Chapter 6

Periodontal Disease and Autoimmunity: What We Have Learned from Microbiome Studies in Rheumatology

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Additional information is available at the end of the chapter

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Abstract

The oral cavity is home to vast populations of commensal microbial organisms which constitute the 'healthy oral microbiome.' Periodontitis is a destructive, infectious, inflammatory condition affecting the gums. Initially, a biofilm structure develops, causing localized inflammation. This biofilm is then colonized by certain anaerobic bacteria, including the 'red complex' organisms. There is an increasing interest in the communication between these organisms and host immune surveillance, a dialog which may plays an important role in the development of autoimmune diseases. Studies have shown an association between periodontitis and other inflammatory conditions including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and systemic lupus. The advent of accessible 16S ribosomal sequencing has led to exciting developments in the characterization of the human microbiome and the ability to study this interaction in more detail. The transmucosal communication between periodontitis and host immunity may provide avenues of discovery regarding the etiology and progression of rheumatic diseases.

Keywords: *Porphyromonas gingivalis*, gums, biofilm, periodontal membrane, microbiome, rheumatology, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, osteoarthritis

1. Introduction

It is known that the human body is covered with microbes. Until recently, many of these have been thought of as indolent, 'commensal' organisms, living in harmony with the host and thought of little relevance. If we consider that a single human being consists of approximately 1 trillion human cells but 10 trillion bacterial cells and, at a genetic level, 20,000 human

genes but between 2 and 20 million bacterial genes, the indolence of these bacteria has to be questioned. There is therefore increasing interest in the roles played by these microorganisms on host immunology and physiology.

The oral mucosa is home to vast populations of these 'commensal' microbial organisms. It is therefore an arena which is ripe for communication between foreign organisms and host immune surveillance, a dialog which may play an important role in the development of autoimmune diseases.

The thrust of this chapter is to provide an update on the current literature regarding the role of microbiota in rheumatological conditions including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, osteoarthritis and systemic lupus.

2. The human microbiome

The term 'microbiome' refers to the sum of bacterial communities that colonize a particular area [1]. In humans, this includes almost any surface, for example, the skin, gut, airways, genitourinary tract and oral cavity. It is estimated that the human body is comprised of 1 trillion human cells [1], with genetic material accounting for approximately 20,000 human genes [2]. The bacteria which colonize the human body are estimated to contribute a further 20 trillion cells and between 2 and 20 million bacterial genes [1]. This does not include estimates of fungi and viruses which inhabit the human corpus. This had led to conjecture that a human is not simply 'an organism' but rather 'a superorganism' comprised of multiple separate organisms. Whether this is the case or not, it is certainly conceivable that the microorganisms that colonize the various niche environments of the human body contribute to physiology, biochemistry and immunity.

Study of the bacterial microbiome was previously limited by culture-dependent techniques which are limited in their ability to identify beyond the most prevalent organisms or that are amenable to culture in the media available. However, there have been exciting developments in the characterization of the human microbiome with the relatively recent advent of accessible 16S ribosomal sequencing.

Prokaryotic cells contain 70S ribosomes which consist of larger 50S and smaller 30S subunits [3]. The latter is comprised of 22 ribonucleoproteins and 16S ribosomal RNA. Due to the slow rate of evolution and highly conserved primer binding sites, 16S ribosomal RNA has been developed as a tool for phylogenetic studies [4]. With developments in the processes of RNA extraction, amplification with 16S rRNA primer and high-throughput sequencing, this has become an increasingly available method of bacterial identification, providing proportionally quantitative data on all bacteria in a sample. Identification libraries are growing and initiatives including the human microbiome project (HMP) [5] in the USA and metagenomics of the human intestinal tract (MetaHIT) [2] in Europe aim to catalogue the microbiomic constituents of the human body in health and disease. Of course, in order to identify changes in the microbiome related to disease, the spectrum of normality must first be established.

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The human microbiome represents a previously unexplored arena which may provide discoveries relating the etiology, progression and management of human disease. However, it must be recognized that the horizons of human-microorganism interaction are vast and include bacterial proteomics, metabolomics, not to mention the human virome. Much endeavor is required to delineate the role played by these organisms in human diseases, including rheumatoid arthritis and periodontitis.

3. Periodontitis and the oral microbiome

3.1. Periodontitis

The periodontium is made up of the gingiva and the underlying attachment tissues. Gingivitis is a reversible form of gingival inflammation characterized by redness, swelling and bleeding. Periodontitis occurs once the inflammation extends to the deeper tissues including the periodontal ligament and alveolar bone. The loss of periodontal attachment and bone produces deepening of the gingival sulcus (periodontal pocket) and progressive loosening of teeth eventually leading to their loss [6].

The prevalence of periodontitis varies internationally; however, approximately 10–15% of the global adult population are affected by the condition [7]. The etiology is multifactorial and is composed of genetic predisposition, bacterial dysbiosis associated with a specific local and systemic host response and environmental factors [8] Although there is a genetic element to periodontitis, it is usually polygenic and so difficult to predict. Known risk factors include smoking, age, diabetes mellitus, educational level, gender and immunological diseases (e.g., HIV) [7, 9].

Plaque-induced periodontitis is the most common presentation. Initially, a biofilm structure develops which causes localized inflammation in the form of gingivitis. This biofilm is then colonized by anaerobic bacteria which causes further inflammation and neutrophilic activation. Matrix metalloproteinases are spilled, leading to tissue destruction, exacerbating the attachment loss and deepening the periodontal pocket. These results in further anaerobic colonization, soft tissue destruction, alveolar bone loss and ultimately tooth loss [8].

Management of periodontitis is aimed at excellent oral hygiene with twice-daily brushing of teeth and use of interdental brush and flossing. Plaque removal with scaling and debridement can be used to prevent excessive buildup of plaque. Low-dose doxycycline can inhibit matrix metalloproteinases such as collagenase and therefore reduce tissue damage. In severe cases and nonresolving gingival inflammation, there are surgical options which could allow for some regeneration of the lost soft and hard tissues [8].

3.2. The oral microbiome

The oral microbiome is composed of the microorganisms found in the oral cavity, or as defined by Joshua Lederberg ‘the ecological community of commensal, symbiotic, and pathogenic

microorganisms that literally share our body space '[10]. Although about 280 species have been cultured, it is estimated that they make up less than half of the bacterial species present in the oral cavity and the true number is likely to be between 500 and 700 [11, 12].

The advent of next generation sequencing has allowed the development of the human microbiome project. Findings suggest that although each individual body site is colonized by a characteristic microbiome, it is the individual who is colonized which is the primary factor affecting the bacterial makeup [11]. In the mouth, there are three distinct bacterial communities: the buccal mucosa, gingivae and hard palate forming one; the saliva, tongue, tonsils and throat forming another; and lastly the supra- and subgingival plaque [13].

Ninety-six percent of the bacterial community of the mouth is the phyla *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes* and *Fusobacteria* [11, 14]. The composition of bacteria in 'healthy' and 'diseased' sites in the mouth is shown in **Table 1**.

Of these bacteria, there is the most evidence that *Porphyromonas gingivalis* has a key role to play in the pathogenesis of periodontitis and that with 'accessory pathogens' it alters the host immune response [8]. For example, *P. gingivalis* has specifically been implicated in blocking complement activation and inhibiting complement function [9].

'Healthy' sites; more gram-positive organisms	**Dental caries**	**Gingivitis; gram-positive aerobes, facultative anaerobes, gram negatives**	**Periodontitis; gram-negative and anaerobic organisms**
Actinomyces	*Streptococcus mutans*	*Actinomyces*	*Porphyromonas gingivalis**
Streptocci	*Streptococcus sobrinus*	*Streptococci*	*Porphyromonas endodontalis*
Veillonella	*Actinomyces*	*Treponema*	*Tannerella forsythia**
Granulicatella	*Lactobacillus acidophilus*	*Synergistetes*	*Treponema denticola**
Corynebacterium	*Bifidobacterium*		*Aggregatibacter actinomycetemcomitans**
Fusobacterium	*Propionibacterium*		*Anaeroglobus geminatus*
Gamella	*Veillonella*		*Eubacterium saphenum*
Rothia			*Filifactor alocis*
Porphyromonas			*Prevotella denticola*
Prevotella			*Prevotella nigrescens*
Staphylococcus			*Fusobacterium nucleatum*
Lactobacterium			
Haemophilis			
Peptostreptococcus			

*Red-complex organisms implicated in periodontitis [11–14].

Table 1. Selection of bacteria found in oral microbiome in health and disease.

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3.3. Measures of periodontitis

In order to carry out high-quality studies investigating the association of periodontitis with other conditions, it is imperative to have valid and reliable measures of periodontitis.

There are a number of measures, shown in **Table 2**, which have been developed, looking at both gingivitis severity and periodontal disease [15, 16].

These measures have significant limitations. Multiple confounders such as age, smoking and immunosuppressant therapy can make them very difficult to interpret [7, 17]. Some measures under- or overestimate periodontal disease as they are affected by gum recession alone. However, the most significant limitation is that there is no single gold standard definition of a threshold for a diagnosis of 'periodontitis'. Most studies use varying thresholds which has a significant impact on prevalence rates and means studies need to be compared with caution [18].

