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Article

Rheumatoid Arthritis and Periodontal Disease Association and Effect of Disease Modifying Anti-Rheumatic Drugs: A Narrative Review

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Abstract— **Associations between periodontal disease (PD) and other diseases, including rheumatoid arthritis (RA), respiratory disease, and chronic kidney disease, have been reported. Patients with moderate to severe periodontitis have a high risk of suffering from RA and vice versa. This bidirectional relationship could be due to genetic (HLA-DR), dysregulation of the inflammatory response, and the role of *Porphyromonas gingivalis* (*P. gingivalis*), which stimulates anti-cyclic citrullinated peptide antibodies via citrullination. This review aims to identify associated factors that contribute to RA and PD relationship and to explore the effects of disease-modifying anti-rheumatic drugs (DMARDs) on PD. A literature search was performed using PubMed and Google Scholar to identify related articles published from the year 1990 to 2020 within the research interest using keyword combinations. Thirty-one articles that fit the research interest and address the research questions for both objectives were selected. As a result, the associated factors for RA and PD relationship, including genetic predisposition, immunoregulatory imbalance, and the role of *P. gingivalis* in the citrullination process as a risk factor of RA. Significant improvement was found in periodontal parameters in RA patients treated with biologic and synthetic DMARDs. This review reported common factors contributing to the RA and PD relationship and the benefits of DMARDs on periodontitis.**

Keywords— **rheumatoid arthritis, periodontal disease, anti-cyclic citrullinated peptide, citrullination, disease modifying anti-rheumatic drugs, *Porphyromonas gingivalis***

I. INTRODUCTION

Periodontal diseases are among the most common oral health problems in adults of most populations all over the world. They are induced by bacteria and bacterial products of dental plaque, which are characterised by inflammatory destruction of periodontal tissues and alveolar bone. Scientific evidence has shown that severe periodontitis may enhance susceptibility to systemic diseases such as cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, RA, and pulmonary infections [1]. Microbial dental plaque is the initiator of the disease, but the progression and form of the disease will depend on the host's susceptibility and immune response. Thus, systemic health will play a role in initiating or modifying PD, explaining the bidirectional relationship between PD and systemic diseases.

RA is a chronic and progressive autoimmune inflammatory disease that primarily affects joints. It is characterized by uncontrolled proliferation of synovial tissue and a wide array of multi-system co-morbidities [2]. The etiology of RA is mainly due to genetics, and it is accompanied by a number of risk factors. Certain environmental triggers, such as stress, smoking, and infectious agents, can precipitate post-translational modification of proteins as a physiological process. However, the modified proteins may break the immune tolerance in genetically susceptible individuals, leading to autoantibody production [3].

An association between RA and PD has been evidenced by various studies over the past decades. According to those studies, the association between PD and RA had been reported in terms of genetic factors, chronic inflammatory events with immunoregulatory imbalances, bacterial factors, and citrullination. Other than that, the usage of DMARDs as one of the standard therapies in the treatment of RA may influence the progression of periodontitis and vice-versa [4-6]. This has been suggested in many studies, thus stipulating the potential advantage of host-modulating therapy to control both disorders [7].

Despite that, the association between RA and PD relationship and the effect of DMARDs on periodontitis were still not extensively studied. Therefore, this review will compile the data from previous research regarding the factors contributing to the PD and RA relationship and the effects of RA treatment on periodontitis, specifically with the use of DMARDs. This narrative review will contribute to a better understanding of the association between RA and PD, and their pathogenesis, as well as to improve the management of periodontitis in RA patients.

II. METHODOLOGY

The literature search was performed using PubMed and Google Scholar to identify related articles that are within the research interest using multiple keyword combinations; "rheumatoid arthritis", "periodontal disease", "periodontitis", "anti-cyclic citrullinated peptide", "citrullination", "disease modifying anti-rheumatic drugs", "*Porphyromonas gingivalis*". Searches were limited to articles that have the keywords of interest, published in English from the year 1990 to 2020, articles regarding RA and PD relationship, and benefits of DMARDs on periodontitis. Editorials, case reports, and articles published before 1990 and in other languages were excluded. Thirty-one articles that fit the research interest and address the research questions for both objectives were selected. Twelve articles that did not fulfil the criteria were excluded (Figure 1).

