Chronic Inflammation; Periodontitis with rheumatoid Arthritis & atherosclerosis: When-Where-How?

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ABSTRACT:
There is increasing documentation of a link between inflammatory periodontal disease affecting the supporting structure of teeth, rheumatoid arthritis, and coronary artery disease. Periodontitis is initiated redominantly by Gram-negative bacteria and progresses as a consequence of the host inflammatory response to periodontal pathogens. Lipopolysaccharide, a cell wall constituent stimulates the production of inflammatory cytokines via the activation of signaling pathways perpetuating inflammatory pathogenesis in a cyclical manner in susceptible individuals; with an element of autoimmune stimulation, not dissimilar to the sequential events seen in RA. Periodontitis, also implicated as a risk factor for cardiovascular disease, promotes mechanisms for atherosclerosis by enhancing an imbalance in systemic inflammatory mediators; more direct mechanisms attributed to microbial products are also implicated in both RA and atherosclerosis. Severe periodontal disease characterized by clinical and radiographic parameters has been associated with ischemic stroke risk, significant levels of C-reactive protein and serum amyloid A, amongst others common to both periodontitis and atherosclerosis. Existing data supports the hypothesis that persistent localized infection in periodontitis may influence systemic levels of inflammatory markers and pose a risk for RA and atherosclerosis. A common nucleus of activity in their pathogeneses provides novel paradigms of therapeutic targeting for reciprocal benefit.

Key words: Chronic Inflammation, Periodontitis, RA

INTRODUCTION
There is growing awareness of the link between periodontal and systemic inflammatory conditions such as (RA) and coronary artery disease based on common etiopathogenic mechanisms. In addition to conventional risk factors for coronary artery disease, emerging risk factors include those associated with chronic inflammatory conditions with an element of autoimmunity in their pattern of progression, such as RA and periodontitis. The latter initiates the loss of supporting structures of the teeth and their eventual loss. These entities have implications in the progression of cardiovascular disease in response to an autoimmune trigger.
from RA.\textsuperscript{1-4} The risk of a cardiovascular event is significantly increased in RA patients regardless of traditional cardiovascular risk factors, with an emerging paradigm of a common inflammatory pathogenesis.\textsuperscript{1-3} This is also relevant to periodontitis which interestingly has links with increased risk of coronary artery disease independent of conventional risk factors\textsuperscript{6-8} and shows similar cytokine-mediated inflammatory pathology as RA.\textsuperscript{9-13}

RA, is characterized by chronic synovitis with the resultant damage to joint cartilage and bone which in turn is accompanied by joint pain and reduced mobility affecting 1\% of the adult population.\textsuperscript{14} Chronic periodontitis, initiated by bacterial plaque\textsuperscript{15} is prevalent in a third of the population beyond the age of 50 years and 10\%-15\% of all adults,\textsuperscript{16} being the main cause of tooth loss in adults. Chronic infection and persistent inflammation are likely to play an important role in the pathogenic progression of atherosclerosis and coronary artery disease.\textsuperscript{17} There is documented evidence of the link between periodontal disease, acute myocardial infarction;\textsuperscript{7,8} and between periodontitis and arthritis.\textsuperscript{18,20} In this context, the concept that RA patients with coronary artery disease will be affected by periodontitis to a greater extent than RA patients without coronary artery disease; and the corollary regarding inflammatory markers being more prevalent in RA patients with coronary artery disease and periodontitis than RA patients with coronary artery disease alone were investigated.\textsuperscript{21} This study showed that the levels of inflammatory mediators were significantly elevated especially in RA patients with coronary artery disease, who were also found to have periodontal disease, emphasizing the relevance of an inflammatory disease burden imposed on the host, which in this case is a central link between the three pathologies. Considering the documented literature in this context, the effective control of significant inflammatory loading from chronic periodontitis as a component of systemic inflammation, has an increasingly probable role in the armamentarium of reducing the risk of morbidity and mortality from systemic diseases. This is subject to the level of inflammation imposed by the periodontal condition, with variations based on disease aggression and its distribution in the mouth.\textsuperscript{10,22} Pathogenic mechanisms common to periodontitis, RA and atherosclerosis, and the potential for therapeutic targeting are discussed.

