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# CONNECTIVE TISSUE OF THE PERIODONTIUM: NORMAL AND DISEASED - A LITERATURE REVIEW

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## ABSTRACT

The periodontium is a distinctive anatomical region that contains four distinct connective tissues the gingiva, periodontal ligament, cementum, and alveolar bone. These tissues are continuously subjected to mechanical and chemical alteration due to the constant masticatory pressures and oral microbiota, but they are nonetheless able to preserve their structural and functional integrity within their physiological limits. However, disease results when the delicate balance between host defence and bacterial pathogenicity is compromised. Following the elimination and control of the offending chemicals, healing of the tissue occurs, and the periodontium's health may be recovered. The periodontal tissues exhibit all of the typical signs and symptoms of a tissue undergoing considerable degradative and reconstructive changes under pathological conditions, which either result in decreased tissue function or healing of the damage. Repair of injured tissues is a crucial physiologic reaction required for the protection of the dentition. However, healing in the form of tissue regeneration is less predictable once the damaging stages reach the deeper periodontal structures. Various diseases seen in clinical practise are linked to changes in the resident cells or connective tissue matrices, or both. Additionally, connective tissue components have a lot of promise for use in tracking tissue changes and might be developed to help with periodontal diagnostics. Many breakdown products from an infected periodontium can be found in the gingival crevicular fluid, including plasma proteins, bacterial and leukocytic enzymes, and inflammatory mediators. Therefore, it would be very useful to create an assay that could identify components specific to periodontal ligament or bone. The aim of this study is to integrate the principles of molecular and cellular biology with rudimentary knowledge of connective tissue and its make-up and same is then applied to normal and diseased connective tissues of the periodontium.

**KEYWORDS:** Connective tissue, periodontitis, collagen, Gingival crevicular fluid.

## INTRODUCTION

The periodontium contains four distinct connective tissues- the gingiva, periodontal ligament, cementum, and alveolar bone. These tissues are continuously subjected to mechanical and chemical alteration due to the constant masticatory pressures and oral microbiota, but they are nonetheless able to preserve their structural and functional integrity within their physiological limits. However, disease and related tissue loss result if the delicate balance between host defence and bacterial virulence is disrupted. Following the elimination and control of the offending chemicals, tissue healing occurs, and the periodontium's health may be recovered.

The fact that periodontal diseases tend to affect a small, localised area is a key characteristic of these conditions. As a result, studies of the local reactions following excisional biopsy of the afflicted areas and their histologic evaluation have been simple to carry out. There is some uncertainty as to whether the periodontium's extracellular matrix is considerably impacted by inflammation. Gingivitis causes tissue alterations that are specific to the gingiva, such as altered histochemical staining patterns of the afflicted matrix components and inflammatory cell infiltration. Repair of injured tissues is a crucial physiologic reaction required for the survival of the dentition. However, healing in the form of tissue regeneration is less predictable once the damaging stages reach the deeper periodontal structures. When there has been significant tissue damage, scarring is frequently caused during the repair process.[1]

Connective tissue elements also have considerable potential for the use in monitoring tissue changes and may be developed as an aid to periodontal diagnosis. Possible parameters that could provide this information would include ongoing loss of attachment or loss of alveolar bone. The gingival crevicular fluid contains many components of break-down products from the diseased periodontium, such as plasma proteins, bacterial and leukocytic enzymes, and inflammatory mediators. As a result, many studies have focused on analysing components of GCF in order to find a potential indicator of active periodontal breakdown. Each of these putative indicators has the unfortunate drawback of reflecting the process taking place in gingiva. Gingivitis and periodontitis cannot be distinguished from one another as a result. The periodontium contains a variety of connective tissue extracellular matrix components, however it is now clear that some of these components have some site specificity. Therefore, the creation of an assay that could recognise components specific to bone or periodontal ligament would be very helpful. It is now clear from a significant amount of basic and applied research that pathogenic, reparative, and regenerative processes take place in a complex milieu that is susceptible to disturbance due to matrix breakdown or interference with fibroblast metabolic activity. A thorough comprehension of these responses is essential to effective therapy as it enables the clinician to determine what constitutes a positive therapeutic outcome.[2]

## CELLS AND FIBRES OF CONNECTIVE TISSUE

Connective tissue develops from mesenchyme, an embryonic type of tissue, which is present in the umbilical cord and the pulp of developing teeth. It is composed of cells and extracellular material called matrix, with the exception of blood and lymph. The extracellular matrix is composed of connective tissue fluid, a ground substance in which the various protein fibres (collagen, reticular, and elastic) are embedded.