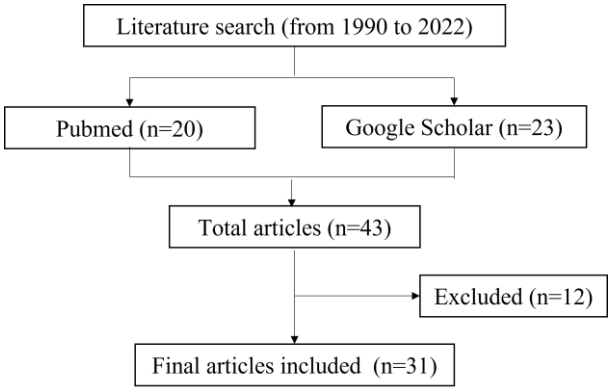

Figure 1: Flowchart of search strategy and selection process.

III. RESULTS AND DISCUSSIONS

Thirty-one articles were compiled regarding the factors contributing to the PD and RA relationship and the effects of RA treatment on periodontitis, specifically with the use of DMARDs in the following Table 1 & Table 2. In this review, the associated factors that relate to PD and RA were investigated through clinical, epidemiological associations and serological studies on the presence of oral bacterial DNA in RA patients, the prevalence of periodontitis in RA patients and vice versa, the role of *P. gingivalis* in associating PD and RA, as well as the effect of citrullination process.

Apart from that, this review also investigated the effects of DMARDs on periodontitis. Based on data analysis, two articles mentioned the presence of oral bacterial DNA in the synovial fluid of RA patients. This might explain the fact that the periodontal pathogens may translocate from the periodontal tissue to the synovium, as what had been found in a study conducted by Témoin and colleagues. The study revealed bacterial DNA was detected in the synovial fluid samples from 5 out of 36 patients [8]. The direct translocations of oral microbiota from gingiva to synovium might occur during transient bacteremia, which may result in bacterial colonization in remote sites. This might also explain the increased risk of cardiovascular disorders in patients with RA[9]. Another study also reported that the systemic diffusion of bacterial lipopolysaccharide (LPS), a cell wall compound of gram-negative bacteria, positively correlated with joint inflammatory response and the severity of joint degradation [10]. Despite the presence of bacterial DNA, the high levels of IgG antibodies in samples of synovial fluid of patients with RA were also detected [11-13].

Another important factor that might explain the relationship between PD and RA is *Porphyromonas gingivalis*. It has a unique ability to secrete the *P. gingivalis*-derived peptidyl arginine deiminase (PPAD) and drive the citrullination process, which converts arginine to citrulline [14, 15]. Our result is comparable with a study by Engström and colleagues, where they discovered that citrullinated proteins were present in most of the gingival tissues of individuals with periodontitis while only in a few of the healthy group [16]. Another study also found that in RA patients, the mean CAL, mean PI, and the number of pockets $\geqslant 5$ mm in severe periodontal conditions were linearly associated with both levels of anti-CCP antibodies [17]. Citrullinated antigens in the periodontal tissues may selectively activate the adaptive immune response and break the self-tolerance, leading to severe aggressive periodontitis and the formation of ACPA [18]. ACPAs encourage the perpetuation of synovial inflammation via binding to citrullinated proteins positioned in the cellular membrane [19]. HLA-DRB1 genetic locus is strongly associated with susceptibility to RA through citrullinated self-peptides binding to HLA-DR molecules [20]. One of the key inherited risk factors that contribute to ACPA-positive RA is the human leukocyte antigen (HLA) class II loci, namely HLA-DRB1, which encodes the HLA class II antigen-presenting molecules [15].

