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Association of Rheumatoid Arthritis with Dental Health - A Mini Review

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ABSTRACT

Autoimmune disorders represent a cluster of diseases related to dysregulation of the immune system or misrecognition of self from non-self. Rheumatoid arthritis (RA) is a chronic inflammatory condition involving the joints. It is one of the most common forms of inflammatory arthritis reported globally. The incidence rate of RA is found to be the highest among middle-aged women. There happens to be a close relationship between RA and dental health. The inflammatory processes triggered by microbes and other endogenous factors affects the bone health resulting in the resorption of bones. This condition is observed in aggressive and chronic periodontitis. The main objective of the present literature review was to evaluate the association of rheumatoid arthritis with dental health such as gingivitis, tooth loss and periodontitis. Furthermore, the present literature review throws light on the common markers which might be associated with both the disease conditions. The current review identified novel markers that were associated with rheumatoid arthritis which were implicated in dental health also. Hence management of rheumatoid arthritis might as well reduce the damage caused by bone resorption and could aid in the prevention of premature tooth loss.

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INTRODUCTION

Autoimmune disorders are a form of disease wherein the self molecules of the system are recognized as non-self, eventually leading to the destruction of tissues. The inflammatory process is considered to be a "double-edged" sword (Lin and Kazmierczak, 2017). Although a protective mechanism against invading microbes, at times a chronic exposure to a pool of inflammatory molecules causes severe damage to the tissues. Rheumatoid arthritis (RA) is one such autoimmune disease characterised by systemic inflammation, persistent synovitis and development of autoantibodies. Genetic factors play a very important role in the aetiology of RA, along with other factors, including smoking. The prevalence of RA is found to be in the range of 0.5 - 1% with an occurrence more common in women. RA can damage joints causing life-long disability and is responsible for aggravating several other co-morbid conditions (Scott *et al.*, 2010).

Effect of rheumatoid arthritis in dental health

Periodontitis is a common disorder experienced by tissue damage due to failure of the immune system to control infectious microbial pathogens and immune response associated with it. Periodontal pathogens such as *Aggregatibacter actinomycetem-*

comitans and *Porphyromonas gingivalis* contributes to the production of RA related antibodies by either directing the post-translational modification of proteins or neo-epitope generation mediated by neutrophils. The invasion of oral pathogens into the blood might also result in chronic inflammatory responses triggering the production of auto antibodies (Cheng *et al.*, 2017; Eriksson *et al.*, 2019). A study conducted by recruiting Danish patients with RA reported a significant proportion of them suffering from periodontal or gingival diseases (Radwan-Oczko *et al.*, 2019). Another study has pointed out the fact that patients with RA more often exhibit the symptoms of periodontitis than patients without RA. The study demonstrated that RA groups were more affected with moderate to severe forms of caries than the control group. The Decayed, Missing and Filled Teeth (DMFT) index was higher in the RA patients indicating the need for dental attention and prompt treatment. In addition, the count of *Streptococcus mutans*, the organism commonly associated with dental caries was significantly more in the RA group (Martinez-Martinez *et al.*, 2019; Ceccarelli *et al.*, 2019). Hence, these reports justify the role of rheumatologist and dentists in management of the disease.

Common biological markers associated with both rheumatoid arthritis and periodontitis

The process of NETosis has been implicated in various autoimmune diseases. Deployment of neutrophils to the site of injury or infection is considered to be the first line of defence for containment of infections by microbial pathogens. The process of NETosis results in the formation of neutrophil extracellular traps (NETs), which includes enzymes and decondensed chromatin embedded with granular material extruded from the neutrophils. Citrullinated histone proteins along with primary and secondary granules such as myeloperoxidase, elastase, gelatinase, proteinase 3, peptidoglycan binding proteins, cathepsin G, lactoferritin are a few components of the NET milieu proven to possess antibacterial activity. The bio-mesh entrap microbes, eventually leading to the clearance of pathogens from the system. Reports on the association of NETosis with autoimmune diseases (Frangou *et al.*, 2019) and other non-communicable (Jayaseelan and Paramasivam, 2020) diseases are well documented. Citrullinated histones were found in the periodontal tissues of patients with RA and periodontitis. A study reported the highest frequency of NETosis associated proteins PAD4 (peptidylarginine deiminases) in 93%, CD68 (cluster of differentiation 68) is 87% and citrullinated histone H3 in 60% of patients. Furthermore, anti-citrullinated H3 antibodies auto antibodies were also identified in about 39% of RA patients with periodontitis (Janssen *et al.*, 2017).