The fibroblast cells, both active and dormant, are the most prevalent cell types in connective tissue. Fibrocytes are the name for the dormant or resting fibroblast. All connective tissue fibres and the extracellular ground substance are produced by fibroblasts, which are fusiform in shape. Other type of cells present are adipose cells, macrophages, mast cells, plasma cells, leukocytes, neutrophils and eosinophils. Residents of connective tissue cells include fibroblast and adipose cells. Other blood components, such as neutrophils, eosinophils, and mast cells, move from blood arteries to connective tissue in various body areas.[3]

The three different categories of connective tissues are reticular, elastic, and collagen. All of them are descended from fibroblast. The function of the tissues or organs in which these fibres are found determines their arrangement. Extracellular matrix, a semifluid gel with a high water content, makes up the ground substance of connective tissue. It contains polysaccharide chains of sticky glycoproteins, proteoglycans, and glycosaminoglycans. The primary glycosaminoglycan is hyaluronic acid, and other glycosaminoglycans combine to form aggregates called proteoglycans that draw water. It enables various content to diffuse more easily across blood vessels and cells, also acts as a barrier to the transmission of diseases. Hyaluronic acid can be hydrolysed by bacteria, which lowers barrier viscosity. It contains a number of cell-binding sticky glycoproteins, including fibronectin.[4]

## HISTOLOGIC FEATURES OF CONNECTIVE TISSUE

The dental follicular tissue that surrounds the tooth gives rise to the periodontium. The follicle gives rise to the cells that make up cementum, alveolar bone, and ligament fibres. The ligament, which joins the cementum to the actual alveolar bone, is made up of bundles of collagen fibres. Blood arteries and nerve trunks are located in interstitial spaces, where they can readily interface with blood vessels and nerves at the apex of the roots and the alveolar bone. High levels of fibroblasts, vascular, neuronal, bone, and cemental cells can be found in this tissue. Support for the teeth is the periodontal ligament's primary job. The ligament has a nutritive function that is crucial to maintaining the ligament's health, which has significant therapeutic ramifications. It also conveys neurological input to the masticatory apparatus.[5]

The names of two primary fibre classifications are based on where they are in relation to the teeth. The dentoalveolar group encircles the teeth's roots, while the gingival group is found around the necks of the teeth. These primary fibres are bundles of collagen fibres that are carefully arranged along the root surface, from the cervical region to the apex of the tooth, at inclinations significant to their functions. Although the majority of supporting fibres are collagenous, others have been described as elastic-like and having a structure distinct from collagen. We term these fibres oxytalan. Smaller in diameter, oxytalan fibres seem to interact with collagen bundles to support both the blood vessel walls and the collagen bundles. These fine elastic-like fibres stain with special stains that reveal their location to be almost longitudinal within the ligament when the fibres are viewed through a light microscope.

The principal fibres of the periodontal ligament in the gingival area are known as the gingival fibres. They consist of four groups of fibres, each having a different orientation and all supporting the gingiva The free gingival fibres arise from the surface of the cementum in the cervical region and pass into the free gingiva. The attached gingival fibres arise from the alveolar crest and pass into the attached gingiva. The circular or circumferential fibres are continuous around the neck of the tooth and resist gingival displacement. The alveolar crest fibres arise from the cementum at the neck of the

tooth and terminate in the alveolar crest. Transseptal fibres originate in the cervical region of each crown and extend to similar locations on the mesial and distal surfaces of each adjacent tooth. The dentoalveolar fibre group consists of five differently oriented principal fibre groups named according to their origin and insertion in the dentoalveolar process. The alveolar crest group originates at the cervical area, just below the dentino-enamel junction, and extends to the alveolar crest, as well as into the gingival connective tissue. These fibres resist intrusive forces. The horizontal fibre group extends in a horizontal direction from the mid root cementum to the adjacent alveolar bone proper. These fibres resist tipping of the teeth. The oblique fibre group extends in an oblique direction from the area just above the apical zone of the root upward to the alveolar bone, and the fibres resist vertical or intrusive masticatory forces. The apical fibre group extends perpendicular from the surface of the root apices to the adjacent fundic alveolar bone, which surrounds the apex of the tooth root. Apical fibres resist vertical and extrusive forces applied to the tooth. Another group of fibres that are located between the roots of multirooted teeth is termed interradicular fibres.