**Oxidative stress induced by cytokines in periodontitis, coronary artery disease and RA**

Periodontal disease has a multifactorial etiopathogenesis, affecting a large proportion of the adult population. Increased levels of C-reactive protein (CRP) and other markers of inflammation are identified. Raised levels of CRP reflect an increased risk of cardiovascular disease. Certain pathological features of atherogenesis are seen in RA, associated with macrophage-activating cytokines tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), the interleukins IL-1, IL-6, raised levels of the inflammatory marker (CRP) and the enhanced expression of endothelial adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1);\textsuperscript{23} which is also relevant to chronic periodontitis. There are deeper associations, cardiovascular deaths accounting for up to 50\% mortality in RA patients, reducing life expectancy by 15\%-20\%. A similar trend is reported for systemic lupus erythematosus (SLE) with a significant increase in stroke and myocardial infarction. Subclinical atherosclerosis associated with increased carotid artery intima thickening, indicative of endothelial dysfunction, is seen in SLE and RA, which is related to clinical and radiographic evidence of severe periodontal disease. Atherogenesis associated with inflammatory plaques susceptible to rupture and thrombosis arises from a lipid deposition disorder. TNF-\(\alpha\), high-sensitivity CRP (hs-CRP) and adipokines are relevant markers of inflammation associated with oxidative stress-induced dysregulation of inflammation and lipid metabolism.\textsuperscript{24} The association between obesity and changes in proinflammatory and immunomodulatory cytokines in pregnancy was investigated.\textsuperscript{25} A cross-sectional study was carried out using maternal serum in the early second trimester to examine inflammatory biomarkers in relation to maternal body mass index (BMI). Leptin and hs-CRP were shown to be significantly raised with increased BMI. It was concluded that maternal obesity in pregnancy was associated with changes in the expression of cytokines, protein hormones and acute phase proteins in the second trimester with increased leptin and hs-CRP associated with the increasing BMI category. The effect of a standardized oral lipid load on parameters of inflammation was investigated in a large sample of healthy adults.\textsuperscript{26} All patients underwent a measurement of BMI, blood glucose, blood pressure, total cholesterol, both
low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, triglycerides, soluble intercellular adhesion molecule-1 (sICAM-1), IL-6, CRP, soluble E-selectin (sE-selectin) and TNF-α. Oral lipid loading produced a complex and massive systemic inflammatory response. There were demonstrable increases in hs-CRP, sE-selectin, IL-6, and TNF-α even before a significant rise in triglyceride occurred. These findings could be extrapolated to metabolic diseases with dysregulation of lipid metabolism, also seen in periodontal patients with coexisting inflammatory diseases and therapeutic targets to combat oxidative stress. Immuno-inflammatory diseases are fuelled by cytokines and regulated by cytokine inhibitors. In order to determine the periodontal disease-specific characteristics in periodontal subjects, relative to patients with more generalized chronic inflammation, patients with juvenile idiopathic arthritis and RA were included to investigate whether peripheral blood monocyte gene expression of clinically important pro- and anti-inflammatory cytokines corresponded with plasma levels. This investigation demonstrated only limited differences in the expression of various cytokine and cytokine inhibitor genes in aggressive periodontitis and chronic arthritis compared with controls. There were some similarities among disease groups although no direct correlation between genetic expression and serum parameters. High levels of heat shock proteins (hsp) of 70 kDa associated with periodontal pathogens and periodontal disease progression, have been isolated in synovial tissue of RA patients. Constant production of inflammatory cells via their Fc receptors, leading to the production of anti-CCP antibody. These antibodies form immune complexes with citrullinated proteins, which can bind to inflammatory cells via their Fc receptors, leading to activation of the complement cascade. The resultant release of inflammatory mediators leads to joint destruction and consequent disability. There is progressive documentation of a link between RA and periodontal disease. Porphyromonas gingivalis (Pg) is a significant periodontal pathogen; it is the only bacterium known to possess a peptidyl arginine deiminase (PAD) which generates a citrullinated peptide by post-translational modification (citrullination) of protein bound arginine; the citrullinated peptide and anti-cyclic citrullinated peptide (anti-CCP) antibody are capable of breaking down self-tolerance and lead to the development of autoimmune RA. There is a significant rise in antibody titer to Pg in patients with RA and there is a significant correlation with anti-CCP antibody isotypes specific to RA. Deaminated forms of the alpha- and betachains of fibrin are major synovial targets of RA-specific anti-CCP antibodies. It has also been shown that PAD produced by Pg is able to deiminate arginine in fibrin found in the periodontal lesion. Citrullination of human leukocyte antigen (HLA) binding peptide causes a 100-fold increase in peptide - major histocompatibility complex (MHC) affinity and leads to CD4+T cell activation in the HLA DRB1 040 allele of transgenic mice. These findings are suggestive of a crucial role for Pg in the pathogenesis of RA associated with periodontitis. Constant production of PAD by Pg could result in citrullination of fibrin in the synovium; antigens presented in association with MHC molecules by antigen presenting cells leads to the production of anti-CCP antibody. These antibodies form immune complexes with citrullinated proteins, which can bind to inflammatory cells via their Fc receptors, leading to activation of the complement cascade. The resultant release of inflammatory mediators leads to joint destruction and consequent disability.