	Measure	Definition	Method	Characteristic
Gingivitis	Bleeding on probing (BOP)	Bleeding of gingiva on gentle probing	Bleeding within 10 seconds, following gentle probing of gingival crevice	Assessment of gingivitis
	Bleeding index	BOP, calculated as an index	Number of sites BOP, divided by the total number of available sites multiplied by 100	Assessment of gingivitis
	Loe and Sillness Gingival index	Degree of gingival inflammation, characterized by erythema, hypertrophy and bleeding	Degree of inflammation given score out of four. The scores of four areas of the tooth are averaged	Assessment of gingivitis
Periodontitis	Missing teeth	Number of missing teeth	Count missing teeth	Crude, may be due to reasons other than periodontal disease
	Alveolar bone loss	Loss of the bone which supports the teeth	Periapical radiograph	Associated with tooth loss secondary to periodontitis
	Probing depth (PD)	Depth of the periodontal pocket	Measure the distance from the gingival margin to the base of the pocket	Measure of current periodontitis
	Clinical attachment level (CAL)	Measurement of the position of the soft tissue in relation to the cementoenamel junction (CEJ)	Calculated using the probing depth and the level of the gingival margin	Measure of cumulative periodontal disease

Table 2. Gingivitis and periodontal disease clinical measures [15, 16].

4. Periodontitis and systemic inflammation

The interest in the systemic inflammatory profile of patients affected by periodontitis has risen in the last 30 years to investigate the plausibility of the hypothesis that periodontal infection might have an impact on the systemic health. Particularly, the effect of periodontitis on the cardiovascular system but more recently a large spectrum of conditions such as neurodegenerative diseases, diabetes mellitus and rheumatoid arthritis, has been investigated. All these diseases are characterized by an increased systemic inflammatory profile, and periodontitis could contribute to their onset and progression by elevating pro-inflammatory markers. Consistent evidence from observational studies has suggested that severe periodontitis is associated with increased serum levels of C-reactive protein (CRP), moderate leukocytosis, as well as increased serum levels of interleukin-1 (IL-1) and IL-6 [19–23]. Furthermore, elevated serum levels of CRP have been associated with presence of keystone periodontal pathogens [24].

A recent systematic review confirmed a weighted mean difference of 1.56 mg/l ($p < 0.00001$) of CRP levels between cases with periodontitis and controls [25]. Further, the review reported on data from six intervention studies, concluding that periodontal treatment produced a 0.50 mg/l (95% CI 0.08–0.93) ($p < 0.02$) reduction of CRP serum levels. A recent meta-analysis on the effects of periodontal therapy and systemic inflammation reported a 0.23-mg/l reduction in CRP levels after treatment (−0.231; $p = 0.000$) [26]. Interestingly, a further analysis confirmed that the anti-inflammatory effect of periodontal treatment was more evident in clinical trials involving patients with periodontitis and other comorbidities like diabetes [27]. Individuals with periodontitis also show increased serum concentration of IL-6 and TNF-α compared to controls. Intervention trials reported inconclusive results on the effect of periodontal treatment on serum levels of these markers [28].

Different plausible mechanisms by which periodontitis could cause an increase in systemic inflammatory levels have been suggested. Firstly, multiple studies have reported the production of inflammatory cytokines in the periodontal pocket [29] and it has been postulated that these mediators could reach the bloodstream leaking from the inflamed periodontal lesions. Some of these mediators (i.e., IL-6) could have an effect on distant tissues and organs such as the liver, triggering an acute-phase response. However, for the time being, there is a limited evidence supporting this mechanism [30].

Secondly, bacteria colonizing the periodontal pockets and/or their by-products have been detected in the peripheral circulation [31]. A disruption of the subgingival epithelium could lead to short-lived bacteremia. This could trigger an immune response as well as allow bacteria to directly impact on the vasculature or distant organs (like the liver or kidney). In support of this hypothesis, periodontal bacteria DNA [32] and viable pathogens [33] have been detected in human atherosclerotic plaques. Thirdly, several antibodies induced by periodontal pathogens might trigger a molecular mimicry with cross-reactive antibodies recognizing host antigens.

Lastly, periodontitis and other comorbidities such as cardiovascular diseases and diabetes, share many common risk factors, including obesity and smoking [34, 35] which both have an effect on the systemic inflammatory profile [36]. This might account for a spurious association between periodontitis and systemic inflammation. However, the majority of the observational

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and experimental evidence available seems to support the concept that periodontitis could independently contribute to systemic levels of different inflammatory mediators and that periodontal treatment could result in their reduction. The systemic low-grade inflammation generated by periodontal infection might represent the link between periodontitis and systemic conditions [37, 38].

5. Periodontitis and rheumatoid arthritis

5.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease characterized by joint inflammation and destruction with extra-articular features including rheumatoid nodules, pulmonary disease, vasculitis and neuro-inflammation [39]. It can lead to chronic disability, early mortality, systemic complications and high socioeconomic burden on society as a whole [40]. The prevalence of RA is 0.5–1.0% [13] with apparent variation according to latitude and urban/rural habitation [41, 42].

It is currently classified according to the 2010 American College of Rheumatology/European League against rheumatism criteria by joint involvement, positive serology for rheumatoid factor or anti-citrullinated protein antibodies (ACPA), raised acute-phase reactants and the duration of symptoms [43]. Treatment regimens traditionally include corticosteroid to induce remission used in combination with maintenance of disease-modifying antirheumatic drugs, though have been much improved by the intervention of biologic agents.

5.2. Pathogenesis of rheumatoid arthritis

The exact etiology of RA is unknown; however, it is thought to be secondary to an interaction between genetic attributes and environmental exposures.

Indeed, genetic studies in twins have estimated approximately 60% heritability of rheumatoid arthritis [44]. Genetic polymorphisms including HLA-DRB1 [45] are implicated. However, other susceptibility alleles including genes involved in the differentiation of T cells, selection of antigens and peptide affinity have been identified by genome-wide association studies.

In terms of environmental insults, smoking has long been associated with RA [46] as have social factors including lower socioeconomic class and education but other areas of interest include silica, exogenous infections, periodontitis and the microbiota of mouth, gut and lung [47].

Autoantibodies to the Fc portion of immunoglobulin are known as rheumatoid factor and antibodies that are known to form against citrullinated proteins are called anti-citrullinated protein antibody (ACPA) or anti-cyclic citrullinated peptide (anti-CCP) antibodies. If either of these are present, they confer 'seropositivity,' which is seen in 70–80% of patients [48]. In addition to forming an element of the diagnostic criteria [43], seropositivity is also associated with more aggressive disease and with the earlier development of erosions. Rheumatoid factor is limited in diagnostic application by low specificity; however, ACPA is 95–98% specific [49].

ACPA has been shown to be present in RA patient sera up to a decade prior to the development of the disease [50] although the amount of ACPA and inflammatory cytokine levels rise sharply a few months before the synovitis presents [51]. It is therefore hypothesized that as well as citrullination of endogenous proteins, a second inflammatory 'hit' is required to stimulate the development of RA. Citrullinated proteins are also associated with other environmental factors such as smoking and pathological conditions including periodontitis.

Peptidyl arginine deiminase (PAD) causes the posttranslational modification of arginine to citrulline. It is hypothesized that this citrullination leads to amino acid chains being recognized as autoantigens, which leads to the development of autoantibodies and the subsequent autoimmune damage that is the signature for rheumatoid arthritis. PAD is produced by human cells, for example, in the lung; however, it is also produced by the microbe *P. gingivalis* [52].

Mucosal surfaces provide a rich opportunity for cross-talk between the immune system and the microorganisms which inhabit them. It is supposed that these microbes are not simply left unattended and indolent, but are held in a constant state of tension by physiological barriers (mucus and immunoglobulin A), epithelial tight junctions, innate immune surveillance (by macrophages and dendritic cells) and adaptive immune response.

The mucosal-joint axis hypothesis is supported by the fact that 20% of chronic inflammatory bowel disease patients develop an enteropathic arthropathy and that reactive arthritis can develop in response to chlamydial and dysenteric organism. A possible mechanism is therefore that disruption in pathogenic-commensal bacterial balance at the mucosal surface leads to innate activation and pro-inflammatory cytokine release, leading to a lasting adaptive immune response. If we then consider that some bacterial epitopes are shared with cartilage [53], it is possible that the adaptive immunity, in response to transmucosal exposure to a microorganism, could lead to sustained autoimmunity.

5.3. *P. gingivalis* and rheumatoid arthritis

PAD production by *P. gingivalis*, an anaerobic prokaryote, has been demonstrated in vitro. Due to this organism's role in the development of periodontal disease and the association of rheumatoid arthritis with periodontitis, it has been hypothesized that *P. gingivalis* provides a causal link between periodontal disease, citrullination and RA [54].

The temporal nature of this association is a point of conjecture, though it has been shown that non-RA (as defined by the American College of Rheumatology (ACR) criteria) patients with risk factors for the development of RA such as first-degree relatives and ACPA positivity had a higher concentration of anti-*P. gingivalis* antibodies [55]. This finding suggests that *P. gingivalis* (one of the 'red complex' organisms) appears prior to the development of rheumatoid arthritis in an 'at risk' population. Indeed, an etiological role of *P. gingivalis* is implicated by the recent finding that anti-*P. gingivalis* antibodies are significantly higher in RA cases compared to controls and, similar to ACPA, are present in sera years before the onset of symptoms of inflammatory arthropathy [56].

In addition to an etiological role, there is longitudinal evidence to suggest that *P. gingivalis* PAD may attenuate response to biologic Disease-modifying anti rheumatic drugs [57].

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Together, these elements suggest a role for this organism in various aspects of rheumatoid disease and pronounce *P. gingivalis* as a viable avenue for further research.

