

Role of Immunoglobulin G and A in Periodontitis: A Review

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A highly discriminatory immune system is fundamental to survival. The Immune system has a powerful collection of defense mechanisms to protect against potential invaders that would otherwise take advantage of the rich source of nutrients provided by the vertebrate host. Unlike the cells of liver, heart or lungs, the cells of the immune system are scattered throughout the body. They are present in the spleen, lymph nodes, bone marrow, and thymus & circulate through the blood and lymphatic fluid. The first line of defense is provided by the intact skin and mucous membranes of the body. There are a group of proteins (immunoglobulins) present in normal adult, they are of five types IgG, IgA, IgM, IgD, IgE. Amongst these IgG and IgA play important role in Periodontitis as IgG are the main circulating antibody in the blood and can pass from blood into tissue spaces whereas IgA protection to mucosal surfaces.

Key words: Immunoglobulins, pathogens, periodontitis.

The Immune system has evolved to protect us from pathogens. Intracellular pathogens infect individual cells, whereas extracellular pathogens divide extracellularly within tissues or the body cavities. A highly discriminatory immune system is fundamental to survival. The Immune system has a powerful collection of defense mechanisms to protect against potential invaders that would otherwise take advantage of the rich source of nutrients provided by the vertebrate host. Over many millions of years, different types of immune defense, appropriate to the infecting pathogens, have evolved in different group of organisms for recognizing & destroying pathogens^{1,2}.

The environment contains a great variety of infectious agents, including bacteria, viruses, fungi, parasites etc., which can enter the body & cause disease & if they multiply unchecked, death

occurs. The primary function of the Immune system is to eliminate infectious agents & minimize the damage they cause. It ensures that most infections in normal individuals are short-lived & leaves little permanent damage. Pathogens use many modes of transmission & reproduction, so the immune system has evolved many ways responding to them. Some pathogens evoke 'humoral immunity', like bacteria evade these formidable defenses by being intracellular pathogens & replicating within the host cells. 'B' cells are responsible for the humoral arm of the adaptive immune system. Immunoglobulins are an essential component of humoral immunity. They are present in serum, tissue fluid or on cell membranes. Amongst the five classes of Immunoglobulin namely IgG, IgA, IgM, IgD, IgE, the immunoglobulin IgG is the predominant immunoglobulin in normal human serum & IgA is predominant immunoglobulin in seromucous secretions. There are several methods to measure these antibodies of which immunoassays, immunoelectrophoresis, radioimmunoassay, ELISA are common^{1,2,3}.

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Bacterial infections have had an enormous impact on human society & despite the discovery of antibiotics it continues to be a major threat to public health. Antibody clearly plays a crucial role in dealing with these pathogens & this important function is performed mainly by IgG & IgA. Because IgG is the immunoglobulin class is found in highest concentration in blood, it plays the major role in antibody-mediated defense mechanisms. These antibodies can be detected in many body fluids, for example, tears urine, milk, saliva, serum, etc. Because antibodies can be isolated in very large quantities from serum, it has been possible to study their structure in great detail, readily sampled & their levels measured⁴⁻⁶.

Periodontitis

Periodontal disease is one of the most prevalent afflictions world wide. The most serious consequence is the loss of the periodontal supporting structures which includes gingiva, cementum, periodontal ligament and alveolar bone^{2,7}. Periodontal disease is an all-encompassing term used to describe all disorders of the supporting structures of the teeth. These structures include the gingiva, periodontal ligament and the underlying alveolar bone. The level of infection can range from gingivitis, which is the inflammation of the gingiva all the way to full-blown periodontitis that can result in tooth loss^{7,8}. Unlike most illness, bacteria that are foreign to the body do not cause periodontal diseases. Rather it's the microbes that inhabit the oral cavity which are responsible for periodontal disease. The attack is triggered by a shift in the balance of oral microflora towards more invasive microbes. These microorganisms can cause inflammation leading to periodontal disease, by either directly invading the surrounding tissues or indirectly by emitting a toxin^{9,10,11}.

The chronic challenge of virulent microorganisms leads to destruction of tooth supporting soft & hard tissues of Periodontium, including alveolar bone, tooth root cementum & periodontal ligament. Although Periodontitis is initiated by the subgingival microbes, it is generally accepted that mediators of connective tissue breakdown are generated to a large extent by the host response to a pathogenic infection, in a susceptible host, microbial virulence factors trigger the release of host derived enzymes & pre-inflammatory cytokines that can lead to colonial tissue

destruction^{9,12}. The implication of periodontal microbes associated by products such as endotoxin on induction of the innate immune response, cells like receptors signaling generation of pathogen associated molecular patterns (PAM's) & their role in periodontal disease pathogenesis are crucial to the extent of disease severity^{2,13}.

