REVIEW ARTICLE

Collagen in Health and Disease

Simarpreet V Sandhu, Shruti Gupta, Himanta Bansal, Kartesh Singla

ABSTRACT

Collagen is the unique, triple helical protein molecule which forms the major part of the extracellular matrix. It is the most abundant protein in the human body, representing 30% of its dry weight and is important to health because it characterizes the structure of skin, connective tissues, tendons, bones and cartilage. As collagen forms building block of body structures, any defect in collagen results in disorders, such as osteogenesis imperfecta, Ehlers-Dalnos syndrome, scurvy, systemic lupus erythematosus, systemic sclerosis, Stickler syndrome, oral submucous fibrosis, Marfan syndrome, epidermolysis bullosa, Alport syndrome. This review discusses the role of collagen in health as well as disease.

Keywords: Collagen, Collagen disorders, Extracellular matrix, Fibroblast, Health.

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INTRODUCTION

Collagen has been studied extensively by a large number of research laboratories since the beginning of the 20th century. It comprises a family of proteins present in the skin, bone, cartilage, smooth muscle and basal lamina and provides rigidity, elasticity and strength. Collagens are produced by several cell types and are distinguishable by their molecular compositions, morphologic characteristics, distribution, functions and pathologies.[1] This is the major fibrous glycoprotein present in the extracellular matrix and in connective tissue and helps in maintaining the structural integrity of these tissues. It has a triple helical structure. Collagen forms the major component of many vital tissues in body and is essential in maintenance of structure and function of body. Various studies have proved that mutations that modify folding of the triple helix result in identifiable genetic disorders.[2] Therefore, this review highlights the role of collagen in normal health and also the disorders associated with structural and functional defects in collagen.

Structure and Types of Collagen

It is the most abundant protein in animals. In humans, collagen encompasses one-third of the total protein, accounts for three-quarters of the dry weight of skin and is the prevalent constituent of the extracellular matrix. Twenty-eight different types of collagens composed of at least 46 distinct polypeptide chains have been recognized in vertebrates (Table 1). Variations among collagen includes difference in assembly of basic polypeptide chain, different length of triple helix, interruptions in helix, difference in termination of helical domains. This fibrous, structural protein comprises a right-handed bundle of three parallel, left-handed polyproline II-type helices. Common characteristic is the presence of hydroxyproline and hydroxylysine and glycine is present at every third position. It is supposed that glycine, because of its small size, permits the close association of the three α-chains. The three α-chains are held together by hydrogen bonds of hydroxyproline whereas hydroxylysine permits the formation of fibrils by binding the tropocollagen molecules to each other and provide collagen molecule with sites of attachment for short carbohydrate chains that are made up of glucose, galactose or both. Collagen fiber bundles are referred to as white fibers because of the fact that collections of collagen fibers appear glistening white in living tissue.[3,4]

Microscopic Appearance

When unstained collagen fibers of connective tissue are usually less than 10 μm in diameter and are colorless. They appear as long, wavy, pink fibers bundles after staining with hematoxylin and eosin. Electron micrographs of collagen fibers stained with heavy metals display crossbanding at regular intervals of 67 nm, a characteristic property of these fibers. These fibers are formed from parallel aggregates of thinner fibrils 10 to 300 nm in diameter and many micrometers in length.[3, 4]

Synthesis of Collagen

Mesenchymal cells and their derivatives (fibroblasts, osteoblast, odontoblast, chondroblasts and cementoblasts) are the chief producers of collagen. Other cell types synthesizing collagen are epithelial, endothelial, muscle and Schwann cells[4] (Fig. 1).

Fibroblast

Fibroblast is the most common cell of connective tissue that produces and maintains the extracellular matrix. Fibroblasts provide a structural framework for many tissues and play an imperative role in wound healing. The key function of fibroblasts is to maintain the structural integrity of connective tissues by continuously secreting precursors of the extracellular matrix, primarily the ground substance and a variety of fibers. They are recognized by their association with collagen fibers bundles. The quiescent fibroblast or fibrocyte

Table 1: Types of collagen[3-5]