to joint destruction and RA. Uncontrolled periodontal disease could play a role in the development of RA via peptide citrullination involved in loss of self-tolerance and autoimmune destruction of synovial tissue. Osteoimmunology involving the interaction of the immune system with skeletal elements leads to the formation of osseous lesions. To investigate the contribution of an acquired immune response in the formation of osteolytic lesion, the periodontal pathogen Pg was injected adjacent to calvarial bone with or without prior immunization against Pg.36 Activation of the acquired immune response elevated osteoclastogenesis and decreased bone formation associated with an increase in nuclear translocation of the transcription factor FOXO1 (forkhead box O1) in vivo, enhanced apoptosis of bone lining cells caspase-3 positive cells and a decrease in bone lining cell density. These activities were induced when a combination of cytokines such as IL-1β, TNF-α, and IFN-γ were tested. It is significant that FOXO1 knockout by a small interfering RNA significantly reduced cytokine-stimulated apoptosis, mRNA levels of proapoptotic genes, cytokines, and caspases-3, -8, and -9. These results indicate that acquired immunity could trigger apoptosis, osteoclastogenesis, and bone resorption. This could occur by stimulation of bone lining cell apoptosis via FOXO1 activation. This study demonstrates commonalities in the pathogenesis of chronic periodontal disease and RA where osteogenesis and bone destruction occur hand in hand in response to activation of an acquired immune response. Periodontal disease has been implicated as a risk factor for RA. Raised antibody titers to Pg in patients with RA are associated with disease-specific autoimmunity. Antibody titers to Pg were characterized in patients with periodontitis, RA and healthy controls for correlation with disease autoantibodies.37 Pg antibody titer was correlated with CRP, antibody to cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF). Antibody titer to Pg was highest in periodontitis, intermediate in RA and lowest in controls (P, 0.0003), showing a greater association with periodontitis and RA than controls. Correlations between Pg titers, concentrations of CRP and autoantibody related to RA is suggestive of the role of Pg in the etiopathogenesis of periodontal disease, being a risk factor for RA and its progression. The impact of controlling periodontal infection, by reducing the concentration of pathogens, with thorough initial phase debridement of periodontal pockets in reducing the severity of active RA has been reported.38 There is evidence that autoantibodies formed against oral anaerobes have important implications in the etiopathogenesis of RA.39 The pathogenesis of RA resembles that of periodontitis, both conditions presenting with a high frequency of HLA-DR4 tissue antigens and there is increasing documentation of the coexistence of the two conditions.18 Antibodies to Gram-negative, anaerobic periodontal pathogens such as Porphyromonas gingivalis, Prevotella intermedia, P. melaninogenica, and Tannerella forsythia have been detected in the serum and synovial fluid of RA patients. These pathogens have been identified in the synovial fluid of RA patients, with higher levels of bacterial DNA in RA patients than in controls.40 Rheumatoid autoantibodies target epitopes created by deamination of arginine residues in autoantigenic proteins such as profilaggrin/filaggrin, fibrinogen/fibrin, keratin and vimentin. Arginine is dominant amongst the amino acids in its autoantigenicity amongst proteins. Expression of a peptidyl deiminase in Pg and arginine specific proteinases in T. forsythia and Treponema denticola have been reported.41 These findings are suggestive of an important role for oral pathogens in the perpetuation of synovial inflammation in response to the antigenic stimulus of their bacterial DNA. The role of the periodontal pathogen P. gingivalis in the pathogenesis of RA was investigated in cell cycle progression and the apoptosis of human articular chondrocytes.42 Monolayer cultures of human chondrocytes were challenged with P. gingivalis and their cell cycle progression was analyzed using scanning electron microscopy, immunofluorescence, flow cytometry, Western blot analysis and labeling techniques. Results showed that P. gingivalis adhered to and infected primary human chondrocytes demonstrated by its intracellular localization. Progression of the cell cycle was also affected. Apoptotic signaling cascades were evidenced by the TUNEL (terminal transferase dUTP nick end labeling) assay showing DNA degradation and an up-regulation of caspase-3 protein expression in infected chondrocytes. This study shows that P. gingivalis could contribute to tissue damage seen in the progression of RA by infecting chondrocytes. Some T-cell receptor genes Vβ genes are more frequently identified in RA patients than in controls.43 It is relevant that the
periodontal pathogen Pg specifically stimulates the expression of Vbeta 8 and Vbeta 17 genes in CD4+ T cells, demonstrating a connection between the immunopathology of periodontal disease and RA. Association of periodontal pathogens with atherosclerosis The pathogen-associated molecular pattern receptors, known as toll-like receptors (TLR), play an important role in immune signaling in response to microbial infection and chronic inflammatory diseases such as atherosclerosis. Deficient TLR signaling reduces inflammatory responses associated with atherosclerosis in hyperlipidemic mice. Specific intervention strategy utilizing immunization in the prevention of pathogenaccelerated atherosclerosis has been shown to be effective. The periodontal pathogen Pg has been implicated in the progression of atherosclerosis. It has been demonstrated to reside in the walls of atherosclerotic vessels and seroepidemiological studies show an association between Pg-specific IgG antibodies and atherosclerosis. Signaling pathways utilized by Pg depends on the cell type. Oral inflammatory bone loss is associated with stimulation of TLR2 by Pg which also expedites atherosclerosis in hyperlipidemic mice demonstrating increased expression of TLR2 and TLR4 in atherosclerotic lesions. Immune and inflammatory mechanisms of atherosclerosis are well documented and their implications in periodontal pathology. Atherogenic forms of dyslipidemia may be seen in subjects with RA with increased cardiovascular risk. In addition to an alteration in plasma lipids it is likely that this population demonstrates smaller LDL molecules and an altered subclass distribution. Elevated levels of plasma triglycerides and decreased levels of HDL-cholesterol were seen in RA patients when compared with healthy controls. Total- and LDL-cholesterol Periodontitis and rheumatoid arthritis were similar. A third of RA patients showed a complete ‘atherogenic-lipoprotein phenotype,’ demonstrating the concomitant presence of elevated triglycerides, decreased HDL-cholesterol and raised levels of small dense LDL. The prevalence of small dense LDL in drug-naive patients with early RA needs further investigation with regard to its influence on the atherogenic process and clinical endpoints. Further associations between dyslipidemic atherogenesis and RA, also relevant to chronic periodontitis, are considered under clinical associations.