Microbial factors have also shown a significant association with both diseases. A study conducted by Bello-Gualtero and colleagues analyzed several bio markers related to the process of inflammation viz., CRP (C-reactive protein), rheumatoid factor, ESR (erythrocyte sedimentation rate), ACAs (anticitrullinated antibodies). Individuals with pre-RA conditions presented with greater levels of plaque index, bleeding on probing and severity of the periodontal disease. The pre-RA individuals had a significant measure of bio markers when compared to those with early RA. Interestingly, the IgG2 antibody was found to be specific for *P.gingivalis* (Bello-Gualtero *et al.*, 2016). Another study reports the bio markers in serum and saliva of RA patients with periodontal problems. Chronic RA patients showed an elevated concentration of MMP-8 (matrix metalloproteinases 8) and IL-6 (Interleukin-6) which is considered to be the reflection of joint inflammation, whilst early RA patients showed elevated concentrations of MMP-8 in saliva (Äyräväinen *et al.*, 2018). A very recent study identified the glutaminyl cyclases (QC and is QC) from human and bacterial sources (*P.gingivalis*). Human QC, ISOQC and PgQC were found to regulate inflammatory responses. The expression of QC, ISOQC and PgQC was measured in patients with chronic periodontitis (CP) and RA. The QC protein was found to be significantly increased in peripheral blood and GCF (gingival crevicular fluid) in CP patients when compared to controls (Bender *et al.*, 2019).

Apart from the common biochemical markers, genetic polymorphisms common for both RA and periodontitis were also assessed. Schulz and team studied the impact of genetic polymorphisms in 13 anti and pro-inflammatory cytokines using sequence-specific PCR. Several markers showed independent as well as combined associations with both the diseases. The G allele of *rs1801275* of *IL4R-alpha* gene and the G allele of *rs361525* of *TNF-alpha* gene was found to be RA associated risk factors. On the other hand, the A allele *rs2430561* of *IFN-gamma* produced significant association with periodontitis in RA patients. A binary logistic regression analysis confirmed *rs2430561* as an independent risk factor for both RA and periodontitis (Schulz *et al.*, 2019).

Treatment and management of RA and periodontitis

Several pharmacological interventions have been used in the treatment of RA. Glucocorticoids, non-steroidal anti-inflammatory drugs, disease-

modifying anti-rheumatic drugs (DMARDs), TNF-alpha inhibitors, Interleukin — 1 beta and interleukin one receptor antagonist, Janus Kinase inhibitors are the commonly prescribed medications for RA. These drugs are found to ameliorate the symptoms by reducing inflammation and progression of the disease, thereby improving the quality of life. Continuous usage of anti-inflammatory drugs and glucocorticoids leads to immunosuppression. This condition has been found to be associated with various changes in the oral cavity leading to candidiasis, xerostomia etc., Despite the fact that studies have demonstrated both beneficial and worse outcomes of periodontitis treatment in RA patients, early diagnosis and prompt treatment of these diseases is sure to slow down the progression of the diseases (de Molon *et al.*, 2019). Researchers have identified phytocompounds which can be used in the treatment of inflammatory conditions (Aafreen *et al.*, 2019). The formulations incorporating herbal components have also been tested against oral pathogens which are involved in caries and deep-seated lesions (Shahana and Muralidharan, 2016; Vaishali and Geetha, 2018)

Intracanal medicaments and herbal mouthwashes have been recently tested to prove their efficacy towards potential dental pathogens (Marickar *et al.*, 2014; Selvakumar and Muralidharan, 2017). Several in silico approaches have been developed to effectively manage PD (Ushanthika *et al.*, 2019; Sivakumar *et al.*, 2020). Since the process of vaccination involves the activation of the immune system, any adverse reactions associated with the process should be addressed if the individual is diagnosed with autoimmune disease state (Pratha and Geetha, 2017). Moreover, eradication of emerging pathogens of the oral cavity (Ashwin and Muralidharan, 2015; Girija *et al.*, 2019) and drug-resistant organisms (Smiline *et al.*, 2018; Priyadharsini *et al.*, 2018b) might also help in alleviating the disease. The eradication of fungal pathogens in the oral cavity is also required to reduce the inflammation (Shahzan *et al.*, 2019). Early diagnosis of co-morbid conditions such as metabolic disorders, hypertension could also have a great impact in modifying the disease state (Priyadharsini *et al.*, 2018a). Hence, Management of chronic metabolic disorders such as diabetes, hypertension, etc., could also reduce the incidence of autoimmune conditions (Paramasivam *et al.*, 2020). The treatment of periodontitis is usually carried out by the mechanical debridement of plaque, which is the microbial biofilm accumulated at the site of infection. The treatment modality used not only helps in reducing the inflammation but also maintains the host-microbe homeostasis. Clinical and experimental studies have proved that the treatment process had reduced potential bio markers such as MMP-8, Il-6, etc., in RA patients.

CONCLUSION

The present mini-review throws light on the vital roles to be played by rheumatologist and dentist in controlling the autoimmune conditions. More research into these converging fields of medicine and dentistry would benefit patients to lead a healthy lifestyle. Focusing on the early diagnosis of RA with the signs and symptoms associated with dental disorders is sure to reduce the pain and progression of such debilitating diseases. Lifestyle modifications are also suggested to avoid the exposure of tissues to chronic inflammatory markers.

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