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CHAPTER

06

General Discussion

Periodontitis and rheumatoid arthritis: what do we know?

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Introduction

In the field of rheumatology there is currently much attention for possible causality between periodontitis and rheumatoid arthritis (RA). Systemic inflammatory and infectious challenges have long been considered to be involved in triggering rheumatoid factor (RF), the first important biomarker for diagnosis and prediction of RA. Later, another auto-antibody system, anti-citrullined protein antibodies (ACPA), was found to be more specific for RA. These antibodies can be present before the disease becomes symptomatic [1]. Why ACPA and RF are induced as well as their role in RA development is still unclear. The relation between periodontitis and RA is not well understood. On one hand, systemic manifestation of increased 'total inflammatory burden' through periodontitis has been documented. On the other hand, infection with *Porphyromonas gingivalis* specifically has been suggested to play a role a because of its unique capacity of protein citrullination [2, 3].
Because causality is ultimately tested in longitudinal cohort studies that do currently not exist for periodontitis and RA, in this commentary the Bradford Hill [4] criteria are applied on existing literature to assess causality as most likely interpretation of this association.

1. Strength and consistency

Quantitative studies on the association between periodontitis and RA performed thus far are mostly case-control studies with a relatively low sample size. Nineteen of these studies, representing participants from different ethnic backgrounds, were included in a recent systematic review [5]. It was concluded that patients with RA, compared to those without RA, have a significantly higher incidence of periodontitis and a higher number of missing teeth. A recent case-control study explored the degree to which the association is affected by shared genetic and/or environmental factors [6]. After multivariable adjustments, including positivity for Human Leucocyte Antigen (HLA)-DRB1 shared epitope (SE) alleles, ever smoking, age, sex, race/ethnicity, body mass index, self-reported diabetes mellitus, marital status, presence of oral dryness, and education), the incidence of periodontitis remained significantly higher in ACPA seropositive RA patients than in controls (odds ratio 1.6). The association between periodontitis and RA is thus relatively consistent; however the strength of the association is uncertain.

2. Biological plausibility

Certain genetic, hormonal, infectious and environmental risk factors, such as smoking, can contribute to a susceptibility background against which RA can develop. In susceptible individuals, deregulation of the immune system occurs and can present itself with formation of autoantibodies such as RF and ACPA, which can be present before the disease becomes symptomatic [1]. Whether and why progression to the symptomatic phase occurs is unknown, but theoretically a 'second hit' could be necessary. In this 'two hit' model, the 'first hit' is the induction of ACPA formation, the 'second hit' is the induction of arthritis and expression of citrullinated antigens in the inflamed joint [7, 8] (Fig. 1, page 93).

ACPA production may be induced in inflamed periodontium

It has been hypothesized that initiation of ACPA production occurs at inflamed mucosal surfaces of lungs and periodontium [9]. Inflamed periodontium contains citrullinated proteins [10] and ACPA have been found in the inflammatory exudates [11]. Independent of smoking status, periodontitis patients and patients with lung mucosal inflammation (e.g., bronchiectasis) without RA have hi-