5.4. Periodontitis in rheumatoid arthritis

Epidemiological studies have shown a strong association between periodontitis and RA [58, 59], though these have been hampered by their cross-sectional nature, variability in definition of periodontitis and dental endpoints, the extent of oral examination and the limited RA information collected. However, despite the above, there remains a significant amount of robust evidence to support the association between periodontitis and RA including a recent meta-analysis of 17 studies and over 150,000 participants, found a significant association between RA and periodontitis with a relative risk of 1.13 (95% CI 1.04–1.23, $p = 0.006$) compared to healthy controls [60].

Shared risk factors, including cigarette smoke, provide possible confounders; however, an increased risk of periodontitis has been demonstrated in a nonsmoking RA group [61], and a comparison of periodontitis in osteoarthritis versus RA demonstrated that RA patients were twice as likely to have moderate to severe periodontitis independent of smoking, age or sex [62]. In addition, there is evidence to suggest that periodontitis responds to RA treatment [63].

5.5. Oral microbiome in rheumatoid arthritis

The association of periodontitis and *P. gingivalis* with rheumatoid arthritis has led to a great deal of interest in the oral microbiome in rheumatoid disease. Indeed, oral bacterial DNA and antibodies to *P. gingivalis, T. forsythia* and *P. intermedia* have been demonstrated in synovial fluid and the site of inflammation in rheumatoid arthritis [64]. It is also interesting that the medications with an antibacterial action against these species (including levofloxacin and clarithromycin) seem to have a beneficial effect in RA [65].

Animal studies have demonstrated a possible role periodontal bacteria in inflammatory arthritis. In a murine model of collagen-induced arthritis, oral infection with bacteria associated with periodontitis in humans developed exacerbated signs of inflammatory arthropathy, raised levels of matrix metalloproteinase 3 and histological evidence of active arthritis [66].

A study by Scher and colleagues used 16S ribosomal RNA sequencing to investigate oral microbiota from the subgingival plaque in patients with new-onset, Disease-modifying anti rheumatic drug naïve rheumatoid arthritis [67]. They found significantly higher levels of *Prevotella* and *Leptotrichia* species in the new-onset RA group compared to controls, which was robust to adjustment for periodontal disease status. In addition, *Streptococcus* and *Corynebacterium* genera were reduced in the new-onset RA group compared to healthy controls. They also investigated a chronic RA (Disease-modifying anti rheumatic drug treated) group and found higher levels of red complex bacteria in the new-onset RA group compared to the established disease group. These findings illustrate the changes in subgingival microbiota over time, and further work is required to delineate any independent roles of these changes in the microbial landscape.

Investigations of the oral microbiome are potentially hampered by the site of sampling as the oral microbiome varies depending on the region sampled. The gingival sulcus, tooth surface, hard and soft palate, saliva and tonsils are home to significantly different compositions of bacterial populations at a baseline. With the addition of the increased expertise required to acquire samples, there are far fewer studies investigating the oral microbiome than the gut microbiome in RA.

5.6. Gut microbiome in rheumatoid arthritis

The gut microbiome is the most densely populated microbial environment in the human body and is the most extensively studied. The benefit of extensive investigation is that the spectrum of the bacterial constituents of a 'normal' gut microbiome is more clearly defined [68] than in the oral cavity.

Disruption of the gut microbiome has been demonstrated in patients with rheumatoid arthritis compared to controls [69], and preceding work in animal models has highlighted possible etiological mechanisms of action.

For example, manipulating the gut microbiome by instilling segmented filamentous bacteria into the small intestine of mice induces CD4 T cells which produce the pro-inflammatory cytokine IL-17 in the intestinal lamina propria [70]. The experimental creation of small bowel bacterial overgrowth leads to reactivation of resolved arthritis in a rat model [71]. The resultant proposed hypothesis is that bacterial overgrowth leads to systemic, transmucosal absorption of Lipopolysaccharide which deposits in the liver and joints, leading to an inflammatory response.

Subtraction of microbiota as well as addition can lead to a pro-inflammatory phenotype, as in an adjuvant-induced arthritis, rat model, gnotobiotic (germ-free) rats demonstrated significantly greater joint inflammation than those with normal gut microbiota [72].

Analysis of the fecal microbiome of patients with rheumatoid arthritis found that haemophilus species were significantly reduced and lactobacillus species were significantly increased [69]. This study also showed that the intestinal dysbiosis was attenuated by Disease-modifying anti rheumatic drugs. *Prevotella copri* is raised in new-onset RA [73] and correlated with shared epitope genes, drawing attention to the organism as a potential environmental trigger for the development of RA.

The rapidly engorging literature regarding the gut microbiome and rheumatoid arthritis acts as encouragement to investigate other mucosal surfaces, and, with the marked associations with periodontitis and oral bacteria, the oral microbiome is a viable candidate for investigation.

5.7. Potential interventions

In addition studies to delineate the role of the microbiome in the etiology and progression of RA, it is worth considering the possible therapeutic interventions which could be developed.

Antibiotic administration is an apparent start, and doxycycline (which was historically used to treat RA) when used in conjunction with methotrexate has been shown to outperform

methotrexate alone [74]. In patients with mild-to-moderate RA, minocycline was shown to significantly improve joint swelling, tenderness and erythrocyte sedimentation rate in a placebo-controlled trial [75]. However, the use of broad spectrum antibiotics introduces the risk of depleting all elements of the microbiome and opening the door to hostile organism invasion.

Other postulated interventions include probiotics, fecal microbiota transplant [64], harnessing bacterial secretions and single-target approaches to modify bacterial composition and by-products. Although they are exciting opportunities for research, these approaches are still in relative infancy.

5.8. Conclusion

There are strong data to support the association between rheumatoid arthritis, periodontitis and *P. gingivalis*. The role of mucosal immunity in the development of autoimmunity has been demonstrated extensively in the gut, and similar pathogenic processes could occur in the oral mucosa, though further investigation is required to clarify the role played by the oral microbiome in RA.

6. Periodontitis and ankylosing spondylitis

6.1. Ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic inflammatory condition primarily affecting the spine and sacroiliac joints. It is characterized by inflammatory back pain caused by enthesitis, bone erosion and new bone formation. Clinical features also include peripheral arthritis, anterior uveitis and rarely lung fibrosis, heart block and aortic regurgitation [76].

The overall prevalence of AS is between 0.1 and 1.4% with most cases coming from Europe [77]. Onset occurs young with 80% of patients presenting before the age of 30 and less than 5% present after the age of 45. Men are 2–3 times more commonly affected than women [77].

The diagnosis of AS is based on clinical features and presence of sacroiliitis on X-ray or MRI [78]. Treatment options are still limited, and emphasis is placed on physiotherapy and nonsteroidal anti-inflammatory medications, with anti-TNF therapy reserved for those who experience a persistently high level of disease activity. However, these have many potential side effects [78] and further understanding of the etiology of AS is needed in order to develop other treatment options.

6.2. Pathogenesis of ankylosing spondylitis

More than 90% of the risk of developing ankylosing spondylitis is determined genetically [79]. An important contribution of this is from human leucocyte antigen B27 (HLA-B27), a class 1 surface antigen encoded by MHC which has a role in presenting antigens to CD8 T cells. HLA B-27 is present in 90–95% of patients with AS, and the risk of developing AS in

HLA-B27-positive individuals is 2–5%. This is increased to 15–20% in HLA-B27-positive first-degree relative of AS patients [77].

The remainder of the risk comes from environmental factors. There is already substantial evidence to support a role of bacteria in the pathogenesis of AS. Reactive arthritis, another subtype of spondyloarthropathy, is triggered by genitourinary infections or enteritis caused by gram-negative enterobacteria. It is believed that the persistence of microbial antigens in the synovium of these patients contributes to the propagation of inflammation [77]. The possible role of these bacteria in the pathogenesis of AS is highlighted by the fact that 10–20% of HLA B27-positive patients with reactive arthritis develop the full clinical picture of ankylosing spondylitis [80]. Furthermore, 54% of HLA B27-positive patients with Crohn's disease develop ankylosing spondylitis, possibly due to the inflammatory processes in the gut allowing interaction of the gut bacteria and immune system [81]. TNF-alpha and T cell response is thought to be an important driver of inflammation in AS.

6.3. Periodontitis and ankylosing spondylitis

The similarities in the pathogenesis of ankylosing spondylitis and periodontitis have led to the hypothesis that periodontitis may allow oral bacteria access to the immune system and perpetuate inflammatory processes in those patients with genetic susceptibility. HLA A9 and B15, both associated with susceptibility to AS, may also be a susceptibility factor in aggressive periodontitis [82]. In particular, T lymphocyte-driven inflammation certainly plays a role in periodontitis [83] as well as in AS [84]. Interleukin (IL)-2, IL-6 and TNF-α are all raised in AS [85] as well as being implicated in periodontitis [86]. In fact, anti-TNF therapy in AS patients leads to a significant improvement in periodontal disease markers [87].

Ratz et al. performed a meta-analysis in 2015 of 6 studies comparing periodontitis measures in cases of AS and controls, and ranging in size between 90 and 40,926 participants [18]. All studies showed a positive correlation between AS and periodontitis severity, but only two showed statistical significance. On meta-analysis, the risk of developing AS in those with periodontitis was almost double with an overall odds ratio of 1.85 (CI 1.72–1.98). Despite no significant difference in probing depth and Clinical attachment level (CAL), there was a significant association in Bleeding on probing (BOP) with those with AS ($p = 0.0005$) [18].

