL-11 GCF levels in aggressive and chronic periodontitis patients: relation to PCR bacterial detection. Mediators Inflamm. 2012;2012:174764.

[125] Linden GJ, Lyons A, Scannapieco FA. Periodontal systemic associations: review of the evidence. J Periodontol. 2013;84:S8–S19.

[126] Leuckfeld I, Obregon-Whittle MV, Lund MB, et al. Severe chronic obstructive pulmonary disease: association with marginal bone loss in periodontitis. Respir Med. 2008;102:488–494.