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Immunology of periodontal diseases in diabetes and covid-19 patients

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Abstract
Periodontal disease pathogenesis is a complex subject, requiring a thorough understanding of the macroscopic and microscopic features of the periodontium (i.e., the supporting structures of the tooth), as well as the role that the immune system plays in the host response. The role of the oral cavity in COVID-19 has been controversial. The inflammatory reaction within the body serves to contain or stop a local microbial attack, and prevents the spread of attacking organism. In Covid patients this may also result in the destruction of surrounding cells, connective tissue matrix and eventually bone.

Keywords: periodontal disease, periodontium, connective tissue matrix, host response

Introduction

The inflammation of periodontium (tooth bearing structures) is termed as periodontitis. Healthy periodontal apparatus ensures good quality of teeth. Recent researches has suggested us that, the periodontal status of an individual has a direct relationship on the systemic health and quality of life. The food habits and the life style modifications in young individuals has resulted in compromised oral hygiene. A serious of inflammation can occur, resulting in loss of teeth and eventually a compromised systemic health. During this covid times, because of long term usage of mouth mask, people tend to drink less amount of water. The anerobic environment, hence caused results in halitosis, dental caries and gum inflammation.

Early inflammatory changes in the gingival margin

Within a few days if plaque growth is undisturbed. Within 10 to 20 days the plaque mass changes composition from mostly gram-positive coccoid and filamentous bacteria to gram-negative rods and spirochetes. A gram-positive plaque is usually associated with periodontal health, while a gram-negative is associated with disease. This complex community of microorganisms is referred to as a biofilm.

Initial Lesion (2-4 days) Clinically, the manifestation of the following events results in the early stages of gingivitis. There may be bleeding on probing, slight gingival swelling along with mild erythema (reddening) of the tissue, and increased flow of gingival crevicular fluid. If a biofilm is allowed to form on the tooth surface, a vast number of bacterial cell products are produced.

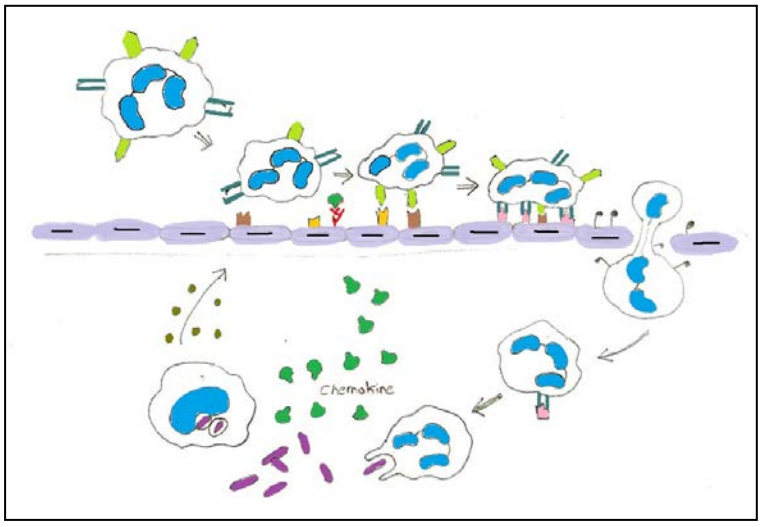

Fig 1

The first is gingivitis, which is defined as inflammation of the gingiva in which the connective tissue attachment to the tooth remains at its original level. The disease is limited to the soft-tissue compartment of the gingival epithelium and connective tissue [1].

If the early lesion persists without resolution, bacterial antigens are processed and presented by lymphocytes, macrophages and dendritic cells. Broadly, two different subsets of lymphocytes have evolved to recognize extracellular and intracellular pathogens after being presented with antigens by the innate immune cells: T-lymphocytes and B-lymphocytes (Figure 1). B-lymphocytes bear immunoglobulin molecules on their surface, which function as antigen receptors [2].

Many of these bacterial products and structures are referred to as Pathogen Associated Molecular Patterns (PAMPs) and can be recognized by membrane receptors called Toll-like Receptors (TLRs). TLRs are part of the innate immune system and are expressed by several different cell types including Epithelial cells, endothelial cells, fibroblasts, cementoblasts, osteoblasts, osteoclasts, dendritic cells, PMNs, macrophages and lymphocytes. When PAMPs bind to TLRs on the cell membrane, an immune response is launched. The result is an inflammatory response that is initiated by the release of pro-inflammatory molecules, called cytokines, and other soluble mediators of inflammation from the cell [2].