## TYPES AND DISTRIBUTION OF COLLAGENS

The extracellular matrix that supports the cells of periodontium and those of other connective tissues controls their actions and functions. Collagens, non-collagenous proteins, and proteoglycans are among the organic components that make up the connective tissue matrix. The collagens are the main structural elements among them.[6]

Collagen molecules have a stiff, rod-like shape that prevents stretching, and collagen-containing fibres have a high tensile strength. As mechanical forces need to be produced without loss in tissues like periodontal ligament and tendon, this protein is crucial for their structural integrity. In addition to its structural function, collagens have the power to affect a variety of cellular processes, including cell differentiation and shape.

### Types of collagens

There are at least 19 different varieties of collagen that have been identified so far, making the collagen a sizable family of proteins. Based on their capacity to generate fibrils, these are essentially categorised into three classes. Collagens that produce banded fibrils are known as fibril-forming collagens, and they are the most immediately recognisable types of collagen. This category includes collagens of types I, II, III, IV, and XI. The proteins that make up the second group of collagens, which are found attached to the surface of collagens that form fibrils, have collagenous domains that are broken up by non-collagenous sequences. Fibril Associated Collagen with Interrupted Triple Helixes (FACIT) is the name of this subgroup. They include collagen types IX, XII, and XIV. They are special because the glycosaminoglycan components they contain are covalently bonded to the protein. The third category contains all other nonfibrillar collagens, including type IV, type VIII, and type X, which form networks, type VI, which forms beads, and type VII, which forms anchoring fibrils. These collagens create protein membranes or sheets that cover tissues and other living things.[7]

### Distribution

A variety of collagen types are present in all tissues, and both the proportion of the various collagen forms and their structural organisation vary widely. Type I collagen makes up between 65% and 95% of all the collagens in mammalian tissue, making it the most prevalent type of collagen. Type III is, numerically, the second major species in soft connective tissues. Type I collagen makes up the majority of the calcified tissues that make up thick connective tissues, including bone, along with very trace amounts of types V, III, XII, and XIV. Type II collagen is the primary fibril-forming collagen found in cartilage, with type XI and FACIT types IX and XII constituting minor species. Only the structures with basement membranes have type IV collagen. This collagen is attached to type VII collagen-based anchoring fibrils. In skin, the lamina densa, which has type IV collagen and laminin-1 on the other end, forms anchoring fibrils that extend to the papillary dermis.

## BIOSYNTHESIS OF COLLAGENS

The collagen molecule is physiologically insoluble. It has two amino acids that are post-transitionally changed from peptidyl prolines and lysines, hydroxyproline and hydroxylysine. Due to the modification enzymes' inaccessibility to the triple helical collagen molecule, this modification can only take place on nascent alpha chains. These factors lead to the creation of a bigger precursor that has extra amino acids at both the N- and C-terminal ends before the collagen molecule is created. Several well-coordinated biosynthetic events taking place in the nucleus, cytoplasm, and extracellular space are required for the synthesis of these pro-alpha chains, their assembly into procollagen, and their conversion to collagen fibres.[8]

Multiple steps are involved in the process of converting procollagen into mature collagen fibres in the extracellular environment. N- and C-procollagen peptidases are used to first eliminate the pro-peptide sequences at the N- and C-terminal ends. The pro-N domains are taken out of this enzyme's substrate, which must be triple helical. Type I, II, and III procollagens have their pro-peptides removed, whereas other collagens may undergo a different processing step or none at all. For instance, N- and C- terminal extensions are preserved in mature fibrils and are not cut off in nonfibrillar collagens. Due to the arrangement of charged and hydrophobic patches on their surface, the fibrillar collagens produced in this way spontaneously assemble as ordered fibrils. This configuration allows for interaction with the side chains of molecules adjacent to it and provides tensile strength to the fibrils and fibres formed.[9]

For orderly fibril formation, the pro-peptide extensions must be removed, and their retention, particularly at the N-terminus, causes poor apposition of the collagen molecules due to steric hindrance. Because of this, fibrils don't grow normally and end up being thinner and less organised. Covalent cross-linking stabilises the collagen fibrillar array. Lysyl oxidase is a necessary enzyme for cross-linking. Cofactors such as pyridoxal phosphate and Cu++ are needed. The remaining elements of the extracellular matrix are subsequently combined with cross-linked collagen molecules to create the three-dimensional scaffolding. Collagens are ultimately organised into fibres according to the unique functional requirements of each tissue, as well as by the presence of minor collagens and proteoglycans like decorin. As a result, while they form branching and anastomosing fibres in the skin, thick collagen fibres made up of type I and III collagens in tendon and ligament are oriented parallel to their long axis.[9]