TABLE I. SELECTED STUDIES ASSESSING THE ASSOCIATED FACTORS OF PD-RA RELATIONSHIP

No.	Source	Studies	General study design and characteristics	Associated factors	Findings	Conclusions/ Comments
1.	Google Scholar	[25]	Case-control clinical study 30 RA patients; 30 patients with PD; 30 healthy controls	Immunoregulatory imbalance (excessive IL-6)	The hypomethylated status of a single promoter region in the IL-6 promoter may lead to increased levels of serum IL-6, implicating a role in the pathogenesis of PD and RA.	Increased levels of IL-6 may play a role in the pathogenesis of PD and RA.
2.	PubMed	[26]	Case-control study Patients: 171 autoantibodies negative; 75 autoantibodies positive; 38 high risks based on the presence of a positive ACPA or positivity to 2 or more RF assays	Role of *P.gingivalis*	Immunity to *P. gingivalis* is significantly associated with the presence of RA-related autoantibodies in individuals at risk of RA.	Infection with *P. gingivalis* plays a central role in the early loss of tolerance to self-antigens that occurs in the pathogenesis of RA.
3.	PubMed	[27]	Case-control clinical study 15 patients with PD; 6 healthy controls; 4 RA patients	Citrullination	Additional citrullinated proteins are formed in periodontitis, apparently similar to those formed in RA-affected synovial tissue.	Periodontitis-induced citrullination may play a role in the etiology of RA.
4.	PubMed	[28]	Case-control clinical study 40 RA patients;40 healthy controls	Dysregulation of the inflammatory response	There was a high prevalence of mild to moderate periodontitis in the RA patients' group, and statistically significant differences were present in the periodontal parameters of the RA group compared to the non-RA group.	An association exists between PD and an underlying dysregulation of the molecular pathways in the inflammatory response.
5.	PubMed	[29]	Case-control clinical study 31 patients with new-onset RA; 34 chronic RA patients; 18 healthy controls	Role of *P.gingivalis*	Patients with new-onset RA exhibited a high prevalence of PD at disease onset, and their subgingival microbiota was similar to that in patients with chronic RA and healthy subjects whose PD was of comparable severity.	PD may represent a risk factor for RA development independent of smoking status. *P. gingivalis* may serve as a shared causal pathway in some cases of RA.
6.	Google Scholar	[30]	Cross-sectional clinical, microbiological, and serological study 95 RA patients; 44 non-RA controls; 36 healthy controls	Citrullination	A higher prevalence of severe periodontitis was observed in RA patients in comparison to matched non-RA controls. Higher antibody titers against *P. gingivalis* in RA patients with severe periodontitis compared to severe periodontitis patients without RA.	The severity of periodontitis is related to the severity of RA Higher antibody titers may be due to the hyperinflammatory state of RA patients with periodontitis and ACPAs directed to citrullinated peptides of *P. gingivalis.*
7.	Google Scholar	[31]	Case-control clinical study 53 RA patients; 53 non-RA volunteers	Effects of RA on periodontal parameters	RA patients had a higher percentage of bleeding on probing (BOP) and clinical attachment loss (CAL).	There are potential effects of RA on periodontal indices.
8.	PubMed	[32]	Case-control clinical study 65 RA patients; 65 healthy controls	Dysregulation of the inflammatory response	BOP, Plaque Index (PI), PPD, and alveolar bone loss are more severe in the RA group. Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) increased in severe periodontitis.	An association between RA and the severity of periodontitis is demonstrated in terms of bone loss.
9.	PubMed	[33]	Case-control study 16 RA patients; 14 Psoriatic arthritis (PsA) patients; 9 osteoarthritis patients (controls)	Presence of oral bacterial DNA in RA patients	Greater variety and concentrations of oral bacterial DNAs were found in synovial fluid compared to the serum of RA and PsA patients.	Synovial inflammation in RA and PsA may favor the trapping of oral bacterial DNAs, which suggests a perpetuating effect of oral pathogens in joint disease.
10.	PubMed	[34]	Case-control study 13779 newly diagnosed RA patients; 137790 healthy controls		There is a statistically significant association between a history of periodontitis and newly diagnosed RA.	There is an association between PD and RA; however, it is weak and limited to a lack of individual smoking status.