Transcription of matrix metalloproteinase genes is very low in healthy periodontal tissue. In periodontal disease, secretion of specific matrix metalloproteinases is stimulated or down-regulated by various cytokines. The main stimulatory cytokines for matrix metalloproteinases are tumor necrosis factor alpha, interleukin-1 and interleukin-6. It is also known that active matrix metalloproteinases are capable of activating other matrix metalloproteinases in a mutual activation cascade [3].

Histamine and kinins released from tissue Mast cells promote vasodilation and increase vascular permeability, enhancing the influx of cells and protein molecules such as antibodies and complement. Plasma proteins called Complement will be activated through a cascade of enzymatic reactions. There are three pathways for the activation of complement (Figure 2): The Classical; Alternative; and Mannose-binding lectin.

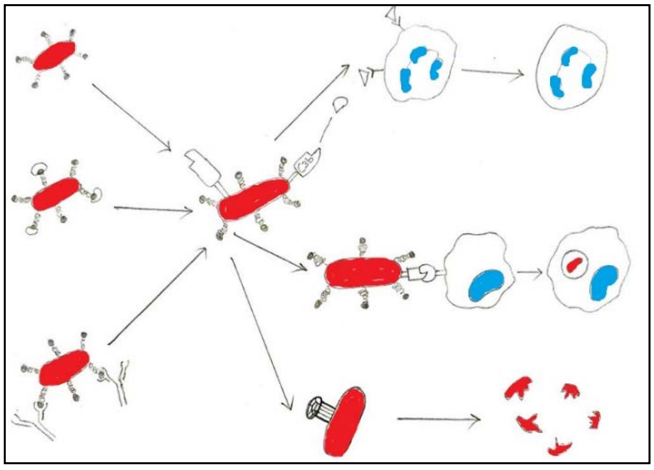

Fig 2: Pathways for activation

Complement has several biologic functions

- C3a activates basophils and mast cells causing release of vasoactive substances including histamine. In concert with antibodies, C3b and C4b opsonize, or clump, the antigens together for easier phagocytosis by PMNs and macrophages C5a and C5a des Arginine enhance PMN activation and chemotaxis. C5b, C6, C7, C8 form a Membrane Attack Complex (MAC) that can destroy [4].

Microscopically

The inflammatory infiltrate is predominated by PMNs located primarily around vessels within the connective tissue, just below the junctional epithelium (JE). Loss of some perivascular collagen will also be seen. Within the sulcular epithelium, the number of dendritic cells called Langerhan's cells will increase.

These cells can internalize pathogen-associated antigens and migrate, via lymphatic channels, to the lymph node where they become Antigen Presenting Cells (APCs). Free antigen may also travel to the lymph node, where macrophages or specialized dendritic cells internalize, process and present the antigen to T Cells.

If the immune response is effective in eliminating the pathogens in the early phase of the acute inflammation, lipoxins from the enzymatic breakdown of arachidonic acid are generated. The lipoxins may act to inhibit PMN chemotaxis, inhibit secretion of proinflammatory mediators, induce apoptosis (cell death) of PMNs, and, recruit macrophages to the site for removal of cell debris. Thus, the inflammation resolves and tissue repairs.

Early Lesion (4-7 days)

If the pathogens have not been eliminated, the immune response will intensify Clinically, there may be more swelling (edema) along with increased redness (erythema). Microscopically, the area of inflammatory infiltrate will increase, occupying as much as 10-15% of the gingival connective tissue beneath the junctional and sulcular epithelium. Loss of extracellular collagen may be as great as 60-70%, with cytopathic changes seen in the gingival fibroblasts. In an attempt to wall-off the growing lesion, JE cells will begin to proliferate in numbers.

Although PMNs are still prominent in number, lymphoid cells can now be seen accumulating subjacent to the junctional epithelium. Many of the lymphocytes come directly from the circulating blood responding to specialized chemokines that signal them to home to the site of the lesion.

