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Rheumatoid Arthritis And Periodontitis

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Abstract

The relationship between periodontitis and other chronic inflammatory destructive diseases such as rheumatoid arthritis has been discussed since long. Inspite of having different etiologies, similar mechanisms of tissue destructions have been seen in both.

Purpose- The purpose of this study was to evaluate the possible interrelationship between rheumatoid arthritis and periodontitis on the basis of information available for the same.

Materials and Methods- A medline and manual search was conducted to identify studies concerned with etiopathogenesis of rheumatoid arthritis, periodontitis or interrelationships between the two.

Results- The studies shows that two diseases could be very closely related through common underlying dysfunction of fundamental inflammatory mechanisms. A common nucleus of activity in their pathogeneses provides novel paradigms of therapeutic targeting for reciprocal benefit.

Key Words

Rheumatoid arthritis, periodontitis, inflammation, therapy.

Introduction

Over the past 10 years, several studies have been published pointing towards an association between periodontal diseases and various systemic disorders or diseases. Of these the possible associations between rheumatoid arthritis and periodontitis have been discussed. To date only few studies have examined the extent of association between Rheumatoid arthritis and periodontal disease and results have been conflicting. There is a unidentified disablement or dysregulation of common pathologic mechanisms operating in these two chronic inflammatory diseases.

Rheumatoid arthritis is a chronic multisystem disease of unknown cause. Although there are a variety of systemic manifestations, the characteristic feature of rheumatoid arthritis is persistent inflammatory synovitis usually involving peripheral joints in a symmetric distribution.[1]

Rheumatoid arthritis was first described clinically in an 1800 doctoral thesis by Landre - Beaurais, a French medical student who called it the "Primary aesthetic Gout." Later in 1859 Sir Alfred Garred established the distinction between rheumatoid arthritis and gout and he called the condition as rheumatoid arthritis.[2]

Periodontal disease is an all encompassing term relating to the destructive inflammatory disorders of the hard and soft tissues surrounding teeth. It is associated with bacteria predominantly gram negative facultative anaerobes present on a biofilm on tooth surface. The periodontal diseases range from the relatively benign form of gingivitis to aggressive periodontitis. Many of these conditions are not only a threat to the dentition, but may also be a threat to general health. There are reports suggesting increased prevalence of diabetes, atherosclerosis, myocardial infarction, and stroke in patients with periodontal disease.[3], [4], [5] Thus, the likelihood of periodontal disease being associated with systemic diseases is becoming established fact.

In addition, a number of other chronic conditions of altered connective tissue metabolism, hormone imbalances and altered immune function have like-wise been associated with increased risk of periodontal disease.[6] Of these, rheumatoid arthritis is of particular interest since it is a chronic inflammatory disease which demonstrates remarkably similar pattern of soft and hard tissue destruction to that noted in chronic periodontitis.[7] Although the etiologies of these diseases are distinctly separate, the underlying pathological process has sufficient similarity and warrant consideration of the hypothesis that individuals at risk of developing rheumatoid arthritis may also be at risk of developing periodontitis and vice - versa.

Materials And Methods

A medline and manual search was conducted to identify studies concerned with etiopathogenesis of rheumatoid arthritis, periodontitis or interrelationships between the two. The following search terms were used: 'rheumatoid arthritis', 'periodontitis' and 'rheumatoid arthritis and periodontitis' In addition, a manual search of the following journals was performed: Journal of American dental association, Arthritis and rheumatism, Journal of associations of physicians of India, Journal of rheumatology, British journal of rheumatology, Australian dental journal, American society of microbiology, Community Dentistry and Oral Epidemiology, Journal of clinical immunology. A further manual search was conducted through the bibliographies of all relevant papers and review articles.

Possible Associations Between Rheumatoid Arthritis And Periodontitis

Disease Progression

Three distinct subpopulations in periodontal disease progression can be seen: 1) no progression of periodontal disease, in which around 10% of the population manifest very little or no disease which is of no particular consequence to the dentition; 2) moderate progression, affecting around 80% of the population and representing a

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very slowly progressing form of disease that generally can be easily managed via routine therapies; and 3) rapid progression, affecting approximately 8% of individuals whereby extensive periodontal destruction occurs which can be very difficult to control.[8]

Similarly atleast three types of disease manifestation can be observed in RA populations: 1) self-limited: in these cases individuals originally presenting for RA have no evidence of disease 3 to 5 years later; [9] 2) easily controlled: the disease is relatively easily controlled with only Nonsteroidal anti-inflammatory drugs (NSAIDs); [10] 3) progressive: these patients generally require second-line drugs, which often still do not fully control the disease.[10],[11]

Can Bacteria Be A Common Etiologic Link Between Periodontitis And Rheumatoid Arthritis?