Molecule type	*Synthesizing cell*	*Function*	*Location in body*
1. Fibril-forming; most common of all collagens	Fibroblasts, osteoblasts, odontoblasts, cementoblasts	Resists tension	Dermis, tendon, ligaments, capsules of organs, bone, dentin, cementum
2. Fibril-forming	Chondroblasts	Resists pressure	Hyaline and elastic cartilage
3. Fibril-forming; also known as reticular fibers. Highly glycosylated	Fibroblasts, reticular cells, smooth muscle cells, hepatocytes	Forms structural framework of spleen, liver, lymph nodes, smooth muscle, adipose tissue	Lymphatic system, spleen, liver, cardiovascular system, lung, skin
4. Network-forming; do not display 67 nm periodicity and α-chains retain propeptides	Epithelial cells, muscle cells, Schwann cells	Forms meshwork of the lamina densa of the basal lamina to provide support and filtration	Basal lamina
5. Fibril-forming	Fibroblasts, mesenchymal cells	Associated with type I collagen, also with placental ground substance	Dermis, tendon, ligaments, capsules of organs, bone, cementum, placenta
6. Microfiber forming collagen	—	Bridging between cells and matrix (has binding properties for cells, proteoglycan, a type I collagen)	Ligaments, skin, cartilage
7. Network-forming; form dimers that assemble into anchoring fibrils	Epidermal cells	Forms anchoring fibrils that fasten lamina densa to underlying lamina reticularis	Junction of epidermis and dermis
8. Meshwork	—	Tissue support, porous meshwork, provide compressive strength	Basal laminae of endothelial cells and smooth muscle cells and Descemet's membrane of cornea
9. Fibril-associated; decorate the surface of type II collagen fibers	Epithelial cells	Associates with type II collagen fibers	Cartilage
10. Meshwork	—	Calcium binding	Hypertrophic zone of cartilage growth plate
11. Fibril collagen fibers	—	Forms core of type II fibers, provides tensile strength	Cartilage and vitreous humor
12. Fibril-associated; decorate the surface of type I collagen fibers	Fibroblasts	Associated with type I collagen fibers	Tendons, ligaments and aponeuroses
13. Transmembrane protein	—	Cell matrix and cell adhesion	Cell surfaces, focal adhesion and intercalated disks
14. FACIT	—	Modulates fibril interactions	
15. Endostatin forming collagen	Endothelial cells	Proteolytic release of antiangiogenic factor	Endothelial basement membrane
16. Cartilage and placenta	—	Unknown	Endothelial, perineural muscle and some epithelial basement membrane, cartilage and placenta
17. Collagen-like protein; a transmembrane protein, formerly known as bullous pemphigoid antigen	Epithelial cells	Cell to matrix attachment	Hemidesmosomes
18. Collagen-like protein; cleavage of its C-terminal forms endostatin and angiogenesis inhibitor	Endothelial cells	Proteolytic release of antiangiogenic factor	Endothelial basement membrane
19. FACIT	—	Unknown	Endothelial, perineural muscle and some epithelial basement membrane, cartilage and placenta
20. FACIT	—	—	Cornea (chick)
21. FACIT	—	—	Stomach, kidney
22. FACIT	—	—	Tissue junctions
23. Membrane-associated collagen with interrupted triple helix	—	—	Heart, retina
24. Fibrillar	—	—	Bones, cornea
25. Membrane-associated collagen with interrupted triple helix	—	—	Brain, heart, testis
26. FACIT	—	—	Testis, ovary
27. Fibrillar	—	—	Cartilage
28. Microfiber forming collagen	—	—	Dermis, sciatic nerve

