Relationship between rheumatoid arthritis and chronic periodontitis

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Abstract
Chronic periodontitis is inflammation of supporting structures of teeth caused by microorganisms, and Porphyromonas gingivalis is one of the most common organisms. Periodontitis has been associated with different systemic diseases and rheumatoid arthritis (RA) is one of them. Periodontitis and RA share several features such as inflammation and bone destruction. Enzyme peptidyl arginine deaminase (PAD) is responsible for citrullination of arginine and citrullinated antigens are generated by post-translational modification. Anti-cyclic citrullinated peptide antibodies and citrullinated peptides (α-enolase, vimentin, fibrinogen, and Type II collagen) are associated with breakdown of self-tolerance in RA. P. gingivalis is the only periodontopathic organism to produce PAD that is responsible for citrullination of arginine. Therefore, patients of periodontitis should be evaluated for RA.

Keywords:
Enzyme peptidyl arginine deaminase, periodontitis, Porphyromonas gingivalis, rheumatoid arthritis

Chronic Periodontitis
Chronic periodontitis is an inflammatory disease of supporting structures of teeth caused by microorganisms, e.g., Porphyromonas gingivalis, Tannerella forsythia, etc. Immune-mediated damage of osseous structures around teeth leads to periodontitis which results in progressive destruction of the periodontal ligament, alveolar bone with pocket formation and gingival recession. Periodontitis is a major public health problem worldwide. Triggering stimulus is Gram-negative rich biofilm belonging to a red complex of periodontal pathogens. More than 500 bacterial species colonize, and red complex is strongly associated with advanced periodontal lesions. The red complex bacteria of periodontal pathogens include P. gingivalis, T. forsythia, and Treponema denticola.

Prevalence
The worldwide periodontal disease is one of the health risks and it is a major cause of tooth loss in adults. Chronic periodontitis is the 6th most common oral disease and its global prevalence is 35%. The World Health Organization (2011) suggested 5-20% of world population is suffering from severe periodontitis, whereas the National Health and Nutrition Examination Survey (NHANE 2009-2010) documented 47% of the studied subjects of 45-64 years had periodontitis which is distributed as mild 8.7%, moderate 30.0%, and severe 8.5%. In the United States of America, 64% people of 65 years or above had moderate or severe periodontitis. Nazir et al., suggested the prevalence of chronic periodontitis as 66.22% and 27.93% in rural and urban population, respectively, with male predominance in Karachi, Pakistan. Similarly, 69% of the patients had gingivitis in Islamabad, Pakistan.

Risk Factors of Chronic Periodontitis
Several local and systemic factors are responsible for chronic periodontitis, e.g., smoking, obesity, alcohol consumption, diabetes mellitus, osteoporosis, stress, psychological factors, and metabolic syndrome. Further, malocclusion, overhanging restorations, poor oral hygiene, poor nutrition, etc., may result in chronic periodontitis.

Immunopathogenesis of Chronic Periodontitis
Dental plaque results in gingivitis which is a reversible condition and mineralization of dental plaque lead to calculus formation. If calculus persists for a long period, it causes periodontitis which is an irreversible and more damaging...
condition. Microorganisms present in calculus, may exert pathogenic effect either directly by tissue destruction or indirectly by activating host response. Substances released from bacteria reach gingival tissue and results in chronic inflammation that leads to activation of B-lymphocytes, T-lymphocytes, neutrophils, monocytes, and macrophages that release inflammatory mediators such as chemokines, proteolytic enzymes, and cytokines. Therefore, local variation and damage of host tissue may manifest as periodontal disease.

**P. gingivalis**

*P. gingivalis* is a non-spore forming, non-motile, obligate anaerobic bacteria which is the most important bacteria responsible for chronic periodontitis. *P. gingivalis* can enter periodontal tissue by releasing specific virulence factors that include lipopolysaccharide, fimbriae, capsule, outer membrane vesicles, hemagglutinins, and organic metabolites such as butyric acid and various enzymes, i.e., collagenase, gelatinase, hyaluronidase, cysteine proteinases (gingipains).