gher serum ACPA levels compared to healthy controls, although lower than in RA patients [12-15].
In addition, it has been suggested that ACPA production is induced by the periodontal pathogen *Porphyromonas gingivalis (P. gingivalis)*, being unique in expressing a variant of the deiminating enzyme necessary for protein citrullination, peptidyl arginine deiminase (PAD) [2, 3]. *P. gingivalis* PAD (PPAD) is able to citrullinate endogenous as well as human proteins, thereby creating antigens that have been presumed to initiate the ACPA response in RA [16].
ACPA in RA include antibodies against citrullinated histones [17]. Histone citrullination is a common event during neutrophil activation and neutrophil death induced by different pathways, including apoptosis and neutrophil extracellular trap (NET) formation. NETs are increased in RA and are a source of citrullinated autoantigens [18]. Neutrophils from patients with periodontitis have been shown to be hyperreactive in terms of baseline, unstimulated generation and release of extracellular reactive oxygen [19]. As NET release is known to be dependent upon production of extracellular reactive oxygen, periodontal disease may be associated with excessive production of NETs, i.e., in a process triggered initially by the response of neutrophils to plaque bacteria. High and concentrated levels of NET associated molecules could lead to a localized chronic inflammatory response, potentially followed by an autoimmune response in genetically prone persons [20].
Recently, Romero et al. [21] identified a different citrullination pattern in PAD expressing RA synovial fluid cells (neutrophils and monocytes), which they termed cellular hypercitrullination because of the broad spectrum of citrullination across the entire range of proteins. Cellular hypercitrullination is induced by two immune-mediated membranolytic pathways, mediated by perforin and the membrane attack complex both leading to calcium influx. These data are supported by Neeli et al. [22], who showed that in human neutrophils PAD4 induces histone citrullination in the presence of calcium ionophore. Up to now, it is unknown whether cellular hypercitrullination is present in inflamed periodontium.

Mutual exacerbation of inflammatory responses

Another interpretation of the 'two-hit' model is that of mutual exacerbation: periodontitis serves as 'first hit', while an (unknown) arthritrogenic hit induces RA ('second hit') that leads, in susceptible individuals, to mutual exacerbation of the inflammatory responses mediating self-perpetuating tissue destruction in both the joint and the periodontium [8] (Fig. 1, page 93).
Neutrophils are the major cell type involved in periodontal inflammatory responses [20]. Besides providing a source of citrullinated autoantigens, neutrophils can cause tissue destruction through release of degradative enzymes (e.g., matrix metalloproteinases) and cytotoxic substances such as extracellular reactive oxygen. Neutrophils indirectly mediate destructive effects by chemotactic recruitment of T-helper 17 (Th17) cells. Th17 cells selectively produce the pro-inflammatory cytokine IL-17 which is crucial for host defense against extracellular pathogens [23]. Uncontrolled Th17 activity has been implicated in joint inflammation and bone destruction in RA, both at onset and in established disease [24, 25]. Presence of IL-17 and Th17 cells in human periodontitis may be associated with disease severity, possibly after activation of innate immune cells by *P. gingivalis* [26]. How this response regulates inflammation-mediated bone destruction has not been fully elucidated (see for illustration of possible mechanisms Hajishengallis et al. [27]).
In both periodontitis and RA, osteoclasts are predominantly activated by mechanisms dependent on upregulation of receptor activator of nuclear factor κB ligand (RANKL), a member of the tumor necrosis factor (TNF)

cytokine family that is also implicated in RA [28]. Mechanisms that underlie chronic joint inflammation in RA have not been clarified, although there is some evidence for both a T-cell dependent autoimmune mechanism and a more progressive fibroblast mediated chronic inflammation [29]. Th17 cells are recognized as effective B-cell helpers for antibody responses in inflammatory conditions [27]. B-cells constitute, along with T-cells, a major source of membrane-bound and secreted RANKL in the periodontal lesions (see for illustration Hajishengallis et al. [27]).

3. Temporal relationship

In both interpretations of the 'two-hit model', periodontitis precedes RA. Commonly, more advanced forms of periodontitis are present at disease onset in patients with new-onset RA [30, 31]. A recent nationwide, population-based case-control study using longitudinal administrative data found an association between a history of periodontitis and newly diagnosed RA in Taiwan (odds ratio 1.2) [32].

4. Specificity regarding *Porphyromonas gingivalis*

The PPAD gene is highly conserved, ubiquitous in *P. gingivalis* and absent in *P. gingivalis* related species (chapter 5). We found no indications that RA patients carry a different PPAD *P. gingivalis* variant than patients without RA (chapter 5). Studies on oral colonization by *P. gingivalis* have shown no difference in subgingival *P. gingivalis* distribution in patients with or without RA independent of periodontal status, detection techniques and RA disease duration [6, 30, 31, 33]. However, DNA of periodontal pathogens has been detected in synovial fluid of RA patients [34]. Of five different periodontal pathogens assessed, only DNA of *P. gingivalis* was more frequently detected in synovial fluid of RA patients than in synovial fluid of non-RA controls [35].