Once activated by Antigen Presenting Cells such as the macrophage or dendritic cell, T Cells may function as helper and / or cytotoxic cells that orchestrate an appropriate immune response. This is accomplished through the production of various cytokines, or by cell to-cell interaction. In a gingivitis lesion, T helper Cells increase the ability of macrophages to kill intracellular and extracellular pathogens, activate PMNs independently of the cytokines produced, and enhance PMN and macrophage phagocytosis. This is probably why T Cells are linked to the "stable lesion" as in gingivitis, since they tend to keep the infection under control.

Established Lesion (2-3 weeks)

The second is periodontitis, which is an inflammation of the supporting tissues of the teeth (Figure 3) [4].

If the T Cell is unable to effectively deal with the infection and it becomes chronic, a more robust immune response

may be required. The inflammatory infiltrate in the Established Lesion occupies a greater area within the connective tissue, with more destruction of collagen matrix. Again, the junctional epithelium will attempt to occupy the space and wall-off the infection by migrating laterally and apically, resulting in early pocket formation [2].

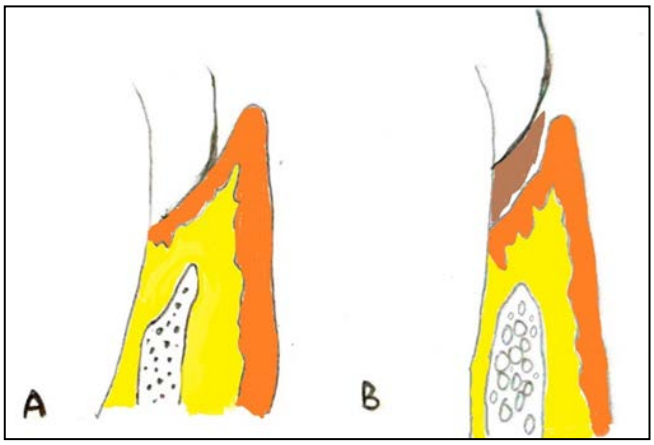

Fig 3

Another significant change from earlier stages of disease is the predominance of Ig producing Plasma Cells within the inflammatory infiltrate. Thus, an increase in extravascular immunoglobulins (antibodies) can now be detected within the connective tissue and junctional epithelium. These changes may be linked to one or more immune system events. It is logical that B Cells have migrated to the site of infection in the Established Lesion. Some are memory B cells that have antigen specific Immunoglobulins (Ig) expressed on their surface membrane. Macrophage activated T helper-2 Cells (Th2), with receptors for the same specific antigen, will link to the B Cell and activate it. The process of activation results in proliferation and differentiation into Ig producing Plasma Cells. Immunoglobulins will subsequently be available to opsonize and neutralize the antigens.

Cytokines IL-3, IL-4, IL-5, IL-6, IL-10 and granulocyte-monocyte colony stimulating factors (GM-CSF), released by the T Cell, are important signaling molecules for proliferation and differentiation of B Cells. Other B Cells that express IgM antigen receptors may be activated independently of T Cell help. These B Cells respond to T-independent antigens, many of which are large bacterial carbohydrates that cross-link the IgM antibodies. In a similar manner, macrophages may also present multiples of the same antigen to B Cells for cross-linking of IgM [5].

Advanced Lesion

Several of the features described for the Established Lesion will persist at this stage. Plasma Cells continue to be the predominant cell type within the inflammatory infiltrate. Further destruction of collagen subjacent to the junctional epithelium is seen, with fibrosis at distant sites. A prime characteristic of the Advanced Lesion is the extension of the lesion into the periodontal ligament and supporting bone. The resulting outcome is bone loss that is exhibited as clinical attachment loss and pocket formation. The mediators of inflammation that have been identified as playing a significant role in alveolar bone resorption include interleukin-1β, interleukin-6, Tumor Necrosis Factor-α (TNFα), and Prostaglandin E2. Every cell involved in the immune response is capable of secreting these molecules. In addition, each of these mediators has been shown to increase in periodontitis sites compared to sites displaying gingivitis or health.

The Receptor Activator of Nuclear Factor κB Ligand, (RANKL) and its decoy receptor, osteoprotegerin. RANKL has been described as the "master switch regulator" of osteoclastogenesis. Since bone homeostasis is a balance between bone formation (osteoblastogenesis) and bone resorption (osteoclastogenesis), provide greater insight into bone diseases where the scale is tipped in favor of resorption [10].