There are a number of shared features between microorganisms that can induce RA in a genetically susceptible host and the recognized periodontal pathogens. Nonetheless, RA is still not largely recognized as a disease resulting solely from bacterial challenge. On the other hand, technological and conceptual advances have permitted the identification of bacteria or groups of bacteria associated with specific periodontal diseases.[12] Close inspection of the virulence factors of periodontal pathogens would suggest that such a response could be feasible. Thus, the possibility that ongoing periodontitis could trigger RA in genetically susceptible individuals is plausible. Notwithstanding the above, these concepts remain speculative until the causative agent for RA can be definitively identified. It is important to recognize that, based on current information, it cannot be proposed that periodontal pathogens cause, or are associated with, RA. The main focus of attention is directed not towards causality but rather associations between two chronic inflammatory conditions that may have common underlying pathogenic mechanisms.

Clinical Features Of Rheumatoid Arthritis And Periodontitis

Pain, swelling and deformity of joints are the prominent features of RA. The most common joints affected include the joints of the hands, wrist and feet. Other organ systems can also be affected as a result of microvessel vasculitis leading to the formation of nodules, pleural effusions, pulmonary fibrosis, cardiac disease and ocular disease.[13] As a response to inflammation, muscles and tendons around an inflamed joint may shorten and undergo spasms. In the severe stages of the disease, synovitis and pannus denude the surface of cartilage and erode juxta-articular bone, creating incompatible articular surfaces. With the complete disappearance of cartilage, the opposing bone surfaces may fuse when immobilized.[14]

The periodontal tissues in health exist in steady-state equilibrium of tissue degradation and repair. With constant mechanical and chemical assaults, the periodontium for the most part manages to maintain its structural and functional integrity. However, if the balance between host response and bacterial virulence is disturbed, disease and consequent tissue destruction will occur.[15] With developing inflammation; there is a marked accumulation of lymphocytes and monocytes within the connective tissue resulting in tissue swelling and matrix degradation.

In contrast to RA, the development of periodontitis is not associated with pain. The clinical consequences of periodontal tissue destruction are gingival bleeding on probing, increased pocket probing depth due to apical migration of the junctional epithelium, periodontal bone loss and increased tooth mobility and ultimately, tooth loss if, disease activity continues.[16]

Immunogenetics

In humans, many of the genes that regulate monocytic cytokine responses have been mapped to the HLA-DR region of chromosome 5 in the area of the TNF-β genes.[17],[18] Both RA and progressive periodontitis are found to be associated with this HLA complex[19],[20], which suggests a genetic basis for the observed monocyte trait, linking RA, progressive periodontitis and other systemic diseases. It is reasonable to suggest that the inter-individual differences in the severity of RA and periodontal disease are partly due to intrinsic differences in the monocyte/T cell response traits. In both diseases, antigenic challenge (e.g. LPS) to the monocytic/lymphocytic axis would result in the secretion of catabolic cytokines and inflammatory mediators, of which PGE2, IL-1, TNF-a and IL-6 would appear to dominate

Mechanisms Of Tissue Destruction

In both RA and periodontitis, tissue destruction is not unidirectional, but an iterative process that is constantly being adjusted by the host response to inciting agents. The destruction of extracellular matrix in both diseases is determined by the balance of MMPs and their inhibitors. Bone destruction in periodontitis and RA is a result of the uncoupling of the normally coupled processes of bone resorption and bone formation, with PGE2, IL-1, and TNF-α, IL-6 as mediators of bone destruction. It is evident in both diseases that the host's immune response is controlled by genes that regulate differences in the monocyte/T cell response traits to different antigens that determine both the nature of the protective antibody response and the magnitude of tissue-destructive inflammatory response.