Other studies since have looked further at the association between spondyloarthropathies, of which AS is a subtype, and periodontitis. In a group of 30 patients with spondyloarthropathy of which 8 had a diagnosis of AS, those patients with more than 5 years of evolution of disease had significantly worse periodontal disease [88]. In contrast, another group found that in 79 spondyloarthropathy patients, of which 19 had AS, levels of insertion loss were lower compared to the control group [89]. The association with *P. gingivalis* is still not certain, with contrasting findings that antibody titers were higher and lower in AS compared to controls [89, 90]

Recently, the oral microbiome has been studied in patients with axial spondyloarthritis. Patients were matched for age, gender and ethnicity to healthy controls. Interestingly, although patients had significantly greater prevalence of periodontitis (PPD ≥ 4 mm at ≥4

sites), a higher plaque index and higher mean bleeding on probing [91], there was no difference in either community structure or in diversity of organisms in the plaque bacterial communities analyzed. However, it is important to note that the small sample size in this study made it unlikely that any small effect size would be measured and so further larger studies are warranted to investigate this.

6.4. Conclusion

Overall, evidence does suggest an association between periodontitis and AS. When small studies were combined in meta-analysis, a significant odds ratio was calculated. Shared pathogenic mechanisms may explain some of this association, but the details of the underlying processes remain largely unknown.

7. Periodontitis and psoriatic arthritis

7.1. Psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with the presence of psoriasis, usually prior to joint involvement. Ninety-five percent are a peripheral arthritis, usually involving more than five joints in an asymmetrical pattern. The spine and sacroiliac joints are also affected in about 5% of patients [92].

Psoriatic arthritis is uncommon in the general population affecting <1%. However, it occurs in up to 30% of patients with psoriasis. It occurs equally in men and women and most commonly in those between 30 and 50 years of age [93].

Diagnosis is made clinically by the presence of inflammatory joint pain, personal or family history of psoriasis and typical X-ray findings. The treatment can be subdivided firstly into the treatment of psoriasis and secondly into the treatment of arthritis with Non-steroidal anti-inflammatory drugs, disease-modifying anti rheumatic drugs and biologics [94]. Again, the treatment options for PsA are limited and further understanding of disease etiology may lead to alternative treatments.

7.2. Pathogenesis of psoriatic arthritis

Similarly to the other seronegative spondyloarthropathies, psoriatic arthritis is thought to be caused by an environmental trigger in a genetically primed individual. Indeed, about 15% of first-degree relatives of a patient with psoriatic arthritis will also be affected and studies have elucidated genetic variants [93]. The most important of these are on the human leucocyte antigen 1 (HLA-1) which is involved in presenting antigens to CD8 T cells. Variants such as HLA-Cw6, HLA-B27 and HLA-B39 are associated with specific phenotypes of PsA. These variants highlight that psoriatic arthritis is not just a subset of psoriasis and provide important clues as to the pathogenesis of PsA in which the CD8 T cell plays a key role [93].

It is hypothesized that the molecules encoded by these HLA variants may recognize self-antigens in the synovium and enthesis. However, the true pathogenesis is likely to be more complex as T cell expanded clones in the synovial tissue of patients with psoriatic arthritis lack common motifs to explain a single trigger. Fitzgerald and Winchester propose that in fact CD8 T cells are stimulated through NK receptors which respond to molecules produced in inflammation and stress [93]. In support of this, both physical trauma and immunization with rubella vaccine have been shown to proceed development of psoriatic arthritis. Stimulation of the inflammatory response leads to infiltration of T cells and cytokines including TNF-alpha, Il-1, IL-6, IL-12, IL-15, IL-17, IL-18 and IF-γ in the synovium and ultimately to the clinical finding of synovitis [93]

7.3. Periodontitis and psoriatic arthritis

The characteristic lymphocytic infiltration of the joint with activated T cells and thus with the secretion of the pro-inflammatory cytokines IL-1 and TNF-α potentiates abnormal bone remodeling and the activation of matrix metalloproteinases in PsA. Interestingly, chronic periodontitis has a similar cytokine profile which has led to research investigating the relationship between them.

In 2013, Ustun et al. compared the periodontal status of 51 patients with PsA to that of healthy controls. Clinical attachment level, the gold standard measure of periodontitis severity and past disease activity, was significantly greater in those with PsA ($p = 0.037$). Although not statistically significant, probing depth was greater in those with PsA [95]. In another study, probing depth was statistically greater in patients with PsA [96]. A much larger Danish nationwide cohort study including 6428 patients with PsA found that incidence rates of periodontitis were significantly greater in patients with PsA compared to reference population. Of note, periodontitis rates were also greater in patients with PsA compared to psoriasis alone [97].

One cause for this may be the trapping of oral bacterial DNAs in synovial fluid. Mean number of oral bacterial species is significantly higher in both sera and synovial fluid of PsA patients, and periodontitis-associated species *P. gingivalis* and *Prevotella nigrescens* have been exclusively detected in PsA sera and synovial fluid [98].

A systematic review in 2016 presented 10 studies which all showed an association between psoriasis and periodontitis [99]. Eight of these, with between 33 and 115,365 cases, found measures of periodontitis including probing depth and CAL were increased in those with psoriasis compared to controls [95, 100–106]. A large population cohort study concluded that self-reported alveolar bone loss and loss of teeth increased risk of subsequent psoriasis [104]. Furthermore, these studies concluded that the presence of psoriasis was associated with greater severity of periodontitis.

7.4. Conclusion

Although there are still a limited number of studies, those which have been carried out provide strong evidence for an association between PsA and periodontitis. Importantly, they also highlight the distinct association of PsA, rather than psoriasis, with periodontitis.

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8. Periodontitis and systemic lupus erythematosus

8.1. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multi-systemic, chronic inflammatory condition which primarily affects connective tissues and is associated with specific serological signatures. Clinical features are extremely varied but common features include facial rash, oral ulcers, photosensitivity and nonerosive and nondeforming arthritis. Almost all body systems can be affected including renal, neurological, cardiac, respiratory, ophthalmic, gastrointestinal and hematological.

The estimated prevalence of SLE in the USA is 51/100,000, with females being affected 9 times more commonly than males. It is more common in people from Afro-Caribbean and Latin American decent. Most diagnosis is between the ages of 16–55 years with about 30% diagnosed younger than 16 or older than 55 years [107].

Diagnosis is based on clinical assessment and laboratory measures. Antibody tests including ANA, Anti-ds DNA and Anti-Sm may aid diagnosis but need to be used in the context of the clinical presentation [107].

Treatment for SLE depends on clinical presentation and disease activity, but the backbone is immunosuppression. However, given that the major cause of mortality in SLE is infection and malignancy which have both been attributed to long-term immunosuppression, there is a need to further understand disease etiology and find ways to prevent disease initiation and progression.

8.2. Pathogenesis of systemic lupus erythematosus

SLE occurs in genetically susceptible individuals, in whom an inflammatory response is triggered by a secondary stimulus. There is a strong genetic predisposition, and siblings of patients with SLE are 30 times more likely to have SLE than the general population [107]. Certain genetic variants which alter the inflammatory process and lead to impaired clearance of immunoglobulins have been implicated. Estrogen-driven stimulation of humeral activity may at least in part explain the female predominance [108]. Known environmental factors include UV light, demethylating drugs and infections such as EBV virus. These lead to the initiation of apoptosis and impaired clearance of cells. The nucleic acids are transferred to endosomal sensors, leading to the activation of endosomal toll-like receptors (TLRs) and dendritic cells which produce IFN alpha. These inflammatory mediators activate the inflammatory cascade, immune complex production and vascular damage. Immune complexes cause tissue destruction by deposition in tissues [109].

8.3. Periodontitis and systemic lupus erythematosus

Several case reports have suggested that patients with SLE have a greater severity of periodontitis [110–114]. The similar mechanisms of tissue destruction for periodontitis and SLE could explain a potential association. Polymorphisms in the Fcγ receptor leading to impaired

clearing of immune complexes have already been implicated in susceptibility to both periodontitis and SLE [115]. The inflammatory cytokine profile is similar in periodontitis and SLE. For example, IL-18 levels are increased in patients with SLE and correlate with SLE disease activity index (SLEDAI) [116], while there is a significant correlation between IL-18 levels and periodontal parameters [116]. Interestingly, higher levels of IF-γ, IL 10, IL-17, IL-1β and IL-14 found in healthy patients with periodontitis are also present in patients with SLE even in the absence of periodontitis [117]

TLRs which modulate the inflammatory response to microorganisms in periodontal disease have also been implicated in SLE. Activation of TLRs which respond to specific pathogen-associated molecular patterns (PAMPs) such as Lipopolysaccharide produced by bacteria, triggers cell signaling pathways and release of pro-inflammatory cytokines. The overexpression of TLR-4 leads to autoimmune lupus and is essential for the production of anti-DsDNA antibodies found in SLE [108]. Therefore, the influence of the microorganisms in periodontal disease may affect the expression of TLRs in SLE and stimulate the autoimmune process.

Periodontitis is common in patients with SLE, with frequency varying between 60 and 93.8% [113, 118]. One Japanese study found that the frequency of periodontitis in SLE patients was 70% as compared to 30% in the general population [115].

Cross-sectional studies have found that periodontitis is more common in SLE than in controls [119–125]. A comparison of periodontal status in 105 SLE patients and geographically matched samples of the Adult Dental Health Survey in the UK found that, with adjustments for age and sex, patients with SLE were significantly more likely to have periodontitis with an OR 7.25 (95% CI 3.84–13.68) [121]. In another study, SLE patients had a significant 1.69-fold increased odds (CI 1.37–3.25) of having periodontitis defined by CAL > 3 mm [125]. These findings have been replicated in juvenile SLE patients where periodontal parameters were significantly higher than in controls [122]. Interestingly, SLE disease activity as measured by SLEDAI index correlates with periodontal condition and is a significant predictor of periodontitis [125, 126].

