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REVIEW ARTICLE

From the acta prize lecture 2014: the periodontal-systemic connection seen from a microbiological standpoint

Summary of the Acta Odontologica Scandinavia Price Lecture 2014 presented at the meeting of the IADR/Pan European Region in Dubrovnik, September 10–13. 2014

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Abstract

Objective. To give an overview of the periodontal-systemic connection seen from a microbiologist. ***Methods.*** Original research papers, review articles and workshop proceedings were consulted. ***Results.*** Periodontal bacteria can cross epithelial cells, enter the circulation, invade endothelial cells, induce endothelial cell dysfunction and activate inflammatory and immune responses. Several studies support the association between periodontitis (PD) and cardiovascular disease. Severe PD involves a risk for development of type 2 diabetes. Maternal PD is moderately associated with adverse pregnancy outcome and pre-eclampsia. Dental plaque can contain respiratory pathogens able to promote chronic obstructive pulmonary disease and pneumonia. Periodontal bacterial DNA has been detected in synovial fluid of patients with rheumatoid arthritis. Minor evidence exists for associations between PD and chronic kidney disease, obesity, cancer, metabolic syndrome and cognitive impairment. Concerns can be raised as to the interpretation of some study results due to heterogeneity in definitions used for PD, too much weight upon *in vitro* studies with a few selected organisms and failing recognition that the majority of the periodontal microbiota is not yet cultivated. ***Conclusion.*** Periodontal bacteria may participate in extra-oral infections such as CVD, diabetes, APO, pre-eclampsia, COPD, pneumonia, RA, CKD, obesity, cancer, MetS and cognitive impairment. Most knowledge is based on associations which do not necessarily imply causality. Future studies should reach consensus on the definition of PD and systemic disease outcomes, recognize the full spectrum of the microbiota in PD and bacteremia, including not-yet-cultivated organisms and delineate the clinical significance of genetic strain variations and the role of period-ontopathogenic vs gut organisms within atheromatous lesions. For demonstration of causality, large, long-term clinical studies should use well-defined criteria for PD and robust disease outcomes to elucidate the importance of PD intervention and prevention.

Key Words: *microbiology, periodontitis, systemic diseases*

Introduction

The implication of periodontal bacteria in the initiation and progression of extra-oral systemic diseases has over the last 10–20 years attracted much attention. Original papers, review articles and workshop proceedings have debated the role of periodontitis (PD) in a number of systemic diseases (Table I) such as cardiovascular disease (CVD), diabetes, adverse pregnancy outcome (APO), pre-eclampsia, chronic obstructive pulmonary disease (COPD), pneumonia, rheumatoid arthritis (RA), chronic kidney disease (CKD), obesity, cancer, metabolic syndrome (MetS), cognitive impairment and other organ inflammations and abscesses [1–16]. Although some association between PD and systemic diseases has been reported, it is clear that associations do not necessarily imply causality. On the other hand, absence of evidence is not evidence of absence. In the present paper, a short overview will be given of where we stand seen through the eyes of a microbiologist.

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Table I. Major systemic diseases where a relationship with periodontitis has been suspected.

Cardiovascular disease (CVD)
Diabetes
Preterm birth-low birth weight (PTW-LBW = adverse pregnancy outcome (APO)) and pre-eclampsia
Chronic obstructive pulmonary disease (COPD)
Pneumonia
Rheumatoid arthritis (RA)
Chronic kidney disease (CKD)
Obesity
Cancer
Metabolic syndrome (MetS)
Cognitive impairment
Other organ inflammations and abscesses

Bacteremia

Periodontal bacteria can cross epithelial cells by a transcellular mechanism [17] and enter the circulation through physical perturbation of the gingiva [18], but also disseminate through immune cells [19]. They can activate the inflammatory and immune response in multiple ways. The immune response can stimulate formation, maturation and exacerbation of atheromas.

Invasion of human cardiovascular cells

Some periodontal bacteria have the ability to invade human cardiovascular cells *in vitro* [4]. The capacity varies though between strains. After invasion, various forms of endothelial dysfunction are induced. Transmission electron microscopy (TEM) may be inefficient to demonstrate bacterial invasion *in vivo*. However, scanning electron microscopy (SEM) can provide proof [20].

Non-invasive mutants

It is noteworthy that non-invasive mutants of *Porphyromonas gingivalis* are less pathogenic in animal models than their parental strains [21]. They are also less pro-atherogenic and induce less pro-inflammatory mediators.

Live periodontal bacteria inside tissue

It has been shown that *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* can keep their viability after invasion of atheromatous tissue [22]. Viability has not been demonstrated in atheromas themselves, but in cell cultures. Distinction between dead and live bacteria in atheromas has not been done.

Bacterial location inside affected tissues

Multiple periodontal bacterial species have been detected in atheromatous tissue [4]. *Streptococcus mutans* was the most frequent species in heart valves and aneurysm walls, implying that also non-periodontal bacteria can invade atheromatous tissue [23]. Some studies have failed to detect bacteria inside atheromas.