Clinical correlations between periodontitis, rheumatoid arthritis and cardiovascular disease

Clinical correlations between chronic periodontitis and RA

The association between circulating proinflammatory mediators TNF-α, IL-1β, prostaglandin E2, serotonin, rheumatoid factor and periodontitis in patients with RA was investigated. Periodontal parameters such as clinical attachment level (CAL) to bone, probing depth (PD) and gingival bleeding on probing (BOP), assessment of furcation invasions and increased tooth mobility were made in addition to the number of teeth present in 30 subjects. 71 subjects were nonsmokers. Measurement of the parameters for gingivitis and periodontal disease showed a high degree of correlation with plasma levels of TNF-α in patients with RA when compared with healthy controls. Documentation demonstrating a higher prevalence of periodontal disease among individuals with RA is limited and sometimes inconsistent. Questionnaires were used to assess potential risk factors for periodontal disease such as smoking, education, alcohol consumption, BMI and coexisting diseases associated with RA and periodontal disease. Periodontal parameters of attachment loss, plaque and bleeding indices were obtained. It is relevant that in a stepwise logistic regression including the above parameters (RA status, age, gender, education, smoking, alcohol consumption and BMI), only RA status and age were significant predictors of periodontal disease. Subjects with RA were shown to have significantly increased odds of periodontal disease when compared with controls (95% confidence interval [CI]: 2.93 to 22.09). After adjustment for plaque and bleeding indices (which accounted for 13.4% of the association between RA and periodontal diseases), the strength of the association remained significant, although attenuated. It was concluded that there was significantly greater periodontal attachment loss in subjects with RA, compared with controls and bacterial plaque was only partly responsible for this association, implying that an overexuberant inflammatory response to optimal amounts of plaque could account for similarities in disease pathogeneses in the two conditions.