Three further studies have found nonsignificant findings that periodontitis is more prevalent in SLE patients [119, 123, 121]. The lack of statistical significance may be due to small sample size, use of immunosuppressants which can affect periodontal disease activity, and age. In fact, one study did highlight the fact that although there was no statistical difference in periodontal status, SLE cases were significantly younger than controls and so one could conclude that periodontitis is premature in SLE patients [120]. A study which did not find that periodontitis is more prevalent in SLE patients may have been due to the use of anti-inflammatory agents and the fact that controls were skewed to being older than cases [127].

No differences in bacterial species have been found in SLE patients compared to controls when specific periodontitis-associated bacteria have been examined [116] However, there have been no studies to date which have sequenced the oral microbiome in SLE patients.

Nonsurgical treatment of periodontitis in patients with SLE significantly improves both periodontitis measures and SLE disease activity index (SLEDAI) at 3 months [128]. This suggests

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treatment of periodontitis leads to a reduction in SLE disease activity and periodontitis may be an important factor in maintaining the inflammatory process in SLE.

8.4. Conclusion

There are some very compelling biological arguments including the shared pathogenesis and specifically a possible role of TLRs which could explain the link between periodontitis and SLE. To date, the evidence from case control studies suggesting an association is promising. However, further work with larger studies and identification of the oral microbiome in SLE patients is required to explain the role of periodontitis both in the initiation and in the maintenance of the inflammatory process in SLE.

9. Periodontitis and osteoarthritis

Osteoarthritis (OA) is a chronic degenerative condition of the joints characterized by cartilage loss, bone remodeling and periarticular muscle weakness. In contrast to RA, PsA, AS and SLE, there is not thought to be a primary inflammatory element in the disease process in OA though, as a patient group, they are considered to be good controls for the inflammatory arthropathies due to a similar demography [129, 54].

Osteoarthritis is extremely common, affecting more than 10% of people over the age of 45 [130]. Diagnosis is made on clinical symptoms and signs, and typical X-ray findings can be helpful although not required.

OA usually occurs due to chronic stress on the joint but can be accelerated by trauma, infection, crystal deposition and inflammatory arthritidies. Interestingly physical factors alone are not responsible for the development of OA. In fact, family history is a significant predictor of disease development and genome-wide association studies have identified multiple significant loci associated with OA [131].

There are elements of oral microbial flora that are of interest. A recent study has demonstrated the presence of periodontal bacteria in the joints of patients following joint replacement that may play a role in loosening and replacement failure [132]. However, compared to RA, the risk of periodontitis is significantly lower in OA [62] and no association has been found between OA and mild, moderate or severe periodontitis [133].

10. Conclusion

The advent of 16S sequencing techniques has allowed further study of the interaction between the oral microbiome and inflammatory arthritidies. It is clear that periodontitis is associated with systemic inflammation. The underlying mechanisms for this are less clear but may be due to the interaction of microbes with the immune system in the periodontal pocket or as a result of bacteremia. There is strong evidence to suggest an association between

periodontitis and rheumatoid arthritis with PAD producing *P. gingivalis*, having a key role in this interaction. There is also accumulating evidence for other inflammatory arthritidies including ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus. Common pathogenic mechanisms may explain this, but details of these interaction still need to be elucidated. Studies have been hampered by different measures of periodontitis, small sample size, multiple confounders and their cross-sectional nature. Further longitudinal studies which address these issues are needed. In the future, there may be a role for antibiotics, probiotics or interventions, targeting specific bacteria in these autoimmune conditions.

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References

[1] Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature [Internet]. 2007 [cited 2017 Mar 6];**449**(7164):804-810. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17943116

[2] Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature [Internet]. 2010 [cited 2017 Mar 6];**464**(7285):59-65. Available from: http://www.nature.com/doifinder/10.1038/nature08821

[3] Maguire BA, Zimmermann RA. The ribosome in focus. Cell [Internet]. 2001 [cited 2017 Mar 6];**104**(6):813-816. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11290319

[4] Kuczynski J, Lauber CL, Walters WA, Parfrey LW, Clemente JC, Gevers D, et al. Experimental and analytical tools for studying the human microbiome. Nature Reviews Genetics [Internet]. 2011 [cited 2017 Mar 6];**13**(1):47-58. Available from: http://www.nature.com/doifinder/10.1038/nrg3129

[5] Peterson J, Garges S, Giovanni M, McInnes P, Wang L, Schloss JA, et al. The NIH Human Microbiome Project. Genome Research [Internet]. 2009 [cited 2017 Mar 6];**19**(12):2317-2323. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19819907

[6] Williams RC. Periodontal disease. The New England Journal of Medicine. 1990;**322**:373-382. Downloaded from nejm.org ST Georg Univ

[7] Dye BA. Global periodontal disease epidemiology. Periodontology 2000. 2012;**58**(1):10-25

[8] Hajishengallis G. Periodontitis: From microbial immune subversion to systemic inflammation. Nature reviews. Immunology. 2015;**15**:30-44

[9] Schmidt J, Jentsch H, Stingu C-S, Sack U. General immune status and oral microbiology in patients with different forms of periodontitis and healthy control subjects. PLoS One. 2014;**9**(10):e109187

[10] McCray LJAT. 'Ome sweet 'omics- a genealogial treasury of words. Scientist. 2001;**15**:8-10

[11] Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner ACR, Yu W-H, et al. The human oral microbiome. Journal of Bacteriology [Internet]. 2010 [cited 2017 Jan 31];**192**(19):5002-5017. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20656903

[12] Zarco MF, Vess TJ, Ginsburg GS. The oral microbiome in health and disease and the potential impact on personalized dental medicine. Oral Dis. 2012;**18**(2):109-120

[13] Wade WG. The oral microbiome in health and disease. Pharmacological Research. 2013;**69**(1):137-143

[14] Alcaraz LD, Belda-Ferre P, Cabrera-Rubio R, Romero H, Simón-Soro Á, Pignatelli M, et al. Identifying a healthy oral microbiome through metagenomics. Clinical Microbiology and Infection. 2012;**18**(Suppl. 4):54-57

[15] Armitage GC. Development of a classification system for periodontal diseases and conditions. Annals of Periodontology. 1999;**4**(1):1-6

[16] Jacob S. Measuring periodontitis in population studies: A literature review Medição de periodontite em estudos populacionais: uma revisão de literatura. Revista Odonto Ciência. 2011;**26**(4):346-354

[17] Chi AC, Neville BW, Krayer JW, Gonsalves WC. Oral Manifestations of systemic disease. American Family Physician2010;**82**(11):1381-1388

[18] Ratz T, Dean LE, Atzeni F, Reeks C, Macfarlane GJ, Macfarlane TV. A possible link between ankylosing spondylitis and periodontitis: A systematic review and meta-analysis. Rheumatology (Oxford) [Internet]. 2015 [cited 2016 Nov 21];**54**(3):500-510. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25213130

[19] Kweider M, Lowe GDO, Murray GD, Kinane DF, McGowan DA. Dental disease, fibrinogen and white cell count; links with myocardial infarction? Scottish Medical Journal [Internet]. 1993 [cited 2017 Mar 6];**38**(3):73-74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8356427

[20] Ebersole JL, Machen RL, Steffen MJ, Willmann DE. Systemic acute-phase reactants, C-reactive protein and haptoglobin, in adult periodontitis. Clinical & Experimental Immunology [Internet]. 1997 Feb [cited 2017 Mar 6];**107**(2):347-352. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9030874

[21] Loos BG, Craandijk J, Hoek FJ, Dillen PMEW, Velden U Van Der. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. Journal of Periodontology [Internet]. 2000 [cited 2017 Mar 6];**71**(10):1528-1534. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11063384

[22] Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS. Acute-phase inflammatory response to periodontal disease in the US population. Journal of Dental Research [Internet]. 2000 [cited 2017 Mar 6];**79**(1):49-57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10690660

[23] Hutter JW, van der Velden U, Varoufaki A, Huffels RA, Hoek FJ, Loos BG. Lower numbers of erythrocytes and lower levels of hemoglobin in periodontitis patients compared to control subjects. Journal of Clinical Periodontology [Internet]. 2001 [cited 2017 Mar 6];**28**(10):930-936. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11686811

[24] Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, Nardin E De. Periodontal infections contribute to elevated systemic c-reactive protein level. Journal of Periodontology [Internet]. 2001 [cited 2017 Mar 6];**72**(9):1221-1227. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11577954

[25] Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. Journal of Clinical Periodontology [Internet]. 2008 [cited 2017 Mar 6];**35**(4):277-290. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18294231

[26] Freitas COT de, Gomes-Filho IS, Naves RC, Nogueira Filho G da R, Cruz SS da, Santos CA de ST, et al. Influence of periodontal therapy on C-reactive protein level: A systematic review and meta-analysis. Journal of Applied Oral Science [Internet]. 2012 [cited 2017 Mar 6];**20(**1):1-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22437670

[27] Teeuw WJ, Slot DE, Susanto H, Gerdes VEA, Abbas F, D'Aiuto F, et al. Treatment of periodontitis improves the atherosclerotic profile: A systematic review and meta-analysis. Journal of Clinical Periodontology [Internet]. 2014 [cited 2017 Mar 6];**41**(1):70-79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24111886

