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PERIODONTITIS AS A RISK FACTOR FOR RHEUMATOID ARTHRITIS: APPLYING BRADFORD HILLS CRITERIA OF ASSOCIATION

Dr. Ritu Phogat*, Dr. Manjunath B. C., Dr. Mamta Rani, Dr. Kiran B., Dr. Manoj Yadav and Dr. Deepak Sindhu

Postgraduate Institute of Dental Science, Rohtak, Haryana.

***Corresponding Author: Dr. Ritu Phogat**

Postgraduate Institute of Dental Science, Rohtak, Haryana.

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ABSTRACT

Rheumatoid arthritis (RA) is a clinical condition occurs as a result of development of disease-related autoantibodies and joint symptoms and signs, which may be considered nonspecific or unclassified for RA. This condition includes the interaction between many genetic and environmental risk factors. Recently there are emerging evidences that periodontitis is potential risk factor for rheumatoid arthritis. But it is difficult to assign any particular condition as a risk factor for RA particularly for periodontitis due to its bidirectional nature of relationship. For that we have Bradford Hill nine criteria have to help determine if observed epidemiologic associations are causal. Here we are exploring the periodontitis as a risk factor for rheumatoid arthritis based on these hill's criteria's. Identifying and modifying risk factors such as periodontitis will be useful in preventing RA in susceptible population.

KEYWORDS: Rheumatoid Arthritis, Periodontitis, Causation, Causal Inference, Bradford Hill.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease shows chronic inflammation characterised by synovitis of the joints, which may lead to cartilage and bone destruction and eventually disabilities.[1] It is a systemic heterogeneous disease with various clinical manifestations and comorbidities. The prevalence of Rheumatoid arthritis is estimated to be approximately nearly 1 per cent in the world.[2] Both genetic and environmental risk factors play a role in the aetiology of this complex disease. One of the environmental factors that have been suspected for decades to be linked to RA is periodontitis.[3] Many clinical and experimental studies have reported an association between RA disease and various degree of periodontitis.[4]

Periodontitis is a common disease worldwide that has a primary bacterial etiology and is characterized by dys-regulation of the host inflammatory response which eventually results in soft and hard tissue destruction. Prevalence of chronic periodontitis ranging from a high of 99 per cent to a low of 7 per cent depending upon threshold chosen.[5] In periodontitis the inflammation is initiated and perpetuated by a subset of bacteria, including *P.gingivalis*, which colonize the gingival sulcus, proliferate in sub gingival plaque & invade periodontal tissue apparatus. It has been noted that periodontal pathogens like *Porphyromonas gingivalis* are able to invade gingival tissues, and from there, are able to gain access to the systemic circulation.[6] These host–bacterial interactions produce a resultant impact on various systems in the human body.[7]

Many studies done recently are presenting conflicting results regarding the relationship between periodontitis and RA. However, a significant association between these two common chronic diseases has been reported recently. Hence, we performed this review to provide information about strength of association and causation regarding periodontal diseases with rheumatoid arthritis.
The listed aspects of association that Hill described in his address have been used to evaluate numerous hypothesized relationships between exposures and disease outcomes. These are.

1. **Temporal relation:** The cause (periodontitis) precede the effect (rheumatoid arthritis) (essential).
2. Biological Plausibility of having rheumatoid arthritis in periodontitis patients (mechanism of action; evidence from experimental animals).
3. Consistency: Similar results been shown in other studies.
4. **Strength:** The strength of the association between the periodontitis and rheumatoid arthritis (relative risk or odds ratio).
5. Dose-response relationship among the severity of periodontitis and rheumatoid arthritis.
6. **Reversibility:** The removal of a periodontitis lead to the reduction of rheumatoid arthritis risk?.

Evidence of Temporality of association between Rheumatoid arthritis and Periodontitis: Temporality is important criterion which epidemiologists suggest and universally agree is essential to causal inference. Hill explained that for an exposure-disease relationship to be causal, exposure must precede the onset of disease. In our case periodontitis must develop before development of rheumatoid arthritis. Thus, study designs which ensure a temporal progression between the two measures are more convincing in association of periodontitis and Rheumatoid arthritis.

Juan M Bello-Gualtero (2016)[8] found out that individuals with pre-RA have significant inflammatory periodontal involvement that established rheumatoid arthritis. There was a significant association between IgG against P. gingivalis and ACPAs in pre-RA and markers of RA activity in individuals with established RA. Leena Äyräväinen(2017)[9] concluded that Patients with Early Rheumatoid Arthritis and Chronic RA presented with poorer periodontal health parameters when compared with controls in Finnish populations.

Evidence of Biological Plausibility between Rheumatoid arthritis and Periodontitis: Biological plausibility represented fundamental concepts implies that epidemiology and biology must interact and reach on common conclusion.[5] Biological plausibility has been considered based on the presence of biological or social models that explain the association of interest in our case *P. gingivalis* is the key organism which explains the connection between the periodontitis and rheumatoid arthritis. Hill's criterion of plausibility is satisfied if the relationship is consistent with the current body of knowledge regarding the aetiology and mechanism of rheumatoid arthritis. In present era of technology there are plenty of evidence which supports the biological plausibility between the periodontitis and rheumatoid arthritis.