Animal disease models for atherosclerosis

P. gingivalis accelerated atherosclerosis in animal models of mice, rabbits and pigs. Rabbits with induced PD developed fatty streaks in the aorta faster than did healthy animals. *P. gingivalis* also induced coronary and aortic lesions in normocholesterolemic pigs and enhanced atherosclerosis in hypercholesterolemic pigs [4].

No evidence that human atheroma isolates cause disease in animal models

So far isolates from human atheromas have not been shown to cause similar disease in animal models. This is in conflict with Koch's postulates.

'*Proofs*' *that periodontal bacteria can cause atherosclerosis*

Several 'proofs' have been listed that periodontal bacteria can cause atherosclerosis [4]: (1) Periodontal bacteria disseminate from the oral cavity to systemic vascular tissues, (2) they are found in affected tissues, (3) live in affected tissues, (4) invade affected cell types *in vitro*, (5) induce atherosclerosis in animal models, (6) non-invasive mutants are considerably less pathogenic than parental strains, (7) microbiological and clinical improvement in periodontal status after treatment of PD was associated with reduced progression of carotid atherosclerosis [24] and (8) periodontal therapy triggers reduced systemic inflammation and improved endothelial function.

PD and type 2 diabetes

PD adversely affects glycemic control and diabetes complications and promotes development of type 2 diabetes [5]. Severe PD increases blood levels of glucose expressed as HbA1c in patients with and without diabetes [5]. Interaction between advanced glycation end products so-called AGEs and their receptor RAGE is thought to cause increased inflammation and destruction of periodontal tissue [25]. In diabetes 2, treatment of PD has a moderate effect on the HbA1c level compared to no treatment [5,6]. There is inadequate evidence that diabetes has any

significant effect on the periodontal microbiota or vice versa [25].

PD, adverse pregnancy outcome (APO) and pre-eclampsia

Maternal PD is moderately but independently associated with pre-term birth and/or low birth weight (PTB-LBW) [8,26], collectively known as APO. There is a significant association between maternal PD and pre-eclampsia [8]. It is believed that periodontal bacteria and their products can reach the fetal-placental unit together with inflammatory mediators [10]. *Fusobacterium nucleatum* is the most frequent species involved in APO, particularly ssp. *polymorphum* [10]. An identical clone of *F. nucleatum* was found in the placenta/fetus and subgingival plaque of the same person [27]. *F. nucleatum* can invade amniotic tissue and induce stillbirth and fetal death in mice [27]. *Treponema denticola* present in the vagina may relate to pre-term delivery [28]. Also, *P. gingivalis*, uncultivated oral *Bergeyella* sp. and *Campylobacter rectus* have been implicated in APO [9]. However, only a few periodontal organisms have so far been evaluated for APO. Non-surgical periodontal therapy has not been found to reduce APO [9].

PD, chronic obstructive pulmonary disease (COPD) and pneumonia

It is clear that oral micro-organisms can cause lung infection and severe PD is associated with pneumonia [2,3]. Lung inflammation may be affected by aspiration of dental plaque, which can harbor respiratory pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Candida albicans* [29]. These organisms can be indistinguishable from isolates recovered from tracheobronchial sites in the same patient. NHANES data suggested an association between PD and COPD [30,31], which was confirmed by Leuckfeld et al. [32]. The association between PD and COPD is weaker than for PD and pneumonia. Improved oral hygiene can reduce the risk of pneumonia [2].

PD and rheumatoid arthritis (RA)

The epidemiological data suggesting an association between PD and RA are inconsistent [3]. However, periodontal bacterial DNA detected in synovial fluid of patients with both RA and PD suggested translocation of these bacteria to the synovium [33]. In one study, patients with PD and RA had identical bacterial clones [34]. There is evidence of increased levels of serum and synovial fluid antibodies against *P. gingivalis*, *Prevotella intermedia*, *Tannerella forsythia* and *A. actinomycetemcomitans* in RA patients [35] and *P. gingivalis* can induce and exacerbate RA in rodents [36]. *P. gingivalis* produces a unique enzyme peptidylarginine deaminase (PPAD) which converts arginine residues in proteins to citrulline [37]. This alters protein structure and function. PPAD may be involved in deregulation of the host's signaling network and immune evasion. Chronic exposure to citrullinated proteins at periodontitis sites may pre-dispose susceptible patients to development of autoantibodies and RA. Noteworthy, there is emerging evidence for a correlation between improved outcomes for RA patients who undergo PD treatment [38].

PD and chronic kidney disease (CKD)

There is a statistically significant and consistent association between PD and CKD in several studies [2,3]. High levels of antibodies to *P. gingivalis*, *T. denticola* and *A. actinomycetemcomitans* were associated with CKD [39]. Treatment of PD reduces chronic inflammation in maintenance hemodialysis patients [40]. However, hypertension and diabetes can be confounding factors.

PD and obesity

Obesity and overweight are associated with periodontal disease progression and may, thus, adversely affect PD [3]. Whether PD can affect obesity is unclear. In rats the first documentation was recently given of obesity-induced insulin resistance in the gingiva [41]. Factors such as lifestyle and diabetes type 2 may confound the linkage beween PD and obesity.