11.	PubMed	[35]	Cross-sectional study 852 PD patients; 668 healthy controls		In patients referred for periodontal treatment, the prevalence of RA in females and subjects over 50 years showed a significantly higher prevalence than their counterparts.	Individuals with moderate to severe PD are at higher risk of suffering from RA and vice versa.
12.	PubMed	[36]	Clinical study 66 RA patients	-	No patients were periodontally healthy. Twenty-four patients were classified as having periodontitis, 18 had moderate periodontitis, 23 had severe periodontitis, and one was toothless.	Most patients with RA in this study showed moderate-to-severe periodontitis and the presence of periodontal pathogens.
13.	PubMed	[37]	Serological study 80 RA patients; 44 PD patients; 82 healthy volunteers	PPAD and auto citrullination	Recombinant PPAD was a potent citrullinating enzyme. Antibodies to PPAD were elevated in the RA sera compared with controls.	The peptidyl citrulline-specific immune response to PPAD supports the hypothesis that it might break tolerance in RA.
14.	PubMed	[38]	Case-control clinical study 100 RA patients; 112 healthy volunteers	Genetic predisposition, the role of the periodontal pathogen, dysregulations of the host immunoinflammatory response	There was a statistically significant difference in periodontal parameters, ESR, and CRP levels between the RA and non-RA groups. The occurrence of periodontitis in the RA group is also higher, and RA subjects are three times more likely to have moderate to severe chronic periodontitis than non-RA subjects. However, among subjects with RA, there was no significant association between rheumatoid disease activity and the severity of PD.	The prevalence and severity of periodontitis are higher in RA patients. This may be due to common genetic predisposition, the role of the periodontal pathogen, as well as dysregulations of the host immunoinflammatory response.
15.	PubMed	[39]	Case-control study 39 RA patients; 36 healthy controls	Citrullination	Untreated periodontitis patients had higher anti-cyclic citrullinated peptide (CCP) antibody titers than healthy controls. Periodontitis patients who smoked demonstrated lower anti-*P. gingivalis*, but similar to anti-CCP in non-smoking periodontitis patients. There is a statistically significant reduction in anti-CCP titers following periodontal treatment.	Smoking and the presence of *P. gingivalis* may modulate anti-CCP circulating antibodies.
16.	Google Scholar	[40]	Case-control clinical study 17 RA patients; 30 healthy controls	Immunoregulatory imbalance (increased TNF-α)	Patients with high levels of time-averaged TNF-α from repeated plasma samples had a higher frequency of BOP as well as increased CAL and PD compared to those with low levels.	Gingivitis and periodontitis are related to high levels of circulating TNF-α in patients with RA.
17.	Google Scholar	[13]	Case-control clinical study 42 RA patients; 114 healthy controls	Presence of oral bacteria DNA in synovial fluid	In patients with RA, DNA of *P. gingivalis* was detected in both oral plaque and synovial fluid more often than in controls. Among the patients' group, the number of missing teeth was correlated with the number of joints with movement restrictions caused by RA.	DNA of periodontopathogens can be found in synovial fluid, and oral bacteria may play a role in the pathogenesis of arthritis.
18.	PubMed	[41]	196 RA patients		There is a high percentage of moderate and severe periodontitis in subjects. Higher age, male gender, previous or current smoking, and high level of plaque score were associated with severe PD.	There is a high prevalence of periodontitis in Thai patients with RA. However, there was no association between RA parameters and periodontal conditions.

					However, no differences in RA parameters were found between groups of patients who had moderate and severe periodontitis.	
19.	PubMed	[42]	Case-control clinical study 287 RA patients; 330 osteoarthritis patients as control	Role of *P.gingivalis*	The presence of PD was more common in patients with RA and patients with anti-citrullinated protein antibody (ACPA) positive. The presence of PD was associated with increased swollen joint counts and greater disease activity. Specific antibodies for ACPA were higher in patients with *P. gingivalis* and subgingival plaque.	PD and *P. gingivalis* appear to shape the autoreactivity of RA and the independent relationship between PD and RA.
20.	PubMed	[43]	Case-control study 16 PD patients; 15 non-PD controls; 1974 RA patients; 377 healthy controls	Genetic predisposition, Role of *P.gingivalis*	There was a significant association between anti-RgpB (*P. gingivalis* virulence factor) IgG and RA, which was even stronger than the association between smoking and RA. In ACPA-positive RA, there were interactions between anti-RgpB antibodies and both smoking and the HLA–DRB1 SE.	*P. gingivalis* is a credible candidate for triggering and/or driving autoimmunity and autoimmune disease in a subset of RA patients.
21.	PubMed	[44]	Case-control study 52 RA patients; 26 healthy controls	Role of PPAD in citrullination	The serum levels of anti-CCP IgG and anti-PPAD IgG were significantly higher in the RA group than in the non-RA group.	This suggests an association between anti-PPAD IgG and anti-CCP IgG responses, implicating a role for PPAD in protein citrullination in patients with RA and periodontitis.
22.	PubMed	[45]	Epidemiological cross-sectional study 22 early RA patients: 22 healthy controls		More advanced forms of periodontitis were found in ERA patients compared with controls, where they had a greater missing number of teeth, deeper periodontal pocket, and greater BOP. The characteristic pathogen in early RA is Tannerella forsythia subgingivally, while Streptococcus anginosus supragingivally.	There is an increased loss of periodontal attachment and alveolar bone loss in early RA patients, suggesting an association between RA and PD.
23.	Google Scholar	[46]	Case-control study 694 early RA patients; 79 healthy controls; 61 PD patients; 54 sicca patients	Role of *P.gingivalis*	Anti-*P.gingivalis* antibody titers did not significantly differ between early RA patients and healthy, sicca, or PD controls.	The results suggest that the association of periodontitis and RA could be linked to other bacterial species than *P. gingivalis* or a mechanism other than citrullination.
24.	PubMed	[47]	Case-control study 16 RA patients; 14 PD patients; 12 RA-PD patients, and 21 healthy controls	Dysregulation of the inflammatory response	There are statistically significant differences in serum MMP-9 between patient groups and control. Serum levels of MMP-9 were similar in RA and RA-PD-associated patients. Gingival crevicular fluid (GCF) recorded increased MMP-9 levels in RA-PD association subjects compared to PD.	MMP-9 may play a role in the pathogenesis of RA-CP association. Therefore, it is a sensitive tool in diagnosing and managing patients affected by PD and RA.
25.	PubMed	[48]	Case-control clinical study 287 RA patients; 330 osteoarthritis patients	Citrullination	ACPA-positive patients with RA had a significantly higher mean percentage of sites with alveolar bone loss compared with patients with OA. Alveolar bone loss was significantly associated with higher serum ACPA concentration.	Greater alveolar bone loss is associated with higher ACPA.