## REGULATION OF COLLAGEN BIOSYNTHESIS

Collagens are the basic structural elements of connective tissues, and each tissue has a typical blend of different collagen types. In order to maintain tissue integrity, the quantity and percentage of collagens within each tissue must be precisely managed. Regulation is required to govern the architecture of the fibres as well as the quantity of collagen generated. The variations in connective tissues characteristics observed when wounds heal serve as one example of this. After an injury, granulation tissue replaces the wound bed first, followed by either normal tissue or a scar. Despite the fact that the connective tissue in all three scenarios may include the same matrix components, its tensile strengths vary. Therefore, scar and granulation tissue cannot perform as well as the regular tissue, despite the fact that they can partially replace tissue qualities.

The level of gene transcription is where regulation of collagen formation happens most crucially. During both healthy development and homeostasis, collagen gene expression is controlled in a cell- and tissue-specific way. Promoter and enhancer elements play a major role in the regulation of transcription rates. The first intron of the COL1A2 gene contains short promotor and enhancer sequences for the type I collagen gene. Through this sequence, TGF-B has been observed to increase collagen gene transcription. The amount of mRNA for collagen's alpha chains determines how much collagen is synthesised. Although the rate of transcription determines these levels primarily, other drugs, such as TGF-B, raise mRNA levels by enhancing their stability. Through this sequence, TGF-B has been observed to increase collagen gene transcription. The amount of mRNA for collagen's alpha chains determines how much collagen is synthesised. Although the rate of transcription determines these levels primarily, other drugs, such as TGF-B, raise mRNA levels by enhancing their stability.[10]

Numerous growth factors, hormones, cytokines, and lymphokines affect collagen production during development, inflammation, and wound healing. The most notable of them is TGF-B, which promotes the synthesis of collagen and other matrix substances. The assessment of fibrotic lesions has also been linked to this growth factor. When there is inflammation, platelets, macrophages, keratinocytes, and fibroblasts secrete numerous growth factors and cytokines that affect collagen synthesis. Their presence at the sites of inflammation and at wound sites typically correlates with changes in collagen synthesis. Same mechanism is followed for the regulation of collagen synthesis in periodontal tissues.[11]

## DEGRADATION AND REMODELLING OF COLLAGENS

Ovulation, embryo implantation, and the involution of the uterus and mammary glands are examples of natural tissue remodelling processes that involve the degradation of collagen and other matrix components. Pathologic changes are also substantially influenced by extracellular matrix degradation. For instance, in conditions like periodontitis, rheumatoid arthritis, and other chronic inflammatory illnesses, matrix degradation is a crucial factor in the breakdown of connective tissue.

The collagenases play a major role in the breakdown of collagen. The collagenases are members of the matrix metalloproteinases (MMP) enzyme family. They have been categorised as collagenases, gelatinases, stromelysins, and matrilysins based on their substrate specificity.[12]

Human epithelial and mesenchymal cell types such as keratinocytes, fibroblasts, and macrophages all generate collagenase- I (MMP-1). Type I, II, III, VI, VIII, and X collagens and gelatins can be hydrolyzed by this enzyme. Collagenase-2 (MMP-8) is a different enzyme that also hydrolyses type I and type III collagens, although it does so more quickly with type I collagens. Only the granules of polymorphonuclear leukocytes contain collagenase-2. A recently identified enzyme called collagenase-3 is present in breast cancer. The 72kd and 92kd are two important MMPs that belong to the gelatinase group. Although both of these enzymes have a strong predilection for gelatin, they also destroy elastins and type IV, VII, X, and XI collagens. In addition to degrading collagens, stromelysins can also break down proteoglycans, the basement membrane, laminin, and fibronectin. So far, stromelysin-1, stromelysin-2, and stromelysin-3 have all been identified. Other MMPs include metalloelastase (MMP-12) and matrilysin (MMP-7).[13]

At least three separate mechanisms prevent the MMPS from acting destructively in vivo. These enzymes are typically found in tissues as inactive precursors, and activation by plasmin, trypsin, or other proteinases is necessary for transformation into an active form. When

necessary (such as during inflammation), the activating proteinases themselves are activated. They are also controlled by other proteins like tissue plasminogen activator.