Different strains of *P. gingivalis* have been identified based on size and amino terminal sequence of fimbrillins. Based on diversity of *fim A* gene *P. gingivalis* consists of six different genotypes, i.e., Type I, Type II, Type III, Type IV, and Type Ib. Type IIb strain is associated with progression of chronic periodontitis.

*P. gingivalis* is the only microorganism that expresses peptidyl arginine deaminase (PAD) which is an enzyme that catalyzes citrullination of arginine. This citrullinated antigen is present in patient’s periodontium of chronic periodontitis which activates adaptive immune response that is exclusive to rheumatoid arthritis (RA).

**RA**

RA is a chronic inflammatory, autoimmune disease commonly seen in the elderly people characterized by joint destruction. Approximately 1.0% of adults have RA worldwide. Synovial membrane of synovial joint capsules of hands and feet is the first structure affected in this disease. Inflammatory changes lead to cartilage and bone destruction. If unchecked, it leads to loss of function, deformity, and chronic pain. Inflammatory mediators such as prostaglandin, tumor necrosis factor-alpha, interleukin-1β (IL-1β), IL-6, IL-17, IL-12, IL-18, granulocyte macrophage colony-stimulating factor (CSF), monocyte CSFs, RANKL, matrix metalloproteinase, nitric oxide and leukocyte inflammatory infiltrate in synovial fluid are responsible for complications of RA. In 1987, American College of Rheumatology established criteria for the diagnosis of RA. Although the exact cause of RA is not known, environmental “trigger” and genetic susceptibility may contribute. Innate and adaptive immune pathways along with cytokines are involved in the disease progression.

**Relationship between RA and Chronic Periodontitis**

Periodontitis is associated with many diseases, e.g., diabetes mellitus, atherosclerosis, myocardial infarction, stroke, osteoporosis, Alzheimer’s disease, respiratory disease, adverse pregnancy outcome, pancreatic cancer, cerebral infarction, etc. Periodontitis and RA share several disease features such as chronic tissue inflammation, bone destruction, risk factors like smoking, and HLA-DRβ1 alleles. RA patients experience more gingival bleeding, missing teeth, clinical attachment loss and increased alveolar bone loss as compared to healthy controls. Specific link between these two diseases has not been established but an increased prevalence of periodontitis in RA patients compared to healthy individuals has been reported.

Since *P. gingivalis* is the only microorganism to produce PAD (PPAD) which is responsible for catalyzing citrullination of arginine, therefore, this organism may be the likely cause of RA. Citrullinated antigens activate adaptive immune response that is selective to RA. Citrullinated peptide is generated through post-translational modification (PTM) of protein. Anti-cyclic citrullinated peptide (anti-CCP) antibodies and citrullinated peptides (a-enolase, vimentin, fibrinogen, and Type II collagen) are associated with breakdown of self-tolerance in RA. RA is genetically associated with HLA DR-4 locus containing shared epitopes, i.e., 0401, 0404, 0405, 0408 which is also associated with severe and aggressive periodontitis. Cells, enzymes, and cytokines are also common in both the diseases.

After non-surgical treatment of patients with combined chronic periodontitis and RA, there was decreased disease activity of RA. Antibody titer of *P. gingivalis* was high in RA patients and its level was significantly correlated with anti-CCP antibodies of immunoglobulin M (IgM) and IgG two subtypes.

**PAD enzymes**

*P. gingivalis* is one of the periodontopathic organisms that PPAD. There are differences in human PAD and bacterial PPAD. Unlike human PAD, PPAD requires higher pH for activation and do not need calcium for activation. PPAD citrullinates C-terminal arginine residues and deaminates free arginine while mammalian PADS do not have this property.