According to the hypothesis that *P. gingivalis* contributes to ACPA production, the association of *P. gingivalis* presence and serum ACPA levels has been assessed. In new-onset RA patients, subgingival presence of *P. gingivalis* was not correlated with ACPA levels as determined using the diagnostic anti-cyclic citrullinated peptide 2 (anti-CCP2) test [30]. In established RA patients, presence of subgingival *P. gingivalis* was not of influence on ACPA levels, but increased reactivity against several citrullinated peptides of fibrinogen, fillagrin, clusterin, histone 2B and apolipoprotein was found when subgingival *P. gingivalis* was present [6, 33].
In periodontitis patients without RA, we found no differences in ACPA levels between *P. gingivalis* positive and –negative periodontitis patients [15], in contrast to Lappin et al. [12] who found that serum ACPA levels in periodontitis patients carrying subgingival *P. gingivalis* were higher compared to periodontitis patients without subgingival *P. gingivalis*. The relatively low patient numbers in both studies and different detection techniques of *P. gingivalis* and ACPA may account for this discrepancy.
Levels of serum anti-*P. gingivalis* antibodies showed no differences in a large cohort of RA patients and a cohort of osteoarthritis control patients [6]. A study in Japanese patients with RA showed higher anti-*P. gingivalis* antibody levels compared to age-, sex-, smoking status-, and periodontal condition-balanced healthy controls [36]. Independent of *P. gingivalis* distribution, we observed a more robust antibody response against *P. gingivalis* in established RA patients with severe periodontitis than in non-RA controls with the same periodontal status [33]. The role of the antibody response in periodontitis is not fully understood, but it may be not protective [27]. No differences in anti-*P. gingivalis* antibody levels were found between ACPA and/or RF seropositive arthralgia patients, who developed or did not develop RA within 2 years follow-up [37].
In established RA patients a weak correlation

between ACPA levels and anti-*P. gingivalis* antibody levels has been found [6, 33]. Nevertheless, anti-*P. gingivalis* antibody levels were found to be significantly higher in children with ACPA positive juvenile idiopathic arthritis compared to children with ACPA negative juvenile idiopathic arthritis, while no differences were noted for anti-*Prevotella intermedia* anti-*Fusobacterium nucleatum* antibody levels [38].

5. Dose–response relationship

A dose–response pattern in the association between severity of periodontitis and RA development was found in a Taiwanese population based on longitudinal administrative data [32]. Also, a large case-control study by Mikuls et al. [6] revealed that presence of periodontitis was associated with increased swollen joint counts, greater RA disease-activity according to the 28-joint Disease-activity Score (DAS28). We showed an association between severity of periodontitis and severity of RA [33]; RA patients with severe periodontitis had significantly higher DAS28 scores than RA patients with no or moderate periodontitis.

Experimental evidence in humans on the effect of periodontal treatment on RA disease-activity is limited. Only four studies met the inclusion criteria according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and were included in the recent meta-analysis of Kaur et al. [39] on the effect of non-surgical periodontal therapy on RA disease activity measured by clinical (DAS28) and laboratory parameters (ESR, TNF-α and CRP levels). These studies generally had a small sample size and a relatively short follow up period (up to 6 months). Microbiology was not assessed; except for one study that measured serum anti-*P. gingivalis* antibodies. Although these studies are considered preliminary and indicate the need for further large-scale intervention studies, they reported a beneficial effect of periodontal therapy on laboratory RA parameters and clinical symptoms of RA.