[28] D'Aiuto F, Orlandi M, Gunsolley JC. Evidence that periodontal treatment improves biomarkers and CVD outcomes. Journal of Periodontology [Internet]. 2013 [cited 2017 Mar 6];**40**:S85–S105. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23627337

[29] Preshaw PM, Taylor JJ. How has research into cytokine interactions and their role in driving immune responses impacted our understanding of periodontitis? Journal of Clinical Periodontology [Internet]. 2011 [cited 2017 Mar 6];**38**:60-84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21323705

[30] Teles R, Wang C-Y. Mechanisms involved in the association between peridontal diseases and cardiovascular disease. Oral Diseases [Internet]. 2011 [cited 2017 Mar 6];**17**(5):450-461. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21223455

[31] Kinane DF, Riggio MP, Walker KF, MacKenzie D, Shearer B. Bacteraemia following periodontal procedures. Journal of Clinical Periodontology [Internet]. 2005 [cited 2017 Mar 6];**32**(7):708-13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15966875

[32] Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. Journal of Periodontology [Internet]. 2000 [cited 2017 Mar 6];**71**(10):1554-1560. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11063387

[33] Kozarov EV, Dorn BR, Shelburne CE, Dunn WA, Progulske-Fox A. Human atherosclerotic plaque contains viable invasive actinobacillus actinomycetemcomitans and *Porphyromonas gingivalis*. Arteriosclerosis, Thrombosis, and Vascular Biolog [Internet]. 2005 [cited 2017 Mar 6];**25**(3):e17–e18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15662025

[34] Bergström J, Minenna L, Farina R, Scabbia A, Trombelli L, Hart A, et al. Periodontitis and smoking: An evidence-based appraisal. Journal of Evidence-Based Dental Practice [Internet]. 2006 [cited 2017 Mar 6];**6**(1):33-41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17138394

[35] Leone A, Landini L, Picano E. Modifying cardiovascular risk factors: Epidemiology and characteristics of smoking-related cardiovascular diseases. Current Pharmaceutical Design [Internet]. 2010 [cited 2017 Mar 6];**16**(23):2504-2509. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20550498

[36] Ritchie CS. Obesity and periodontal disease. Periodontology 2000 [Internet]. 2007 [cited 2017 Mar 6];**44**(1):154-163. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17474931

[37] D'Aiuto F, Parkar M, Nibali L, Suvan J, Lessem J, Tonetti MS. Periodontal infections cause changes in traditional and novel cardiovascular risk factors: Results from a randomized controlled clinical trial. American Heart Journal [Internet]. 2006 [cited 2017 Mar 6];**151**(5):977-984. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16644317

[38] Pussinen PJ, Tuomisto K, Jousilahti P, Havulinna AS, Sundvall J, Salomaa V. Endotoxemia, immune response to periodontal pathogens, and systemic inflammation associate with incident cardiovascular disease events. Arteriosclerosis, Thrombosis, and Vascular Biology [Internet]. 2007 [cited 2017 Mar 6];**27**(6):1433-1439. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17363692

[39] Fuggle NR, Howe FA, Allen RL, Sofat N. New insights into the impact of neuro-inflammation in rheumatoid arthritis. Frontiers in Neuroscience [Internet]. 2014 [cited 2017 Feb 23];**8**:357. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25414636

[40] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. The New England Journal of Medicine. 2011;**365**(23):2205-2219.

[41] Alamanos Y, Voulgari PV., Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: A systematic review. Seminars in Arthritis and Rheumatism [Internet]. 2006 [cited 2017 Feb 23];**36**(3):182-188. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17045630

[42] Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis Research [Internet]. 2002 [cited 2017 Feb 23];**4**(Suppl 3):S265. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12110146

[43] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Annals of the Rheumatic Diseases [Internet]. 2010 [cited 2017 Feb 23];**69**(9):1580-1588. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20699241

[44] MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis & Rheumatism [Internet]. 2000 Jan [cited 2017 Feb 23];**43**(1):30-37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10643697

[45] Kallberg H, Padyukov L, Plenge RM, Ronnelid J, Gregersen PK, van der Helm-van Mil AHM, et al. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. The American Journal of Human Genetics. 2007;**80**(5):867-875.

[46] Hutchinson D, Moots R. Cigarette smoking and severity of rheumatoid arthritis. Rheumatology (Oxford). 2001;**40**(12):1426-1427.

[47] Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet [Internet]. 2016 [cited 2017 Feb 23];**388**(10055):2023-2038. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27156434

[48] El-Gabalawy H. The preclinical stages of RA: Lessons from human studies and animal models. Best Practice & Research: Clinical Rheumatology. 2009;**23**(1):49-58.

[49] Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: A systematic literature review. Annals of the Rheumatic Diseases. 2006;**65**(7):845-851.

[50] Nielen MMJ, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MHMT, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: A study of serial measurements in blood donors. Arthritis & Rheumatism. 2004;**50**(2):380-386.

[51] Sokolove J, Bromberg R, Deane KD, Lahey LJ, Derber LA, Chandra PE, et al. Autoantibody epitope spreading in the pre-clinical phase predicts progression to rheumatoid arthritis. PLoS One. 2012;**7**(5):e35296.

[52] Sofat N, Wait R, Robertson SD, Baines DL, Baker EH. Interaction between extracellular matrix molecules and microbial pathogens: Evidence for the missing link in autoimmunity with rheumatoid arthritis as a disease model. Frontiers in Microbiology. 2014;**5**:783

[53] Van den Broek MF, Van de Putte LB, Van den Berg WB. Crohn's disease associated with arthritis: A possible role for cross-reactivity between gut bacteria and cartilage in

the pathogenesis of arthritis. Arthritis & Rheumatism [Internet]. 1988 [cited 2017 Feb 23];**31**(8):1077-1079. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3408509

[54] Mikuls TR, Payne JB, Yu F, Thiele GM, Reynolds RJ, Cannon GW, et al. Periodontitis and *Porphyromonas gingivalis* in patients with rheumatoid arthritis. Arthritis & Rheumatology (Hoboken, NJ). 2014;**66**(5):1090-100

[55] Mikuls TR, Thiele GM, Deane KD, Payne JB, O'dell JR, Yu F, et al. *Porphyromonas gingivalis* and disease-related autoantibodies in individuals at increased risk of rheumatoid arthritis. Arthritis & Rheumatology. 2012;**64**(11):3522-3530

[56] Johansson L, Sherina N, Kharlamova N, Potempa B, Larsson B, Israelsson L, et al. Concentration of antibodies against *Porphyromonas gingivalis* is increased before the onset of symptoms of rheumatoid arthritis. Arthritis Research & Therapy [Internet]. 2016 [cited 2017 Feb 23];**18**(1):201. Available from: http://arthritis-research.biomedcentral.com/articles/10.1186/s13075-016-1100-4

[57] Kobayashi T, Ito S, Yasuda K, Kuroda T, Yamamoto K, Sugita N, et al. The combined genotypes of stimulatory and inhibitory fcγ receptors associated with systemic lupus erythematosus and periodontitis in Japanese adults. Journal of Periodontology [Internet]. 2007 [cited 2016 Nov 16];**78**(3):467-474. Available from: http://www.joponline.org/doi/10.1902/jop.2007.060194

[58] Persson GR. Rheumatoid arthritis and periodontitis—inflammatory and infectious connections. Review of the literature. Journal of Oral Microbiology. 2012;**4**:11829

[59] Demmer RT, Molitor JA, Jacobs DR, Michalowicz BS. Periodontal disease, tooth loss and incident rheumatoid arthritis: results from the First National Health and Nutrition Examination Survey and its epidemiological follow-up study. Journal of Clinical Periodontology. 2011;**38**(11):998-1006.

[60] Arleevskaya MI, Korotkova M, Renaudineau Y, Sofat N, Fuggle NR, Smith TO, et al. Hand to mouth: A systematic review and meta-analysis of the association between rheumatoid arthritis and periodontitis. Frontiers in Immunology. 2016;**7**:80.

[61] Potikuri D, Dannana KC, Kanchinadam S, Agrawal S, Kancharla A, Rajasekhar L, et al. Periodontal disease is significantly higher in non-smoking treatment-naive rheumatoid arthritis patients: results from a case-control study. Annals of the Rheumatic Diseases. 2012;**71**(9):1541-1544.

[62] Dissick A, Redman RS, Jones M, Rangan B V., Reimold A, Griffiths GR, et al. Association of periodontitis with rheumatoid arthritis: A pilot study. Journal of Periodontology [Internet]. 2010 [cited 2017 Feb 22];**81**(2):223-230. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20151800

[63] Assuma R, Oates T, Cochran D, Amar S, Graves DT. IL-1 and TNF antagonists inhibit the inflammatory response and bone loss in experimental periodontitis. The Journal of Immunology. 1998;**160**(1):403-409

[64] Jethwa H, Abraham S; The evidence for microbiome manipulation in inflammatory arthritis. Rheumatology (Oxford) 2016; 275, 53, 263 kew374. doi: 10.1093/rheumatology/kew374

[65] Ogrendik M. Periodontal pathogens are likely to be responsible for the development of ankylosing spondylitis. Current Rheumatology Reviews. 2015;**11**(1):47-49

[66] Chukkapalli S, Rivera-Kweh M, Gehlot P, Velsko I, Bhattacharyya I, Calise SJ, et al. Periodontal bacterial colonization in synovial tissues exacerbates collagen-induced arthritis in B10.RIII mice. Arthritis Research & Therapy [Internet]. 2016 [cited 2017 Feb 23];**18**(1):161. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27405639

[67] Scher JU, Ubeda C, Equinda M, Khanin R, Buischi Y, Viale A, et al. Periodontal disease and the oral microbiota in new-onset rheumatoid arthritis. Arthritis & Rheumatism. 2012;**64**(10):3083-3094.