Since periodontitis is an inflammatory disease characterized by alveolar bone loss, controlling the expression of RANKL in the periodontal lesion may be a useful treatment approach. Osteoblasts express RANKL on their cell membrane. When this ligand binds to the RANKL receptor on a pre-osteoclast, it signals the cell to differentiate into an active osteoclast. The decoy receptor for RANKL, called osteoprotegerin, blocks this activation mechanism, thus helping to maintain bone homeostasis [10].

In periodontitis, the ratio of RANKL to osteoprotegerin increases, whereas in health, the ratio is decreased. This ratio appears to be more important in identifying bone resorbing sites than the concentration of either RANKL or osteoprotegerin alone. Osteoblasts and periodontal ligament fibroblasts express RANKL on their cell membrane. T Cells not only express membrane bound RANKL, but also secrete it in soluble form. The pro-inflammatory cytokines interleukin-1β and interleukin-6, Tumor Necrosis Factor-α and the eicosanoid Prostaglandin E2 signal these cells to express membrane-bound RANKL, and the T Cell to secrete RANKL.

Recall that these molecules have already been shown to be increased in the periodontal lesion and indirectly involved in periodontal bone loss. Thus, when the lesion has advanced toward the periodontal ligament and alveolar bone, the up-regulation of RANKL may lead to bone loss and subsequent deepening of the periodontal pocket. The osteoprotegerin/ RANKL pathway is a key regulator of bone metabolism through its effect on the development and activation of osteoclasts [11].

Diabetes & Periodontal disease

Oliver *et al* showed that large number of Poly morpho nuclear cells were present in inflamed gingival crevices of poorly controlled diabetics. Defects in PMN function have been considered as a potential cause of bacterial infection in diabetic individuals. A prostaglandin E2 hypersecretory response to lipopolysaccharides in monocytes from patients with early onset form of the disease. The gingival capillaries of diabetic patients have greater basement membrane thickness. Poor wound healing has been a common finding in diabetics and is characterized by a decrease in the amount of wound collagen and lowered tensile strength. Decreased granular tissue and reduced amount of protein and DNA have also been reported in diabetic rat. The defective wound healing may be due to non-enzymatic glycosylation of collagen and other proteins during the period of hyperglycemia. Impaired growth factor secretion may be a key mechanism for impaired wound healing in diabetics. The monocyte is the principal cell involved in wound debridement and growth factor secretion. The shift in monocyte from a reparative regenerative cell to an

inflammatory phenotype may represent a common underlying mechanism for both impaired wound healing and exaggerated inflammatory response in diabetics [12].

Periodontal disease is clearly of an inflammatory origin and, as such, has a close association with the Immune System. Unraveling the intricate mechanism by which the host responds to pathogens colonizing the tooth will lead to more sensitive means to detect subtle changes in disease activity, and more effective and predictable therapeutic modalities[6]

COVID & Periodontal disease

The risk of COVID-19 complications is significantly higher among patients with moderate-to-severe periodontitis compared to those with milder or no periodontitis. Periodontitis shares common risk factors with most chronic inflammatory diseases known to influence COVID-19 severity.

The strong associations observed between periodontitis and COVID-19 severity. Takahashi *et al* suggested that aspiration of periodontopathic bacteria might aggravate COVID-19 by inducing the expression of angiotensin converting enzyme 2, a receptor for SARS-CoV-2, and inflammatory cytokines in the lower respiratory tract. Also, it was suggested that periodontopathic bacteria might enhance SARSCoV-2 virulence by cleaving its S glycoproteins [7]. Sahni *et al* suggested that the strong Th17 response in severe periodontitis could exacerbate the cytokine storm in COVID-19 [8].

Periodontitis was significantly associated with a higher risk of complications from COVID-19, including ICU admission, need for assisted ventilation and death and increased blood levels of markers linked worse COVID-19 outcome such as D-dimer, WBC and CRP [9].

Conclusion

If a causal link is established between periodontitis and increased rates of adverse outcomes in COVID-19 patients, then establishing and maintaining periodontal health may become an important part of the care of these patients

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