Modulation of MMP synthesis is the second mechanism by which it is controlled. Numerous mediators, such as growth factors and cytokines, stimulate the production of MMP. IL-1 and TGF-B, two important regulators of MMP production, are abundant in tissues that are inflamed. IL-1, TNF-a, and PGE2 stimulate fibroblast and keratinocyte production of MMP in these and other tissues. Lipopolysaccharides (LPS) promote macrophage MMP production, and IFN-gamma, IL-4, and IL-10 suppress MMP production. MMP synthesis is additionally inhibited by glucocorticoids and retinoid hormones.[14]

Finally, inhibitors found in serum and tissues block the activities of MMPs. A2-macroglobulin, a significant serum inhibitor, functions as a powerful inhibitor of the collagenase MMP-1 by attaching to this MMP with a greater avidity than collagen, which serves as MMP-1's natural substrate. The term "tissue inhibitor of metalloproteinases" (TIMP) refers to a class of inhibitors found in many different tissues and bodily fluids.

## DISEASES ASSOCIATED WITH COLLAGEN ALTERATIONS

Two of the most prevalent chronic inflammatory illnesses affecting people as well as many other animal species are gingivitis and periodontitis. These illnesses are caused by the accumulation of bacteria on tooth surfaces proximal to the supra- and subgingival tissues, which triggers inflammatory reactions in the host.

A generalised acute inflammatory reaction to the bacteria primary colonising on the tooth surface adjacent to the gingiva causes gingivitis. Gingivitis can develop into a serious condition over time, but it can also stay contained to the superficial gingival connective tissues and can display all the typical signs of a chronic inflammatory lesion. The lesion is known as periodontitis if the existing inflammatory reaction extends from the gingiva to the deeper periodontal tissues and alveolar bone leading to its destruction. Uncertain mechanisms govern the transition from gingivitis to periodontitis. Gingivitis may occasionally be the first stage in the development of periodontitis. Gingivitis, however, may exist in some people as a standalone clinical disorder without developing into periodontitis.[15]

## PATHOPHYSIOLOGY

Within days after supragingival plaque buildup, bacteria, particularly lipopolysaccharides (LPS), engage CD14-cell surface receptors of epithelial cells (keratinocytes) through an interaction with a serum protein. These chemicals may interact with endothelial cells, fibroblasts, and leukocytes after entering the gingival connective tissue. These pathways allow for the delivery of instructional messages to the vasculature, triggering the initial inflammatory responses such as polymorphonuclear leukocyte margination and extravasation as well as vascular fluid exudation. Leukocytes and fluid discharge go towards the gingival sulcus to bathe the forming plaque together. This early host response might not be enough to stop the microbial threat. The first stages of matrix degradation, which pave the way for more cell migration and the population of the gingival connective tissues, start with the emigration of polymorphonuclear leukocytes. If the bacterial plaque is allowed to build up, gingivitis will manifest clinically. Around 4 to 7 days following the buildup of plaque, early gingivitis becomes established. The inflammatory responses continue and start to show symptoms of amplifying, as seen by the ongoing infiltration of macrophages and lymphocytes as well as the continued loss of collagen.[16]

## GINGIVITIS AND PERIODONTITIS-MATRIX CHANGES

The loss of gingival connective tissue is a defining characteristic of inflammatory periodontal disorders. The perivascular extracellular matrix, where the majority of the collagen within the foci of inflammation is destroyed, is where tissue degradation starts with the development of gingivitis. In gingivitis, matrix metalloproteinases produced by polymorphonuclear leukocytes play a major role in the matrix's degradation. However, in periodontitis, the breakdown of the matrix is aided by the matrix metalloproteinases produced by polymorphonuclear leukocytes, macrophages, keratinocytes, and fibroblasts. The gingival lesion may persist for years or even decades and reoccur with episodic illness stages in which the inflammatory foci show signs of scarring and fibrosis. Dogs do not exhibit this type of gingival fibrosis, but it is present in humans, baboons, and chimpanzees with slowly progressing periodontitis. In patients with the above disorders, gingival collagen undergoes both quantitative and qualitative alterations. Collagen in the gingiva becomes more soluble, a sign of recent and active production. Collagens of types I and III are depleted in inflammatory foci. The ratios of the different types of collagen change; type V collagen amounts rise and may surpass type III levels; and type I trimer, a novel type of collagen, can be found in inflamed gingiva.