Osteoclast Activation and Vascular Damage

Most recently, studies have begun to investigate the co distribution of cytokines involved in vascular damage and bone resorption in biopsies from graded rheumatoid arthritis and periodontitis lesions. Since the tumor necrosis factor (TNF)-like molecules and their receptors have been shown to be involved in both processes, studies are based on receptor activator of nFkappa B ligand (RANKL), osteopretogerin (OPG), and TNF-related apoptosis inducing ligand (TRAIL) to determine at least one molecular mechanism common to both conditions.

The cell surface TNF-like molecule, RANKL and its receptor, RANK have been shown to be key factors regulating osteoclast formation and activation.[21],[22] It has been shown that when RANKL binds to RANK on the surface of osteoclast precursors, these cells differentiate to form mature osteoclasts. It is now clear that RANKL, together with macrophage-colony stimulating factor (M-CSF), is required for osteoclast formation. The soluble TNF "receptor-like" molecule, OPG, is a natural inhibitor of RANKL.[23] OPG binds to RANKL and prevents its ligation to RANK. The importance of these molecules in regulating bone metabolism has been demonstrated by transgenic and gene knock-out studies in mice.[24] Since these factors control physiologic osteoclast formation, it is reasonable to

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propose that they may also be key regulators of pathological bone resorption.[25],[26] Although RANKL is normally provided by osteoblast-like cells in bone,[26],[27] there are reports suggesting that lymphocytes present in rheumatoid tissues may be the main source of RANKL in inflammatory arthritis.[28] Furthermore, CD3+ T cells from the human rheumatoid joint express RANKL and can promote osteoclasts formation from rodent spleen precursors. In addition to lymphocyte production of RANKL, inhibition of RANKL by OPG treatment in vivo reduces both bone and cartilage destruction in a model of adjuvant arthritis.[29]

Under certain conditions, human osteoclasts are derived from osteoclast precursor cells present in or near to the tissues of arthritic joints.[30],[31] More recent reports in humans[32],[33] and animals[29] show that RANK/RANKL interactions may be required for osteoclasts formation and bone resorption in the RA joint. Accordingly, it has been recently demonstrated that OPG and RANKL are expressed in biopsies of inflamed rheumatoid synovium and periodontitis lesions.[34] In addition, it has been found that another ligand for OPG, TRAIL, is expressed in the both types of tissue (although not from the same patient). In these studies, it is noted that OPG decreases with inflammation, RANKL increases with inflammation, and TRAIL increases with inflammation. These findings may be of considerable significance in light of OPG's ability to block the activity of TRAIL (and vice versa) and TRAIL's anti-inflammatory properties.[35]

The production of OPG by endothelial cells may be significant for reasons other than its effects on bone metabolism, and there is now evidence to suggest that OPG might also regulate endothelial cell function. OPG has been reported to be required for endothelial cell survival and growth.[36] In addition, OPG knock-out mice have been shown to develop arterial calcification[37],[38] as well as severe osteoporosis, suggesting that vascular endothelial expression of OPG may have a role in vascular homeostasis.[29] One of the most unexpected findings from recent studies of diseased periodontal and synovial tissues was the observation that endothelial cells produce large amounts of OPG.

In response to proinflammatory cytokines TNF-α and IL-1β, OPG mRNA expression was dramatically enhanced, resulting in secretion of newly synthesized OPG and a reduction in cell-associated OPG. Vascular damage due to apoptosis is thought to precede vascular calcification[39] and contribute to atherosclerosis.[40] In addition; diabetic endothelial cell dysfunction is associated with DNA damage induced by poly (ADPribose) polymerase activation. The exact cause of endothelial cell dysfunction is not known but it is possible that molecules such as TRAIL, expressed in nearby cells and tissues, may be important.[26],[41] Studies confirm that OPG binds to TRAIL, although with less affinity than RANKL, in vitro, and blocks its activity. The final piece of compelling evidence for the role of OPG in vascular damage comes from the fact that OPG knock-out mice develop vascular calcification. It is significant to note that calcification cannot be reversed by systemic treatment with recombinant OPG postpartum.[38] This supports the concept that OPG must be expressed within the endothelial cells, either in an appropriate form or associated with other molecules, and this only occurs following normal synthesis within the healthy endothelial cells.