Linda Johansson (2016)[10] investigated anti-*P. gingivalis* antibodies pre-date symptom onset and ACPA production by applying case control study design and they found out that ACPA precede RA onset by years, and that anti-*P. gingivalis* antibody levels are elevated in RA patient. Anti-*P. gingivalis* antibody concentrations were significantly increased in RA patients compared with controls, and were detectable years before onset of symptoms of RA, supporting an aetiological role for *P. gingivalis* in the development of RA. Jan Schmickler (2015)[11] concluded that a trend for higher *F. nucleatum* and *P. gingivalis* concentrations in aCCP-positive patients with RA was found.

Evidence on Consistency of positive association of rheumatoid arthritis and periodontitis: Hill's *consistency* criterion is upheld when multiple epidemiologic studies designs using a variety of locations, populations, and methods show a consistent association between two variables with respect to the null hypothesis. Hill stressed the importance of repetitive findings because a single study, no matter how statistically sound, cannot be relied upon to prove causation due to ever-present threats to internal validity. This criterion is still very appropriate for determining causal relationships; however, data integration practices have led to an evolution in thought on what constitutes consistency.

Common and severe in patients with RA compared to patients with OA. Safa k (2011)[14] evaluated the periodontal status of rheumatoid arthritis patients in khartoum state.The results showed statistically significant relationship between periodontal disease and Rheumatoid Arthritis does exist. Ryan T. Demmer (2013)[15] studied the periodontal Disease, Tooth Loss and Incident Rheumatoid Arthritis: Results from the First National Health and Nutrition Examination Survey and its Epidemiologic Follow-up. The participants with periodontal disease or≥5 missing teeth experienced higher odds of prevalent/incident RA. Silvestre-Rangil (2016)[16] evaluate the main oral manifestations of patients with rheumatoid arthritis (RA), particularly salivary flow, and of its possible association to periodontal disease. The patients with RA had greater periodontal pocket depths (with moderate depths in most cases), as well as greater attachment loss and more bacterial plaque.

Evidence of strength of the association between the Rheumatoid arthritis and periodontitis: Hill's first criterion for causation is *strength of the association*. As he explained, the larger an association between exposure and disease, the more likely it is to be causal. To illustrate this point, Hill provided the classic example of Percival Pott's examination of scrotal cancer incidence in chimney sweeps. The tremendous strength of association between that occupation and disease—nearly 200 times greater than seen in other occupations—led to a determination that the chimney soot was likely a causal factor. Contrarily, Hill suggested that small associations could more conceivably be attributed to other underlying contributors (i.e. bias or confounding) and, therefore, are less indicative of causation.

Rosamma Joseph (2013)[17] evaluated the association between chronic periodontitis and rheumatoid arthritis in a hospital-based case–control study. The relative odds ratio for moderate to severe periodontitis was found to be 3.055. This indicates that RA subjects are three times more likely to have moderate to severe chronic periodontitis than non-RA subjects. The occurrence and severity of periodontitis was found to be higher in RA subjects as compared to subjects without RA, suggesting a positive relation between these two chronic inflammatory diseases.

Evidence on reversibility of association of Rheumatoid arthritis and Periodontitis: Al-Katma MK (2007)[18] studied if eliminating periodontal infection

and gingival inflammation affects the severity of active rheumatoid arthritis (RA) in patients with chronic inflammatory periodontal disease. There was a statistically significant difference in DAS28 (4.3 +/- 1.6 vs. 5.1 +/- 1.2) and erythrocyte sedimentation rate (31.4 +/- 24.3 vs. 42.7 +/- 22) between the treatment and the control group. Ortiz P (2009)[19] examine the effect of non-surgical periodontal treatment on the signs and symptoms of RA in patients. He found out that non-surgical periodontal therapy had a beneficial effect on the signs and symptoms of RA, regardless of the medications used to treat this condition.

CONCLUSION

Regrettably, there are no completely reliable criteria for determining whether an association is causal or not. Causal inference is usually tentative and judgements must be made on the basis of the available evidence: uncertainty always remains. Evidence is often conflicting and due weight must be given to the different types when decisions are made. In judging the different aspects of causation referred to above, the correct temporal relationship is essential; once that has been established; the greatest weight may be given to plausibility, consistency and the dose–response relationship. The likelihood of a causal association is heightened when many different types of evidence lead to the same conclusion. Evidence from well-designed studies is particularly important, especially if they are conducted in a variety of locations. When the causal pathways are established on the basis of quantitative information from epidemiological studies, the decisions about prevention may be uncontroversial. In situations where the causation is not so well established, but the impacts have great potential public health importance, the “precautionary principle” may be applied to take preventive action as a safety measure; this is called “precautionary prevention”.

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