6. Experimental evidence

The most widely studied model of RA is collagen-induced arthritis (CIA) in genetically susceptible mice. Balb/c mice with pre-existing periodontitis, induced by oral inoculations of *P. gingivalis*, developed more severe CIA at a faster rate compared to CIA mice without periodontitis [40]. Micro-CT analysis of joint and periodontal bone loss provided evidence for a bidirectional relationship between periodontitis and arthritis; mice with CIA only showed alveolar bone loss, whereas mice with periodontitis only showed bone loss within radiocarpal joints [40]. The severity of adjuvant arthritis in Dark Agouti rats was increased when there was a pre-existing extra-synovial chronic inflammatory lesion induced by subcutaneous sponges impregnated with heat-killed *P. gingivalis* [41]. No evidence of arthritis development occurred in Dark Agouti rats with a *P. gingivalis* extra synovial inflammatory lesion only, however, using computer assisted morphometric analysis, periodontal bone loss after adjuvant arthritis induction was seen in Lewis rats as measured on defleshed jaws [42].

Experimental evidence for involvement of periodontitis in pathogenesis of RA via cellular immunity comes from a murine model of T-cell–dependent experimental arthritis. Periodontitis induced by oral inoculations with *P. gingivalis* and *Prevotella nigrescens* significantly aggravated severity of CIA characterized by increased arthritic bone erosion in DBA/1 mice via induction of an antigen specific Th17 response [43]. A model in which experimental periodontitis and arthritis were co-induced in an inflammation-prone mouse strain using oral inoculations with *Aggregatibacter actinomycetemcomitans* and *P. gingivalis* in pristane-induced arthritis showed that co-induction in control mice did not alter the course of both periodontitis and arthritis. It was concluded that the interaction between periodontitis and arthritis in

mice involves a shared hyper-inflammatory genotype and functional interferences in innate and adaptive immune responses [44]. Experimental evidence for PPAD as key player in the link between periodontitis and RA comes from aggravation of CIA in DBA/1 mice, which appeared dependent on the expression of PPAD [45]. Increased serum ACPA levels were measured after infection with wild type *P. gingivalis* W83 as compared to mice infected with *P. gingivalis* W83 with PPAD deletion. Moreover, at the site of infection with wild type strain higher levels of citrullinated proteins were found as compared to the site of infection with the PPAD knock-out strain. These results were confirmed by Gully et al. [46] using another murine model for experimental periodontitis and another *P. gingivalis* strain (W50); in BALB/c mice, the extent of CIA was significantly reduced in animals exposed to prior induction of periodontal disease through oral inoculation of a PPAD knock-out *P. gingivalis* W50 strain versus prior periodontal infection with the *P. gingivalis* W50 wild type stain. Furthermore, serum ACPA tended to be lower in mice prior infected with PPAD-deficient *P. gingivalis* compared to ACPA levels in CIA mice with periodontitis induced by the wild type strain.

7. Coherence

Animal models have shown that pre-existing periodontal infection (first hit) leads to exacerbation of arthritis after an arthritogenic hit (second hit) [40, 41]. In the same animal models, a bidirectional relationship between experimental periodontitis and experimental arthritis existed, e.g., experimental arthritis leads to alveolar bone loss, and experimental periodontitis leads to joint inflammation [40-42]. This is in concordance with observations that newly diagnosed and early RA patients have more frequently periodontitis and more periodontal attachment loss compared to controls [30-32]. In human periodontitis patients joint inflammation has not been systematically assessed.

Mutual exacerbation of the inflammatory responses in animal experiments, where both diseases co-existed, was shown to involve Th17 mediated immunity and to be dependent on a shared hyperinflammatory genotype [43, 44]. The correlation of RA disease-activity with the severity of periodontitis in humans [33] can probably be contributed to mutual exacerbation of inflammatory responses of both diseases. The importance of Th17 mediated immunity is increasingly acknowledged in human RA and periodontitis [24, 26] while gene polymorphisms within the IL-1 gene cluster are associated with cytokine levels in patients with periodontitis and in patients with RA, but not in healthy controls [47]. The latter supports the hypothesis of a shared genetic background for cytokine profiles [47]. IL-10 gene polymorphisms are also suggested to contribute to susceptibility for both RA and periodontitis. Three of several polymorphisms of IL-10 have been studied in some detail regarding to RA susceptibility. Meta-analysis of twenty-two relevant studies on these IL-10 polymorphisms, all located in putative regulatory regions of the gene promoter, suggest that these IL-10 polymorphisms contribute to susceptibility of RA in European, Asian, and Black populations [48]. Recently, an IL-10 polymorphism, also located in the genetic region upstream of IL-10, was validated as a candidate gene in aggressive periodontitis in European patients [49].