In light of the above, it can be proposed that at least one underlying common molecular pathway in common between rheumatoid arthritis and periodontitis may lie within the RANK/OPG/TRAIL axis whereby OPG decreases leading to decreased vascular protection. In addition, with an increase in RANKL and TRAIL within the tissues, not only is vascular damage possible, but significant activation of osteoclasts may result.

The Dual Purpose Therapies Based On Possible Links Between Ra And Periodontitis

Tetracyclines And Its Analogues

The tetracyclines are a group of broad-spectrum antimicrobial agents. They are active against a number of gram-positive and gram-negative bacteria. In the 1980s, periodontal research revealed that tetracyclines also inhibited collagenase activity. Collagenases are a large family of enzymes that breakdown macromolecules in the connective tissue; they include matrix metalloproteinases (MMPs). Tetracyclines reduce the activity of MMPs by depriving them of divalent cations, which are cofactors necessary for their activity. They chelate these ions thereby reducing their protein degrading activity.[42] This action of tetracyclines is observed at sub antimicrobial doses.[43] Enhanced activity of the MMP has been demonstrated in synovial fluid and synovial fibroblasts of patients with rheumatoid arthritis and is partly responsible for joint destruction in these patients.[44] Tetracyclines by virtue of their anti-MMP activity are useful in patients with rheumatoid arthritis. Several clinical trials have shown that minocycline administration in patients with rheumatoid arthritis was associated with significant reduction in disease activity.[45]

Soft and hard tissue destruction in periodontitis is partly due to bacterial virulence factors/enzymes and partly due to MMPs.[46] Tetracyclines and their analogues have been shown to be useful in the treatment of patients with rapidly progressive and refractory periodontitis.[47] They act both by suppressing the growth of putative microorganisms implicated in periodontitis and by decreasing the destruction of collagen in gingival, periodontal ligament and alveolar bone by inhibiting MMPs in these patients.[46]

Nonsteroidal anti-inflammatory drugs (NSAIDs)

The principal mechanism by which NSAIDs act is by inhibition of cycloxygenase-the enzyme responsible for the biosynthesis of prostaglandins. Studies have shown that periodontally diseased tissues have higher prostaglandin levels, especially prostaglandin E2, than in healthy tissue.[48] In vivo studies have also shown that bone resorption in periodontitis is mediated in part by prostaglandins, showing that these may be important mediators of periodontal disease.[49] If prostaglandins are important mediators of bone resorption in periodontitis, the use of NSAIDs should be effective in preventing inflammation-induced bone loss. Both animal and human studies have demonstrated that inhibiting prostaglandin E2 synthesis with NSAIDs has been associated with unequivocal therapeutic efficacy in patients with periodontitis.[50]

NSAIDs find their chief clinical application as and-inflammatory agents in the treatment of rheumatoid arthritis to reduce pain and inflammation. It has been documented that certain NSAIDs can directly inhibit the activation and function of neutrophils.[51]They also

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inhibit TNF-α release from monocytes and non-killer (NK) cells.[52] These cycloxygenase independent effects may also contribute to the efficacy of NSAIDs in the treatment of rheumatoid arthritis.

Bisphosphonates

Osteoclasts are responsible for the absorption and removal of bone. Agents that affect osteoclast function may be effective in the treatment of periodontitis and rheumatoid arthritis. A class of drugs known as bisphosphonates inhibits osteoclasts. They are incorporated into the bone and incapacitate osteoclasts thereby inhibiting lysosomal enzyme transport and secretion by osteoclasts.[53] Focal bone damage and generalized bone loss are features of rheumatoid arthritis. Studies have shown that new-generation bisphosphonates, like zoledronic acid, reduced the development of new bony erosions in patients with rheumatoid arthritis suggesting a structural benefit with bisphosphonate therapy in these patients.[54]

Alveolar bone loss is an important complication of the inflammatory process in periodontitis. Markers of inflammation like TNF-α stimulate osteoclastic bone resorption in these patients. Bisphosphonate therapy is useful in them as they inhibit bone resorption and increase bone mass. Bisphosphonate treatment also improves the clinical outcome in patients with periodontitis and may be an important adjunctive treatment for periodontitis therapy for prevention of bone loss.[55]