Five isoforms of PAD have been identified, i.e., PAD-1, PAD-2, PAD-3, PAD-4/5, and PAD-6 that have different functions and are distributed at different locations. The activity of PAD is dependent on calcium levels and is physiologically expressed in different locations.

PAD-1 is involved in keratinization of skin and it is expressed in epidermis and uterus, whereas its absence or hypofunction leads to psoriasis. PAD-2 is expressed in skeletal muscles, central nervous system and hematopoietic tissues while its abnormal function causes multiple sclerosis. PAD-3 is present in hair follicles, whereas PAD-4 is present in neutrophils, eosinophils, spleen and secretory glands. PAD-4 is involved in the generation of new autoantigens in RA. PAD-6 is present in eggs, ovaries,
testes, spleen, lungs and liver. PAD-2 and PAD-4 is associated with RA.\textsuperscript{[28,29]}

The physiological substrates of PAD are trichohyalin, flaggerin, Type I and II cytokeratins, myelin basic proteins and glial fibrillary acid protein. PTM of these proteins results in modification and modulation of molecular interaction.\textsuperscript{[30]} Inhibition of PADs may act as a therapy for RA as it inhibits generation of auto antigens.\textsuperscript{[31]} PAD inhibitor, i.e., C1-amidine (Pan PAD inhibitor) and YW3-56 (PAD-4 inhibitors) reduces severity of disease, synovial citrullination and histological joint damage.\textsuperscript{[30]}

**PTMs of proteins**

PTMs of proteins can be carbamylation, citrullination or glycosylation which are involved in the pathogenesis of RA. PTMs are enzyme mediated reactions observed in many physiological processes and their dysregulation lead to pathological conditions, i.e., RA.\textsuperscript{[30]} One of the PTMs is citrullination or deamination which is a common PTM of arginine mediated by PAD. Since periodontopathic microorganism (P. gingivalis) PPAD, therefore, periodontitis is thought to be a risk factor for RA.\textsuperscript{[32]}

Tissue citrullination is a physiological process occurring in many tissues, i.e., in epithelial keratinization, inflammation and increased apoptosis.\textsuperscript{[33]} Extra articular citrullination occurs in lungs of smokers.\textsuperscript{[22]} During citrullination, arginine is converted into citrulline that results in change in mass of citrulline by 0.984 Da and loss of one positive charge which also has effect on isoelectric point (pI). The pI value of arginine and citrulline is 11.41 and 5.91, respectively. This change in amino acid influences hydrogen bond ability and interaction with other amino acid residues, therefore, conformational change may lead to functional alteration and change in half-life. Thus, a new protein is created expressing new epitopes called cryptic epitopes against which there is no tolerance. Loss of tolerance against citrullinated proteins in genetically susceptible patients leads to auto antibodies (anti-citrullinated peptide antibodies [ACPA]) in synovium of RA patients.\textsuperscript{[29]}

**ACPA**

ACPA family of auto antibodies includes antiperinuclear factor, anti-keratin, anti-vimentin and anti-flaggerin antibody. In 1964, these antibodies were identified as IgG binding to keratohyalin granules in the cytoplasm of buccal mucosal cells.\textsuperscript{[24]} Almost 1 year before the diagnosis of RA, ACPA have been identified in 50% of patients and it has high predictive value for RA, therefore, it has emerged as a specific serological marker for this disease. It has the specificity of 85-95% and sensitivity of 80%.\textsuperscript{[30]} ACPA is also associated with more severe and worse clinical outcome.\textsuperscript{[33]}

**Conclusion**

Chronic periodontitis and systemic diseases have a strong association. Good plaque control, removal calculus deposits, and granulation tissue may lead to reduction of periodontitis as well as decreased risk of systemic diseases such as RA. Periodontal lesions are suggested as a risk factor for RA. Therefore, RA patients should be evaluated for periodontitis and vize versa. Further studies are required to evaluate the basic mechanism of link between periodontitis and RA.

**References**