Role of Immunoglobulin

An increased prevalence of immunoglobulin (Ig) A deficiency has been documented in a number of autoimmune diseases¹⁴; Immunopathological studies have shown that, as human inflammatory periodontal disease progresses, the nature of the cellular infiltrates change^{5,15,16}. The mild gingivitis stage is characterized by the predominance of small lymphocytes which have the membrane characteristics of thymus-derived (T) lymphocytes. As the disease progresses, there appears to be an expansion of a small focus of IgG immunoglobulin-bearing lymphocytes and plasma cells which is first seen at the sulcular epithelium-lamina propria junction in sections of gingiva from patients with mild gingivitis. In periodontitis, the numbers of plasma cells frequently exceeds the number of infiltrating lymphocytes. The majority of plasma cells and IgG-bearing lymphocytes in periodontitis have cell-associated immunoglobulins IgG1, IgG3, or IgG4 subclasses^{10,13,17}. The lack of cell-associated IgG2 antibodies in severe gingivitis and periodontitis was a consistent finding. Secretory immunoglobulin A (SIgA) constitutes the predominant immunoglobulin isotype in secretions, including saliva. It is considered to be the first line of defense of the host against pathogens which colonize or invade surfaces bathed by external secretions. The main function of SIgA antibodies seems to be to limit microbial adherence as well as penetration of foreign antigens into the mucosa¹⁸. Naturally occurring SIgA antibodies reactive with a variety of indigenous bacteria have been detected in saliva. Furthermore, indigenous bacteria of the oral cavity have been found to be coated with SIgA. In vitro experiments have shown that SIgA may inhibit or promote the adherence of oral bacteria to teeth^{19,20}. IgA-deficient humans were found to be more or less susceptible to caries and periodontal diseases²¹. Immunoglobulins which form immune complexes are known to provoke complement

fixation or stimulate the release of other mediators in inflammation. Studies with myeloma proteins showed IgG 1 and IgG3 subclasses were avid fixers of complement²². Such complexes are presumed to mediate many of the pathological manifestations of human periodontal disease^{6, 20}. However, other investigators have been unable to isolate insoluble immune complexes from diseased gingiva. In some chronic inflammatory diseases, the appearance of circulating soluble antigen-antibody complexes in the serum serves as an index of disease activity²³. Circulating immune complexes in the sera from patients with rheumatoid arthritis is now a well-recognized diagnostic parameter²⁴. The major factors regulating the destruction of tooth-supporting periodontal structures are inflammatory mediators released by host cells. Gaffen & Hajishengallis describe periodontal health as "a dynamic state where the activity of pro-inflammatory/antimicrobial cytokines to control infection is optimally balanced by anti-inflammatory mechanisms to prevent unwarranted inflammation". Cellular and humoral components of blood can reach the gingival crevice of the oral cavity by the flow of gingival fluid through the junctional epithelium²¹. Even in the healthy state, there is a continuous flow of small quantities of fluid and leukocytes from the gingival capillaries through the crevicular epithelium into the gingival crevice^{25,26}. This flow increases greatly with inflammation induced by plaque accumulation. The continuous flow of gingival fluid from the crevice to the oral cavity removes nonadherent bacterial cells. Gingival fluid also contains antimicrobial substances including IgM, IgG, IgA, complement, and leukocytes. These factors are primarily protective against microbial invasion, but, as seen above, the inflammation may become destructive, resulting in loss of periodontal attachment²⁴⁻²⁸. The IgG, IgM, and IgA antibodies directed against a variety of oral microorganisms have been detected in plasma and crevicular fluid even in healthy individuals. These antibodies may influence the oral microbiota by interfering with adherence or by inhibiting bacterial metabolism^{29,30}. Furthermore, the IgG antibodies may enhance phagocytosis and killing of oral microorganisms through activation of complement or opsonisation³¹. It has been demonstrated that systemic immunization of animals with periodontopathogens may reduce the colonization of these bacteria in the gingival crevice and reduce periodontal destruction³².

However, since periodontal diseases are of multifactorial origin, systemic immunization with periodontopathogens may also enhance the destruction of alveolar bone³³. The immune response itself may contribute significantly to the periodontal destruction, sometimes even more than the pathogens. The predominance of IgG in gingival organ culture supernatants and the statistically significant findings that the overall mean levels of IgG between mild gingivitis and periodontitis and between severe periodontitis and periodontitis suggested a possible indicator of periodontal disease. The inhibition of IgG synthesis by cyclohexamide confirmed the contention that IgG was a product of de novo synthesis and not serum derived. The presence of IgG in gingival organ culture supernatants was shown to be a product of actively secreting plasma cells^{34,35}.

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