Emerging Therapies

Ornidazole

A synthetic nitroimidazole with potent antiprotozoal and antibacterial activity. Ornidazole has good activity against most of the periodontopathic bacteria and is a commonly used drug for the treatment of periodontitis.[56] The usefulness of ornidazole has also been documented in patients with rheumatoid arthritis though its mechanism of action is not known. Ogrendik et al.[57] showed that the administration of ornidazole in patients with active rheumatoid arthritis was associated with a significant reduction in pain, duration of morning stiffness, erythrocyte sedimentation rate (ESR) and C-reaction protein levels. An overall reduction in disease activity was observed. Ornidazole was well tolerated in these patients at a dosage of 500-1000 mg/day with few adverse effects, such as headache, dry mouth, and nausea.

Chemically modified tetracyclines (CMTs)

These are the drugs that were developed to eliminate the antimicrobial properties of tetracyclines while retaining their non antimicrobial properties by modifying the tetracyclic naphthacene carboxamide ring of tetracyclins.[58] CMTs inhibit the synthesis of MMPs.[59] Non antibiotic analogues of doxycyclin (CMT-3) and minocyclin (CMT-8) have been shown to be potent inhibitors of osteoclastogenesis in vitro.[60] CMT-8 has also been shown to exert anti-inflammatory effects by inhibiting nitric oxide (NO) synthesis, and it can also modify cell viability by exerting a strong apoptotic activity.[61] Such CMTs may reduce tissue breakdown and bone resorption in rheumatoid arthritis and periodontitis and might emerge as future disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis.

Osteoprotegrin (OPG)

Recent evidence shows that the interaction between the receptor activation of nuclear factor kappa B ligand (RANKL) and its receptor activator (RANK) has an essential role in the activation of osteoclast and bone resorption.[62] OPG is a naturally occurring high affinity soluble decoy receptor for RANKL. It inhibits RANKL interaction with RANK thereby inhibiting osteoclast activation as a result of this interaction. RANKL appears to be the important pathogenetic principle that is responsible for the destruction of bone matrix in patients with both rheumatoid arthritis and periodontitis.[63] It has also been documented that OPG expression on synovial lining cells is deficient in patients with rheumatoid arthritis with active synovitis and in gingival cervical fluid in patients with periodontitis.[62], [64] In view of the ability of OPG to block RANK-RANKL interaction and osteoclast activation, it may have a therapeutic role in conditions where bone destruction is a major sequel of chronic inflammation such as rheumatoid arthritis and periodontitis.

Conjugated linoleic acid (CLA)

It has been found to be an important inhibitor of osteoclastogenesis. It acts by modulating the RANKL signalling pathway. CLA has also been shown to positively influence calcium and bone metabolism. Thus, it may have important therapeutic implications in the treatment of inflammatory diseases associated with bone destruction.[65]

Summary And Conclusion

There is no question that periodontitis and RA have many pathologic features in common. Emerging evidence suggests a strong relationship between the extent and severity of periodontal disease and RA. While this relationship is unlikely to be causal, it is clear that individuals with advanced RA are more likely to experience more significant periodontal problems compared to their non-RA counterparts, and vice versa. Hence, the possibility exists that both conditions result from a common underlying dysregulation of the host inflammatory response. The precise nature of this dysregulation remains to be established.

It must be recognized that periodontitis differs in one significant way from RA through our understanding that the subgingival biofilm is a key etiologic factor. Unlike periodontal disease, no specific bacterial etiology has been identified for RA. Thus, while host modification of disease processes is possible for periodontitis, controlling the bacteria that cause periodontal infections remains a significant focus for periodontal treatment and prevention. At best, host modification can be only an adjunct treatment for periodontitis. However, until an etiologic factor can be found for RA, host modification remains the mainstay of treatment.

There is accruing evidence to support the notion that both conditions manifest as a result of an imbalance between proinflammatory and anti-inflammatory cytokines. As a result, new treatment strategies will emerge for both diseases that may target the inhibition of proinflammatory cytokines and destructive proteases. Through a better understanding of these two common chronic inflammatory conditions, it is hoped that areas of similarity can be exploited to determine the true relationship between these diseases and common areas of treatment. Already, it can be predicted that the periodontal status of patients with RA should be carefully screened.

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