PD and cancer

Some periodontal bacteria can alter cells and tissues consistent with cancer [3]. PD has been identified as a possible risk factor for orodigestive and pancreatic cancers [2]. Inflammatory bowel disease has been recognized as a risk factor for colorectal cancer which can harbor significantly elevated levels of *F. nucleatum* [42]. Whether *F. nucleatum* is a cause or consequence of the cancer is unknown. *P. gingivalis* has been suggested to be a risk modifier to cancer [43].

PD and metabolic syndrome (MetS)

Only one study that met the required criteria for PD has established an association between PD and MetS [44]. It is clear that more robust evidence needs to be developed [3]. Type 2 diabetes may confound the linkage.

PD and cognitive impairment

Imprecise definition of PD and heterogeneity in the cases presented has made it difficult to demonstrate a clear association between PD and cognitive impairment [3]. Underlying biological mechanisms are also unclear.

Subjects who developed mild cognitive impairment and Alzheimer's disease (AD) had significantly increased antibody levels to *P. intermedia* and *F. nucleatum* [45]. Those who developed AD had also increased antibody to *T. denticola* and *P. gingivalis* at baseline In ApoE (−/−) mice *P. gingivalis* actively invaded the brain contributing to complement activation with bystander neural injury [46].

Other organ inflammations and abscesses

F. nucleatum is the periodontal bacterium most frequently associated with inflammation and abscesses in the body, e.g. in brain, lung, liver and spleen [16]. Other organisms involved are *P. intermedia*, *P. gingivalis* and *T. denticola*. In one study *F. nucleatum* played a major role in infective appendicitis [47].

General conclusions

Despite the fact that Koch's postulates are not completely fulfilled for animal models [4], a variety of studies support that periodontal pathogens can contribute to CVD. PD imparts increased risk for future CVD. Given the high prevalence of PD, even a low-to-moderate excess risk is important. No evidence exists for an association between PD and incident coronary heart disease (CHD) in subjects > 65 years, not either between PD and secondary cardiovascular events [12].

PD adversely affects glycemic control and diabetes complications and promotes development of type 2 diabetes. There is also some evidence for an association between PD and APO, pre-eclampsia, COPD, pneumonia, RA, CKD, obesity, cancer, MetS and cognitive impairment. These associations can be unidirectional or sometimes bidirectional and do not necessarily imply causality, except that PD can cause pneumonia.

Concerns

Heterogeneity in the definitions used for PD (CDC threshold rarely met) makes interpretation of some study results difficult. Also the systemic outcomes are often imprecisely defined. It is necessary to reach a consensus on the definition of PD and systemic outcomes for future studies. It should be stressed that mono-infections may not adequately reflect the *in vivo* capabilities of periodontopathogens. We may risk that our thoughts are dismissed if we link PD to many diseases. Concentrations of model bacteria vs effector cells may not reflect relations *in vivo*. Bacterial species can have strains with varying virulence and specific host cell lines can vary considerably as effector targets. The oral microbiota is very diverse and complex, as demonstrated by *16S rDNA* and high-throughput sequencing. The high diversity and complexity of also the subgingival microbiota could mean that new species and consortia are important to PD and related systemic diseases. There is now moderate evidence in the literature to support the association of as much as 17 species or phylotypes with PD [48]. These are from the phyla *Bacteroidetes*, *Candidatus Saccharibacteria*, *Firmicutes*, *Proteobacteria*, *Spirochaetes* and *Synergistetes*. Even the *Archaea* domain seems to have an association with PD. Some of the organisms giving moderate evidence of being periodontal pathogens have not yet been cultivated. Considering the fact that the oral cavity contains at least 700 major bacterial species the limitation of periodontal pathogens to a handful of bacterial species may be too narrow. Neither is it likely that the limited number of periodontopathogens usually studied is alone involved in systemic diseases. The importance of not-yet-cultivated biofilm bacteria [49], probably present in large numbers in bacteremias, has not been considered. Our concepts on periodontal bacteria and their association with systemic diseases may, therefore, be under-developed. The application of new technologies in the assessment of the microbiomes of PD and systemic diseases will probably lead to acknowledgement of an increased repertoire of putative pathogens. In these efforts a combination of open-ended and targeted methods should be used.

Future research

Future research should deal with systemic effects *in vivo* of a broader spectrum of periodontal bacteria including not-yet-cultivated ones. With the full genome sequencing approach, genes encoding virulence and other disease-associated factors should be screened for. To what extent specific periodontal bacteria correlate with biomarkers of systemic diseases should be elucidated. We should also better understand the full extent of bacteremias associated with periodontal diseases and non-oral diseases. Furthermore, we should define better the role of the periodontal microbiota in atheromatous lesions compared to that of intestinal bacteria. We should also know more about genetic and epigenetic factors important for PD and systemic diseases. Last, but not least, large future long-term studies based on well-defined threshold criteria for PD and robust disease outcomes should try to determine the clinical importance of PD intervention and prevention. Surrogate markers of CVD like carotid intima media thickness (cIMT) may be useful for demonstration of positive effects of periodontal treatment on CVD development.

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