Potential mechanisms relevant to the association between periodontal and synovial
inflammation include commonalities in cellular, molecular and pathological features. Particularly, the progression of destructive changes in associated tissues shows similarities. Anti-citrullinated protein antibodies (ACPA) are highly specific antibodies for RA. They are specific risk markers for RA which are demonstrable years before onset of the disease. There is evidence to suggest that immune tolerance could be disrupted by the periodontal pathogen P. gingivalis by enhancing autoimmune responses to citrullinated antigens. This sequence of events could trigger the initiation and progression of RA in genetically susceptible individuals. Improved treatment strategies could modify the progression of diseases with an inflammatory pathogenesis, to the advantage of the patient. A greater prevalence of periodontal disease and tooth loss has been reported amongst subjects with RA. Autoimmune inflammatory responses that occur in RA may be sustained as a result of periodontal inflammation which could represent a risk factor for RA, altered by treatment. Common genetic and environmental factors could predispose to both independently. Both RA and periodontal disease have a wide prevalence amongst inflammatory diseases with several common mechanisms in their pathogenesis associated with tissue destruction. Some of the common clinical and biological links between the two disease entities have been reviewed recently. Particularly limited number of studies in this area make it difficult to provide conclusive evidence. Juvenile idiopathic arthritis (JIA) is a severe disease of childhood comprising a diverse group of clinical entities associated with abnormal function of the immune system which could result in abnormalities in growth and development, affecting the temporomandibular joint and mandible. An increased prevalence in caries and periodontal disease in JIA patients may be partly attributed to unfavorable dietary practices, difficulty in maintaining good plaque control and side effects from long-term medication; and in the case of periodontal disease progression an association with JIA is based on a dysregulated inflammatory response relevant to its pathogenesis. The periodontal condition in children and adolescents with JIA was compared with age-matched healthy controls. Forty-one JIA patients were compared with 41 controls. The frequency of sites with plaque, calculus, bleeding on probing and probing depth of 2 mm was significantly greater in JIA patients. There were no sites with attachment loss or reduced marginal bone levels. It was concluded that the results were partly explained by joint pain, making it difficult to perform good oral hygiene procedures, general disease activity and medication. The association of the HLA in patients with juvenile idiopathic arthritis, generalized aggressive periodontitis and chronic periodontitis was evaluated in comparison to healthy controls. Females suffering from JIA and chronic periodontitis demonstrated HLA-DRB3 to a greater extent than controls, with a greater likelihood of attachment loss in JIA cases with this configuration. It is possible that JIA and chronic periodontitis among females pose a common risk factor in HLA-DRB3.

Summary and conclusions

Our understanding of the pathogenesis of atherosclerosis has evolved from a lipid deposition disorder to a focal, chronic inflammatory disease affecting arteries, characterized by inflammatory plaques susceptible to rupture and thrombosis. Atherosclerosis shares certain pathological features with other inflammatory diseases including autoimmune RA and chronic periodontitis. Common features include macrophage activating cytokines such as TNF-α, IL-1 and IL-6, the presence of CD4+ and CD28- regulatory T-cells, raised inflammatory markers including CRP and the enhanced expression of endothelial adhesion molecules including VCAM-1, providing a common nucleus for disease control with focused therapeutic targeting. However, the association between atherosclerosis and RA extends beyond common pathogenic mechanisms. Standardized mortality ratios for cardiovascular disease in RA range from 1.2 to 5, and cardiovascular death accounts for up to 50% of mortality with life expectancy reduced by 10-15 years. A similar trend observed in SLE, with a marked increase in stroke and myocardial infarction has been reported. This outcome data reflects the presence of increased carotid artery intima thickening, vascular stiffness and impaired flow-mediated vasodilation in RA and SLE, indicating endothelial dysfunction and subclinical atherosclerosis. The current challenge to clinicians is the development of treatment regimens that suppress underlying RA disease activity, inhibit endothelial dysfunction, retard the progression of atherosclerosis and effectively control periodontal disease progression with adjunctive therapies targeted at inflammatory excess addressed in this.
review. These inflammatory processes share common ground, providing targets for therapeutic intervention aimed at controlling an overexuberant immune response fuelled by cytokines and the side effects of a progressive pathogenesis.

Disclosure
The author report no conflicts of interest in this work.

References