## ENZYME-MEDIATED DAMAGE BY HOST CELLS

Extracellular degradation of the matrix occurs via the release of numerous matrix metalloproteinases (MMP). These enzymes can efficiently degrade interstitial or basement membrane collagens, laminin, fibronectin, and the core proteins of proteoglycans. In the inflamed tissues, these enzymes are derived from polymorphonuclear leukocytes, macrophages, fibroblasts, keratinocytes, and endothelium. The secreted matrix metalloproteinases subsequently activated by

proteinases such as plasmin, which in turn are regulated by tissue protein factors such as plasminogen activators.

**TISSUE-DEGRADING ENZYMES FROM BACTERIAL PLAQUE**

Many bacteria in the dental plaque secrete a wide variety of enzymes that have the potential to break down matrix components that may hydrolyse collagens to peptides in culture such as Porphyromonas gingivalis, Clostridium histolyticum, Treponema denticola, and Bacteroides forsythus. Furthermore, it should be highlighted that in order for an enzyme to destroy a matrix, at least three conditions must be met. First the enzyme must be present in the tissues in an active form, not complexed with an inhibitor or present in a reactive state. Second in order for the enzyme's catalytic site to be active, it must also be in the proper conformation. In this regard, the surrounding matrix is likely to play a significant role in the configuration of a molecule through the interplay of complex physiochemical interactions between the matrix and the enzyme. Third the substrate also needs to be in a form that gives the enzyme access to the cleavage sites. While collagenase may able to break down pure collagen in a test tube, it is still unclear if it can access cleavage sites to break down native collagens complexed with various other matrix elements.[17]

**PHAGOCYTOSIS**

The phagocytosis of extracellular matrix components by fibroblasts and macrophages is thought to play a substantial part in the degradative route for collagen during physiologic turnover of the periodontal connective tissues. Prior to the cell ingesting collagens, the phagocytic process necessitates some type of proteolytic breakdown. Such proteolytic digestion may be carried out by enzymes present on the cell surface or right next to lysosomal or matrix metalloproteinases in the extracellular matrix. However, phagocytosis has been observed to continue even if such enzyme activity is prevented by blocking antibodies to collagenase or the addition of cysteine proteinase inhibitors. The precise method by which collagen is phagocytosed is still unknown. During the physiologic turnover of the periodontal connective tissues, the phagocytosis of extracellular matrix components by fibroblasts and macrophages is assumed to play a significant role in the degradative pathway for collagen. The phagocytic process demands some sort of proteolytic degradation before the cell consumes collagens. Enzymes on the cell surface or close to lysosomal or matrix metalloproteinases in the extracellular matrix may perform such proteolytic digestion. However, it has been found that phagocytosis still occurs even if collagenase-blocking antibodies are used or cysteine proteinase inhibitors are added. It is still unclear how exactly collagen gets phagocytosed.

**FREE RADICALS IN TISSUE DESTRUCTION**

Free radicals are independent atoms, ions, or molecules that have one or more unpaired electrons in their outer orbit. The oxygen-derived free radicals (ODFR), which are byproducts of regular cellular metabolism and include superoxide and hydroxyl radicals, are of special importance in tissue damage. Other elements of oxygen metabolism, besides free radicals, include hydrogen peroxide and hypochlorous acid (HOCI).[18]

Reactive oxygen species are created during normal cellular metabolism through a variety of different mechanisms, and they are present in particularly high concentrations in cells that are experiencing respiratory bursts at inflammatory locations. These are either formed as a result of electron transport chains or metabolic processes, or by certain enzyme systems that are made specifically to make free radicals. In rare circumstances, tiny molecule auto-oxidation may also produce radicals. Two enzymes that are particularly active during the respiratory burst of activated neutrophils and macrophages are myeloperoxidase and NADPH oxidase, which cause the generation of superoxide and hydroxyl radicals as well as hypochlorite. It has been discovered that the chain of events connected to arachidonic acid metabolism produces free radicals. During inflammatory reactions, tissues may be exposed to a variety of free radicals, especially when polymorphonuclear leukocytes and macrophages are in high concentrations and produce large amounts of oxygen-derived free radicals, which can cause serious cellular and tissue damage. The superoxide radical is the least hazardous of the reactive oxygen species produced for cells or tissues.