[68] González A, Vázquez-Baeza Y, Knight R. SnapShot: The human microbiome. Cell [Internet]. 2014 [cited 2017 Feb 23];**158**(3):690-690.e1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25083877

[69] Zhang X, Zhang D, Jia H, Feng Q, Wang D, Liang D, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nature Medicine [Internet]. 2015;**21**(8):895-905. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26214836\nhttp://www.nature.com/nm/journal/v21/n8/full/nm.3914.html?WT.ec_id=NM-201508&spMailingID=49267143&spUserID=ODM2MjM4OTIwNAS2&spJobID=741033692&spReportId=NzQxMDMzNjkyS0

[70] Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell [Internet]. 2009 [cited 2017 Feb 23];**139**(3):485-498. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19836068

[71] Lichtman SN, Wang J, Sartor RB, Zhang C, Bender D, Dalldorf FG, et al. Reactivation of arthritis induced by small bowel bacterial overgrowth in rats: Role of cytokines, bacteria, and bacterial polymers. Infection and Immunity [Internet]. 1995 [cited 2017 Feb 23];**63**(6):2295-2301. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7768612

[72] Kohashi O, Kuwata J, Umehara K, Uemura F, Takahashi T, Ozawa A. Susceptibility to adjuvant-induced arthritis among germfree, specific-pathogen-free, and conventional rats. Infection and Immunity [Internet]. 1979 [cited 2017 Feb 23];**26**(3):791-794. Available from: http://www.ncbi.nlm.nih.gov/pubmed/160888

[73] Nakayama J, Watanabe K, Jiang J, Matsuda K, Chao S-H, Haryono P, et al. Diversity in gut bacterial community of school-age children in Asia. Scientific Reports [Internet]. 2015 [cited 2017 Feb 23];**5**:8397. Available from: http://www.nature.com/articles/srep08397

[74] O'Dell JR, Elliott JR, Mallek JA, Mikuls TR, Weaver CA, Glickstein S, et al. Treatment of early seropositive rheumatoid arthritis: Doxycycline plus methotrexate versus methotrexate alone. Arthritis & Rheumatism [Internet]. 2006 [cited 2017 Feb 23];**54**(2):621-627. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16447240

[75] Tilley BC, Alarcón GS, Heyse SP, Trentham DE, Neuner R, Kaplan DA, et al. Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA Trial Group. Annals of Internal Medicine [Internet]. 1995 [cited 2017 Feb 23];**122**(2):81-89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7993000

[76] Tam L-S, Gu J, Yu D. Pathogenesis of ankylosing spondylitis. Nature Reviews Rheumatology [Internet]. 2010 [cited 2017 Jan 26];**6**(7):399-405. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20517295

[77] Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;**369**:1379-1390. www.thelancet.com

[78] Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. The New England Journal of Medicine. 2016;**26374**:2563-2574.

[79] Reveille JD. The genetic basis of ankylosing spondylitis. Current Opinion in Rheumatology [Internet]. 2006 [cited 2017 Jan 26];**18**(4):332-341. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16763451

[80] Leirisalo-Repo M, Helenius P, Hannu T, Lehtinen A, Kreula J, Taavitsainen M, et al. Long-term prognosis of reactive salmonella arthritis. Annals of the Rheumatic Diseases [Internet]. 1997 [cited 2017 Jan 26];**56**(9):516-520. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9370874

[81] Purrmann J, Zeidler H, Bertrams J, Juli E, Cleveland S, Berges W, et al. HLA antigens in ankylosing spondylitis associated with Crohn's disease. Increased frequency of the HLA phenotype B27,B44. The Journal of Rheumatology [Internet]. 1988 [cited 2017 Jan 26];**15**(11):1658-1661. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3266250

[82] Stein JM, Machulla HKG, Smeets R, Lampert F, Reichert S. Human leukocyte antigen polymorphism in chronic and aggressive periodontitis among Caucasians: A meta-analysis. Journal of Clinical Periodontology [Internet]. 2008 [cited 2017 Jan 26];**35**(3):183-192. Available from: http://doi.wiley.com/10.1111/j.1600-051X.2007.01189.x

[83] Bartold PM, Marshall RI, Haynes DR. Periodontitis and rheumatoid arthritis: A review. Journal of Periodontology. 2005;**76**(11 Suppl):2066-2074.

[84] Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. Annals of the Rheumatic Diseases [Internet]. 2002 [cited 2017 Jan 26];**61**(Suppl 3):iii8–iii18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12381506

[85] Bal A, Unlu E, Bahar G, Aydog E, Eksioglu E, Yorgancioglu R. Comparison of serum IL-1 beta, sIL-2R, IL-6, and TNF-alpha levels with disease activity parameters in ankylosing spondylitis. Clinical Rheumatology. 2007;**26**(2):211-215.

[86] Pischon N, Pischon T, Kröger J, Gülmez E, Kleber B-M, Bernimoulin J-P, et al. Association among rheumatoid arthritis, oral hygiene, and periodontitis. Journal of Periodontology. 2008;**79**(6):979-986.

[87] Fabri GMC, Pereira RMR, Savioli C, Saad CGS, de Moraes JCB, Siqueira JTT, et al. Periodontitis response to anti-TNF therapy in ankylosing spondylitis. JCR Journal of

Clinical Rheumatology [Internet]. 2015 [cited 2016 Nov 21];**21**(7):341-345. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00124743-201510000-00002

[88] Londoño J, Romero-Sánchez C, Bautista-Molano W, Segura S, Cortes-Muñoz A, Castillo D, et al. AB0569 Association between periodontal condition with disease duration and activity in colombian patients with spondyloarthritis. Annals of the Rheumatic Diseases [Internet]. 2013 [cited 2016 Nov 21];**72**(Suppl 3):A963.2–A963. Available from: http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2013-eular.2891

[89] Giraldo Q S, Romero-sanchez C, Bautista-Molano W, Bello-Gualtero JM, De-Avila J, Chila ML, et al. AB0675 is the periodontal clinical and microbiological condition in spondyloarthritis similar than rheumatoid arthritis? Annals of the Rheumatic Diseases. 2016;**75**(Suppl 2):1135-1136.

[90] Rueda JC, Bautista-Molano W, Ávila J De, Bello-Gualtero JM, Castillo DM, Lafaurie GI, et al. FRI0422 periodontal disease in spondyloarthritis subtypes. Is there a difference? Annals of the Rheumatic Diseases. 2016;**75**(Suppl 2):588-588.

[91] Stebbings SM, Bisanz JE, Suppiah P, Thomson WM, Milne T, Yeoh N, et al. The oral microbiome of patients with axial spondyloarthritis compared to healthy individuals. PeerJ. 2016;**4**:e2095

[92] Gilliland WR. Arthritis associated with psoriasis and other skin conditions. In: West SG, editor. Rheumatology Secrets. 3rd ed. Philadelphia: Elsevier Mosby; 2015. pp. 284-288.

[93] FitzGerald O, Winchester R. Psoriatic arthritis: from pathogenesis to therapy. Arthritis Research & Therapy [Internet]. 2009 [cited 2017 Feb 14];**11**(1):214. Available from: http://arthritis-research.biomedcentral.com/articles/10.1186/ar2580

[94] Gossec L, Coates LC, de Wit M, Kavanaugh A, Ramiro S, Mease PJ, et al. Management of psoriatic arthritis in 2016: A comparison of EULAR and GRAPPA recommendations. Nature Reviews Rheumatology [Internet]. 2016 [cited 2017 Feb 22];**12**(12):743-750. Available from: http://www.nature.com/doifinder/10.1038/nrrheum.2016.183

[95] Üstün K, Sezer U, Kısacık B, Şenyurt SZ, Özdemir EÇ, Kimyon G, et al. Periodontal disease in patients with psoriatic arthritis. Inflammation. 2013;**36**(3):665-669

[96] Mayer Y, Elimelech R, Balbir-Gurman A, Braun-Moscovici Y, Machtei EE. Periodontal condition of patients with autoimmune diseases and the effect of anti-tumor necrosis factor-a therapy. Journal of Periodontology. 2013;**84**(2):136-142

[97] Egeberg A, Mallbris L, Gislason G, Hansen PR, Mrowietz U. Risk of periodontitis in patients with psoriasis and psoriatic arthritis. Journal of the European Academy of Dermatology and Venereology [Internet]. 2017 [cited 2016 Nov 21]; **31**(2):288-293. Available from: http://doi.wiley.com/10.1111/jdv.13814

[98] Moen K, Brun JG, Valen M, Skartveit L, Eribe EKR, Olsen I, et al. Synovial inflammation in active rheumatoid arthritis and psoriatic arthritis facilitates trapping of a variety of oral bacterial DNAs. Clinical and Experimental Rheumatology. 2006;**24**(6):656-663.