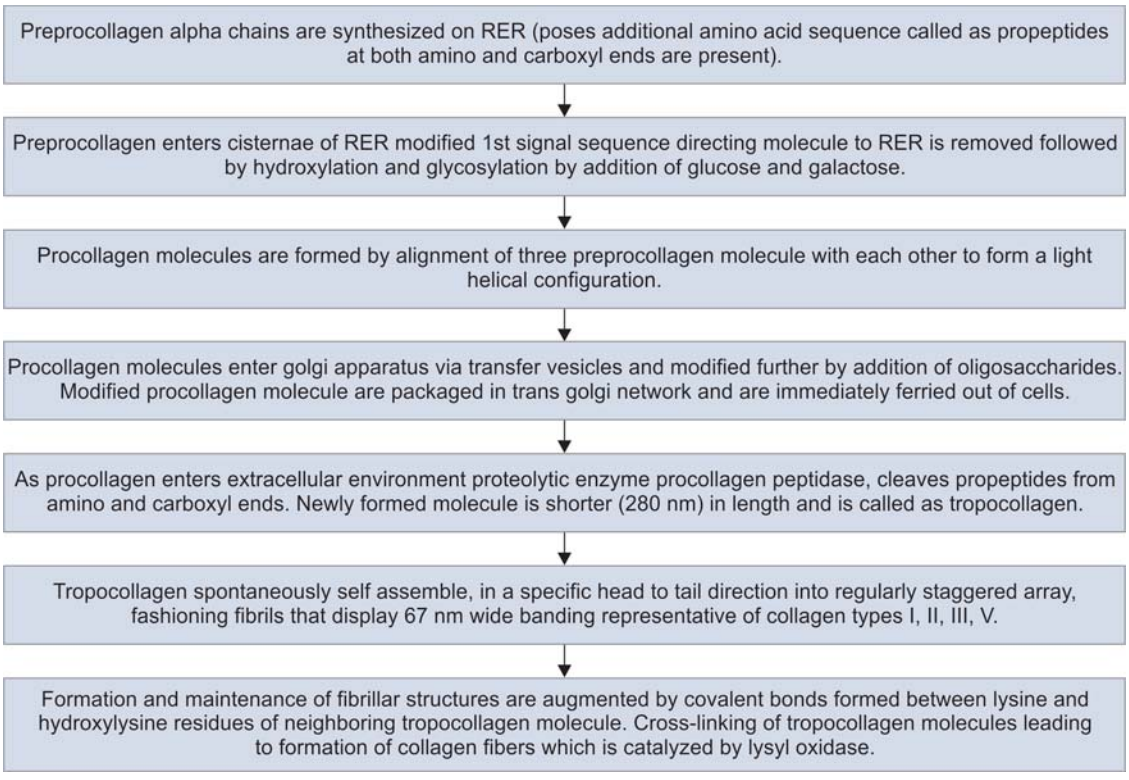

Fig. 1: Synthesis of collagen

is smaller than the active fibroblast and is usually spindle-shaped. It has fewer processes; a smaller, darker, elongated nucleus; and more acidophilic cytoplasm with much less rough endoplasmic reticulum. They have a branched cytoplasm surrounding an elliptical, speckled nucleus having one or two nucleoli. Active fibroblasts can be recognized by their oval, pale- staining nucleus and greater amount of cytoplasm, abundant rough endoplasmic reticulum, golgi apparatus, secretory vesicles and mitochondria (Fig. 2). Fibroblasts exhibit contractility and motility which are important during connective tissue remodeling and formation and during wound repair. In certain tissues, fibroblasts have significant contractile properties and are called as myofibroblasts.[3,5]

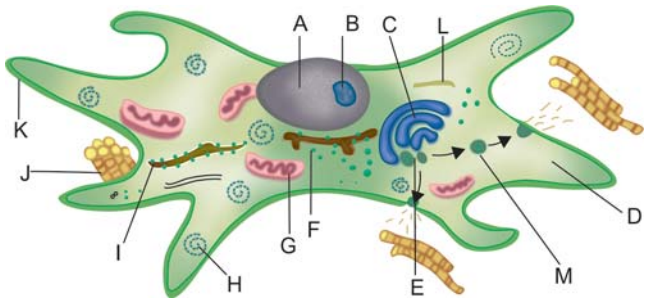

Fig. 2: Structure of fibroblast. A: Nucleus; B: Nucleolus; C: Golgi apparatus; D: Cytoplasm; E: Intermediate/transfer vesicles; F: Ribosomes; G: Mitochondria; H: Polyribosomes; I: Rough endoplasmic reticulum; J: Collagen fibrils; K: Cell processes; L: Microtubules; M: Secretory granules

Degradation of Collagen

Mechanisms involved in degradation of collagen are: (1) Secretion by cells of enzymes that sequentially degrade collagen and other matrix molecule extracellularly, (2) selective ingestion of collagen fibrils by fibroblasts and their intracellular degradation. Collagen triple helix is highly resistant to proteolytic attack. Matrix metalloproteinases (MMP) is a large family of proteolytic enzymes that includes: Collagenases (MMP-1, 8, 13), gelatinases (MMP-2, 9), metalloelastases (MMP-12), stromelysins (MMP-3, 10, 11), matrilysin (MMP-7) that are involved in degradation of collagen. Collagenase 1, 2 and 3 degrades type I, II, III, V collagen, collagenase 3 can degrade type I, II, III, IV, IX, X, XI, fibronectin and other extracellular matrix component. Gelatinases A and B which is produced by alveolar macrophages and stromeolysins 1, 2 and metalloelastases degrade type I collagen and basement membrane component (type IV) collagen, fibronectin, elastin respectively.[5,6]

Collagen in Health

Collagen is sometimes referred to as the body's cement that holds everything in place. Collagen is important to health because it dictates the structure of skin, connective tissues, tendons, bones and cartilage.