**EFFECTS OF SOLUBLE MEDIATORS ON CONNECTIVE TISSUE CELLS**

Fibroblasts produce and maintain the components of the matrix mostly in soft periodontal connective tissues. whereas the matrix in alveolar bone and cementum is produced by osteoblasts and, presumably, cementoblasts. The actions of these cells are governed by a wide range of environmental elements. Numerous of these compounds have been investigated for their effects on periodontal fibroblasts in terms of cell proliferation as well as collagen and proteoglycan synthesis. Numerous isoforms of the molecules platelet-derived growth factor (PDGF), epidermal growth factor (EGH), prostaglandin E (PGE), interferon-gamma, tumour necrosis factor (TNF)-alpha, and interleukin-1 (1L-1) are among those that are investigated. In rheumatoid arthritis, periodontitis, and other inflammatory illnesses, as well as in bone resorption, IL-1 is a key cytokine implicated in matrix breakdown. The stimulation of collagenase, gelatinases, and stromelysin-I genes is thought to be how IL-1 works.274,275 IL-1a, IL-1ß, TNF-alpha, IL-6, IL-8, and IFN-gamma are found in gingival crevicular fluid and inflamed gingival tissues, and it is thought that their presence raises the levels of matrix-degrading enzymes in the gingival tissue.[19]

The age of the cells, the environment in the area, and the stage of the cell cycle all play a role in how the fibroblasts react to different substances. For instance, the

matrix promotes differentiation and suppresses cell division, whereas cells continue to divide in the absence of the matrix. The kind and quantity of different substances in the immediate surroundings dictate how cells react to and control the development of healing and repair activities.

The factors obtained from epithelium may affect fibroblast activity in both healthy and pathologic circumstances. Although fibroses and overgrowths are frequently linked to larger epithelia, little is known about how the epithelium interacts with the underlying connective tissue. It indicates that epithelium is a significant source.[20]

## CLINICAL ASPECTS

### Gingival Crevicular Fluid: Connective Tissue Elements As Diagnostic Markers

When diagnosing periodontal conditions, emphasis needs to be given to each of the following processes: bacterial infection, genetic vulnerability, metabolic reactions, and anatomical changes. These events are linked to the development of periodontitis. It seems uncertain that a single measure will ever be employed as a universal diagnostic tool due to the complex character of the condition.

GCF, a connective tissue element seems to be an ideal medium for evaluating the alterations brought about by periodontal disease development. Its kinetics and composition are intimately correlated with the environment of the periodontal tissues, and it can be collected non-invasively. More than 40 components have been identified in the gingival crevicular fluid and have been classified by Cimasoni (1983) into cellular elements, electrolytes, organic compounds, bacterial products, metabolic products, enzymes, and enzyme inhibitors. In particular, attention has focused on biochemical mediators of inflammation, tissue-degrading enzymes, and tissue breakdown products in the gingival crevicular fluid as markers of the inflammatory response and possible indicators of some aspects of periodontal disease activity.[21]

### Periodontal Regeneration

Restoring diseased periodontal tissues to their native structural form and function is the primary objective of periodontal therapy. This necessitates the restoration of dropping bone, a formation of cementum, the regeneration of the gingival connective tissues that were destroyed by inflammation, and the reestablishment of connective tissue fibres into the previously infected root surface. Many substances take role in controlling the mechanisms that lead to periodontal regeneration. Based on their mechanism of action, these chemicals can be categorized into three groups: (1) growth factors and other inflammatory mediators, including cytokines, lymphokines, and chemokines; (2) adhesion molecules, such as fibronectin and laminin; and (3) matrix components such as collagens, proteoglycans, and hyaluronan. Considering the aforementioned, it is evident that periodontal wound healing is more intricate than basic soft tissue healing due to the need for the participation of a minimum of four distinct tissues, all of which are distinct in both structure and biology.

## CONCLUSION

The periodontium is a distinctive anatomical region that contains four distinct connective tissues the gingiva, periodontal ligament, cementum, and alveolar bone. These tissues are continuously subjected to mechanical and chemical alteration due to the constant masticatory pressures and oral microbiota, but they are nonetheless able to preserve their structural and functional integrity within their physiological limits. However, disease results when the delicate balance between host defence and bacterial pathogenicity is compromised. Following the elimination and control of the offending chemicals, healing of the tissue occurs, and the periodontium's health may be recovered.

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