TABLE 2. STUDIES ON THE EFFECT OF DMARDS ON PERIODONTITIS.

No.	Source	Studies	Patients (Number)	Sex (M/F)	Age (Years, Mean±SD)	RA Duration (Years, Mean±SD)	Type of DMARDs	Effect on Periodontal Parameters
1.	PubMed	[49]	36	10/26	40.8 ± 12.3	-	Biologic (anti-TNF-α therapy)	Significant improvements in periodontal indices of inflammation, GI, and BOP. However, OHI and PD did not undergo significant changes
2.	EBSCO	[50]	13	5/8	52.38±7.92	8.38±8.27	Biologic (anti-TNF-α therapy)	There are no significant differences in periodontal parameters (GI, PD, and CAL) except for BOP when compared to the non-RA group
3.	Google Scholar	[51]	30	8/22	-	1.67±0.758	Synthetic (Methotrexate and sulfasalazine)	Statistically significant differences in periodontal parameters (PD, CAL, and PI) were observed in all groups
4.	PubMed	[52]	28	5/23	52±11	14.67±9.73	Biologic (anti-TNF-α therapy)	BOP decreased significantly, but not PD
5.	PubMed	[53]	10 (received infliximab) (RA+) 10 (without anti-TNF-α therapy) (RA-)	3/7 5/5	50.73 ± 9.1 47±16	16±13 5±2	Biologic (anti-TNF-α therapy) -	Patients with RA receiving anti-TNF-α medication had lower periodontal indices (GI, BOP, PD, and CAL)
6.	PubMed	[54]	41 (juvenile idiopathic arthritis) 17 take DMARDs	12/29	13.6±2.3	7.4±4	Biologic (anti-TNF-α therapy)	Children who take anti-TNFα had a lower frequency of sites with BOP compared to the 24 patients not taking anti-TNFα

The similarities in pathological and immunological characteristics between PD and RA are increased infiltration of inflammatory and immune cells, including neutrophils, monocytes, and T and B lymphocytes, increased release of pro-inflammatory mediators, such as the tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and matrix-degrading enzymes (MMPs, Cathepsin) [21]. There is also an increased activation of the receptor activator of the factor nuclear kappa B (NF-κB) ligand (RANK-L) pathway induced by soluble mediators released by immune cells, with subsequent osteoclast differentiation and maturation [22].

Our literature search found that there is a significant improvement in periodontal parameters in RA patients treated with biologic and synthetic DMARDs. This result is comparable with a study conducted by Kobayashi and colleagues, where it was found that there is a significant decrease in periodontal parameter measurements after treatment with biologic DMARDs. This might be related to the differences in serum protein profiles before and after the DMARDs therapy [23]. Systematic DMARDs may ameliorate PD burden in RA patients with periodontitis, where they can decrease gingival inflammation and periodontal destruction [23]. However, there is only one study that found that there is no statistically significant difference in the response to nonsurgical periodontal treatment in multiple conventional synthetic DMARDs therapies and the addition of NSAIDs and/or steroids to conventional synthetic DMARDs in the RA group [24].

IV. CONCLUSION AND LIMITATIONS

The associated factors for RA and PD relationship include genetic predisposition, immunoregulatory imbalance, and the role of *P. gingivalis* as a key pathogen involved in the citrullination process as a risk factor of RA. Significant improvement was also found in periodontal parameters in RA patients treated with biologic and synthetic DMARDs. A similar study can be conducted with a larger sample size in the future to obtain more convincing findings.

This review was performed in a limited period due to time constraints. A comparison of the study findings was done on a specific area or topic in the related articles. A larger number of articles can be reviewed in a longer stipulated time and may yield better results or more conclusive findings.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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