Animal experiments have shown that there is an important role for PPAD in protein citrullination, ACPA formation and development and aggravation of experimental arthritis [45, 46]. There are, however, no differences in PPAD gene and endogenous citrullination patterns of *P. gingivalis* isolated from patients with or without RA (chapter 5). Also, oral colonization by *P. gingivalis* is not different in RA patients compared to patients without RA, independent of periodontal status, detection techniques and RA disease duration [6, 30, 31, 33]. At this moment the relevance of PPAD in priming autoimmunity and RA development in humans is not clear.

8. Analogy

Infections have been shown to be highly associated with the onset of systemic lupus erythematosus (SLE), a chronic destructive autoimmune disease characterized by immune dysregulation and hyperproduction of different autoantibodies. Particularly Epstein-Barr virus (EBV), parvovirus B19, retrovirus, and cytomegalovirus (CMV) infections might play a pathogenetic role, however, the etiopathogenesis of SLE is far from being completely elucidated [50]. Viral (e.g., parvovirus B19, EBV and CMV) and microbial (e.g., *Campylobacter*) infections play a role in acute arthritis, but the role of infection in the development of RA needs further prospective controlled studies [51]. Approximately 10–20% of patients with early RA have serological evidence of recent infection, however, no single infectious agent is predominant, which indicates that total infectious exposure can represent a risk factor that could trigger RA [51].

Summary

From an epidemiological point of view, RA patients have a higher incidence of periodontal disease than subjects without RA. In addition, there is a dose–response pattern in the association between the severity of periodontitis and RA disease-activity.
There are indications that periodontitis precedes RA, but there is yet no evidence available to show that *P. gingivalis* plays a direct role in this temporal relationship. The role of the unique characteristic of citrullination by *P. gingivalis* remains unexplained. In animal models however, periodontal pathogens and PPAD play a distinct role in development and aggravation of experimental arthritis.
Although the role of periodontal pathogens in RA remains speculative, a causative role for periodontitis as a chronic inflammatory disease caused by infectious agents in RA seems biologically plausible. Considering the great variety in disease manifestation of both periodontitis and RA, a causal relationship, if existing, may only be present between certain forms of periodontitis and RA.

Future perspectives

More evidence in humans is needed to rate the association between periodontitis and RA in susceptible individuals. It has to be mentioned that when systemic effects are subtle, determining cause-and-effect mechanisms is complicated. Therefore, it is worthwhile to assess the influence of periodontitis on arthritis development in prospective follow-up studies with distinct and well described patient groups with a minimum of confounding factors. Given the complex etiology of periodontitis and RA, periodontitis patients and patients at risk for developing RA should be assessed at the microbiological level, based on the presence of oral dysbiotic microbial communities [52], and should be assessed for genetic factors that may predispose to or protect from disease.

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Figures

Fig. 1 Hypothetical two hit model proposed for contribution of periodontitis to RA.

Periodontitis and RA share certain genetic and environmental risk factors including smoking and infection with P. gingivalis. The named risk factors contribute to a susceptibility background against which periodontitis and/or RA can develop. In this 'two hit' model, the 'first hit' is induction of anti-citrullinated protein antibodies (ACPA), possibly in the inflamed periodontium, and the 'second hit' is induction of arthritis and expression of citrullinated antigens in the inflamed joint [7]. Another possible sequence regarding the 'two-hit' model is that of mutual exacerbation: periodontitis as a chronic inflammation serves as 'first hit', while an (unknown) arthritogenic hit ('second hit') induces RA, which leads, in susceptible individuals, to mutual exacerbation of inflammatory responses mediating self-perpetuating tissue destruction (including bone loss) in both joints and periodontium [8] (white arrow).