[99] Monson CA, Porfirio G, Riera R, Tweed JA, Petri V, Atallah ÁN. Periodontal aspects for psoriasis: A systematic review. Clinical Research in Dermatology: Open Access. 2016 [cited 2017 Jan 24]; **3**(1):1-8. Available from: www.symbiosisonlinepublishing.com

[100] Preus HR, Khanifam P, Kolltveit K, Mørk C, Gjermo P. Periodontitis in psoriasis patients. A blinded, case-controlled study. Acta Odontologica Scandinavica [Internet]. 2010 [cited 2017 Feb 14];**68**(3):165-170. Available from: http://www.tandfonline.com/doi/full/10.3109/00016350903583678

[101] Kathariya R, Pradeep AR. Chronic plaque psoriasis and plaque-induced chronic periodontitis; is there any association: A cross-sectional study. Journal of Periodontology & Implant Dentistry [Internet]. 2011 [cited 2017 Feb 14];**3**(1):13-20. Available from: http://dentistry.tbzmed.ac.ir/jpid

[102] Keller JJ, Lin H-C. The effects of chronic periodontitis and its treatment on the subsequent risk of psoriasis. British Journal of Dermatology [Internet]. 2012 [cited 2017 Feb 14];**167**(6):1338-1344. Available from: http://doi.wiley.com/10.1111/j.1365-2133.2012.11126.x

[103] Lazaridou E, Tsikrikoni A, Fotiadou C, Kyrmanidou E, Vakirlis E, Giannopoulou C, et al. Association of chronic plaque psoriasis and severe periodontitis: A hospital based case-control study. Journal of the European Academy of Dermatology and Venereology [Internet]. 2013;**27**(8):967-972. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22703187

[104] Nakib S, Han J, Li T, et al. Periodontal disease and risk of psoriasis among nurses in the United States. Acta Odontologica Scandinavica. 2013;**71**(6):1423-1429

[105] Skudutyte-Rysstad R, Slevolden EM, Hansen BF, Sandvik L, Preus HR. Association between moderate to severe psoriasis and periodontitis in a Scandinavian population. BMC Oral health. 2014; Volume 14, Number 1, Page 1

[106] Sharma A, Raman A, Pradeep A. Association of chronic periodontitis and psoriasis: periodontal status with severity of psoriasis. Oral Diseases [Internet]. 2015 [cited 2017 Feb 14];**21**(3):314-319. Available from: http://doi.wiley.com/10.1111/odi.12271

[107] Bertsias G, Cervera R, Boumpas DT, Espinosa G, D'cruz D. Learning objectives: Systemic lupus erythematosus: Pathogenesis and clinical features. Eular On-line Course on Rheumatic Diseases -module n°17. 2009. Available online; [http://www.eular-online-course.org/sample_chapter/module17.pdf]

[108] Marques CPC, Maor Y, De Andrade MS, Rodrigues VP, Benatti BB. Possible evidence of systemic lupus erythematosus and periodontal disease association mediated by Toll-like receptors 2 and 4. Clinical & Experimental Immunology. 2016;**183**(2):187-192

[109] Tsokos GC. Mechanisms of disease systemic lupus erythematosus. The New England Journal of Medicine. 2011;**36522365**(1):2110-2121.

[110] Jaworski CP, Koudelka BM, Roth NA, Marshall KJ. Acute necrotizing ulcerative gingivitis in a case of systemic lupus erythematosus. Journal of Oral and Maxillofacial Surgery. 1985;**43**:43-46.

[111] Meyer U, Kleinheinz J, Gaubitz M, Schulz M, Weingart D, Joos U. Oral manifestations in patients with systemic lupus erythematosus. Mund Kiefer Gesichtschir [Internet]. 1997 [cited 2016 Nov 16];**1**(2):90-94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9410618

[112] Nagler RM, Lorber M, Ben-Arieh Y, Laufer D, Pollack S. Generalized periodontal involvement in a young patient with systemic lupus erythematosus. Lupus [Internet]. 1999;**8**(9):770-772. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10602452

[113] Rhodus NL, Johnson DK. The prevalence of oral manifestations of systemic lupus erythematosus. Quintessence International [Internet]. 1990 [cited 2016 Nov 17];**21**(6):461-465. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2243950

[114] Vogel RI. Periodontal disease associated with amegakaryocytic thrombocytopenia in systemic lupus erythematosus. Journal of Periodontology [Internet]. 1981 [cited 2016 Nov 17];**52**(1):20-23. Available from: http://www.joponline.org/doi/10.1902/jop.1981.52.1.20

[115] Kobayashi T, Ito S, Yamamoto K, Hasegawa H, Sugita N, Kuroda T, et al. Risk of periodontitis in systemic lupus erythematosus is associated with Fcγ receptor polymorphisms. Journal of Periodontology [Internet]. 2003 [cited 2016 Nov 16];**74**(3):378-384. Available from: http://www.joponline.org/doi/10.1902/jop.2003.74.3.378

[116] Areas A, Braga F, Miranda LA, Fischer RG, Figueredo CM, Miceli V, et al. Increased IL-18 serum levels in patients with juvenile systemic lupus erythematosus. Acta Reumatológica Portuguesa [Internet]. 2007;**32**(4):397-398. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18159210

[117] Marques CPC, Victor EC, Franco MM, Fernandes JMC, Maor Y, de Andrade MS, et al. Salivary levels of inflammatory cytokines and their association to periodontal disease in systemic lupus erythematosus patients. A case-control study. Cytokine. 2016;**85**:165-170.

[118] Novo E, Garcia-MacGregor E, Viera N, Chaparro N, Crozzoli Y. Periodontitis and anti-neutrophil cytoplasmic antibodies in systemic lupus erythematosus and rheumatoid arthritis: A comparative study. Journal of Periodontology [Internet]. 1999 [cited 2016 Nov 16];**70**(2):185-188. Available from: http://www.joponline.org/doi/10.1902/jop.1999.70.2.185

[119] Al-Mutairi K, Al-Zahrani M, Bahlas S, Kayal R, Zawawi K. Periodontal findings in systemic lupus erythematosus patients and healthy controls. Saudi Medical Journal. 2015;**36**(4):463-468

[120] Calderaro DC, Ferreira GA, Dias Corrêa J, Maria S, Mendonça S, Silva T, et al. Is chronic periodontitis premature in systemic lupus erythematosus patients? Clinical Rheumatology. 2017;**36**:713-718

[121] de Pablo P, Dewan K, Dietrich T, Chapple I, Gordon C. AB0603 periodontal disease is common in patients with systemic lupus erythemathosus. Annals of the Rheumatic Diseases [Internet]. 2015 [cited 2016 Nov 16];**74**(Suppl 2):1101.2-1101. Available from: http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2015-eular.6245

[122] Fernandes EG, Savioli C, Siqueira JT, Silva CA. Oral health and the masticatory system in juvenile systemic lupus erythematosus. Lupus [Internet]. 2007;**16**(9):713-719. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=2007485131

[123] Meyer U, Kleinheinz J, Handschel J, Kruse-Losler B, Weingart D, Joos U. Oral findings in three different groups of immunocompromised patients. Journal of Oral Pathology & Medicine [Internet]. 2000 [cited 2016 Nov 17];**29**(4):153-158. Available from: http://doi.wiley.com/10.1034/j.1600-0714.2000.290402.x

[124] Wang C-Y, Chyuan I-T, Wang Y-L, Kuo MY-P, Chang C-W, Wu K-J, et al. β2-Glycoprotein I-dependent anti-cardiolipin antibodies associated with periodontitis in patients with systemic lupus erythematosus. Journal of Periodontology [Internet]. 2015;**86**(8):995-1004. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25817824

[125] Zhang Q, Yin R, Fu T, Zhang L, Li L, Gu Z. Periodontal disease in patients with systemic lupus erythematosus. In 2016. Available from: http://ovidsp.tx.ovid.com/sp-3.22.1b/ovidweb.cgi?&S=PCLHFPJKPODDDNDKNCHKMFOBGPPFAA00&Abstract=S.sh.36%7c3%7c1

[126] De Araújo L, Sales R, Vassalo S, Das M, Afonso G, Chaves M, et al. Periodontal disease and systemic lupus erythematosus activity. Revised Interdisciplinary Estud Exp. 2009;(1):14-20.

[127] Mutlu S, Richards A, Maddison P, Scully C. Gingival and periodontal health in systemic lupus erythematosus. Community Dent Oral Epidemiol [Internet]. 1993 [cited 2016 Nov 17];**21**(3):158-161. Available from: http://doi.wiley.com/10.1111/j.1600-0528.1993.tb00742.x

[128] Fabbri C, Fuller R, Bonfa E, Guedes LK, D'Alleva PS, Borba EF. Periodontitis treatment improves systemic lupus erythematosus response to immunosuppressive therapy. Clinical Rheumatology [Internet]. 2014;**33**(4):505-509. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24415114

[129] Coburn BW, Sayles HR, Payne JB, Redman RS, Markt JC, Beatty MW, et al. Performance of self-reported measures for periodontitis in rheumatoid arthritis and osteoarthritis. Journal of Periodontology. 2015;**86**(1):16-26.

[130] Bedson J, Jordan K, Croft P. The prevalence and history of knee osteoarthritis in general practice: a case-control study. Family Practice [Internet]. 2004 [cited 2017 Feb 17];**22**(1):103-108. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15640302

[131] arcOGEN Consortium, arcOGEN Collaborators, Zeggini E, Panoutsopoulou K, Southam L, Rayner NW, et al. Identification of new susceptibility loci for osteoarthritis (arcOGEN): A genome-wide association study. Lancet [Internet]. 2012 [cited 2017 Feb 17];**380**(9844):815-823. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22763110

[132] Ehrlich GD, Hu FZ, Sotereanos N, Sewicke J, Parvizi J, Nara PL, et al. What role do periodontal pathogens play in osteoarthritis and periprosthetic joint infections of the knee? Journal of Applied Biomaterials & Functional Materials. 2014;**12**(1):13-20.

[133] Kandati; SUSKEI. Osteoarthritis and periodontal disease—is there an association? In: 142nd APHA Annual Meeting and Exposition 2014; 2014.

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