1. *Skin health:* Collagen plays an important role in skin health. Type I and III collagen are formed in human skin in a higher proportion relative to other types and are maintained in a fixed proportion relative to one another in normal skin tissue. Collagen type I constitutes approximately 70% of

collagen in the skin, with type III being 10% and trace amounts of collagen types IV, V, VI and VII. Collagen maintains firmness and elasticity of skin. Collagen in the form of collagen hydrolysate keep skin hydrated. A lack of collagen becomes obvious during the aging process as skin begins to sag and lines and wrinkles begin to form. In formation of scar tissue as a result of age or injury, there is change in the abundance of types I and III collagen as well as their proportion to one another. Type III collagen synthesis decreases with age resulting in changes in skin tension, elasticity and healing.[7]

2. *Wound healing:* Collagen is a key protein in connective tissue and play an imperative role in wound healing by repair and formation of scar. Collagen deposition and remodeling contribute to the increased tensile strength of the wound, which is approximately 20% of normal by 3 weeks after injury gradually reaching a maximum of 70% of that of normal skin. Collagen overproduction can form abnormal scars, which impede wound healing. A chronic wound burden among the elderly has been documented and much of this age-related, delayed wound healing is caused by impaired collagen synthesis and increased degradation. Increase in fibroblasts and collagen during healing suggested that a correlation might exist between number of fibroblasts, quantity of collagen and tensile strength of a scar. [8]
3. *Bone:* Bone is a complex and dynamic tissue that provides structural support for the body, protection of internal organs and acts as levers to which muscles are attached, allowing movement. Out of 22 to 25% of organic component 94 to 98% is mainly collagen type I and other noncollagen proteins and 2 to 5% are cells. The combination of hard mineral and flexible collagen makes bone harder than cartilage without being brittle. Combination of collagen mesh and water forms a strong and slippery pad in the joint that cushions the ends of the bones in the joint during muscle movement. [9, 10]
4. *Cartilage, tendon, ligaments:* Collagen, in the form of elongated fibrils, is predominantly found in fibrous tissues such as tendon and ligament. It is a flexible and stretchy protein that is used by the body to support tissues and thus it plays a vital role in the maintenance of the cartilage, tendons and ligaments. Normal tendon consists of soft and fibrous connective tissue that is composed of densely packed collagen fibers bundles aligned parallel to the longitudinal tendon axis and surrounded by a tendon sheath also consisting of extracellular matrix components. Collagen constitutes 75% of the dry tendon weight and functions chiefly to withstand and transmit large forces between muscle and bone.[11] Collagen also forms a major constituent of cartilages. Cartilage collagen fibrils consist of collagen II, the quantitatively minor collagens IX and XI. [4,5]
5. *Muscles:* In muscle tissue, it serves as a major component of the endomysium. Collagen constitutes 1 to 2% of muscle tissue, and accounts for 6% of the weight of strong, tendinous muscles. [4,6]
6. Dental tissues:
   a. *Dentin:* The mature dentin is made up of approximately 70% inorganic material, 20% organic material and 10% water by weight. The organic phase is about 30% collagen (mainly type I with small amounts of types III and V) with fractional inclusions of lipids and noncollagenous matrix proteins. Collagen type I acts as a scaffold that accommodates a large proportion (estimated at 56%) of the mineral in the holes and pores of fibrils.[12]
   b. *Pulp*: The extracellular compartment of the pulp or matrix consists of collagen fibers and ground substance. The fibers are principally types I and III collagen. The overall collagen content of the pulp increases with age, the ratio between types I and III remains stable and the increased amount of extracellular collagen organizes into fiber bundles.[13]
   c. *Cementum:* Predominant collagen present in cementum is type I collagen (forms 90% of the organic matrix). Other collagens associated with cementum include type III, a less crosslinked collagen found in high concentrations during development and repair and regeneration of mineralized tissues and type XII that binds to type I collagen and also to noncollagenous matrix proteins. Collagens found in trace amount in cementum are types V, VI and XIV.[14]
   d. *Periodontal ligament:* Periodontal ligament is composed of collagen fibers bundles connecting cementum and alveolar bone proper. The predominant collagens of the periodontal ligament are types I, III and XII, with individual fibrils having a relatively smaller average diameter than tendon collagen fibrils. The vast majority of collagen fibrils in the periodontal ligament are arranged in definite and distinct fiber bundles and these are termed as principal fibers. The periodontal ligament has also the capacity to adapt to functional changes. When the functional demand increases, the width of the periodontal ligament can increase by as much as 50 % and the fiber bundles also increase markedly in thickness.[14]
7. *Basement membrane:* The epithelial basement membrane and adjacent area is termed the epithelial basement membrane zone. The lamina densa consisting of type IV collagen that is coated by heparan sulfate, a glyco-saminoglycan and anchoring fibrils, that are composed of type VII collagen and extend from the lamina densa to the connective tissue.[15]

Table 2: Categorization of collagen disorders

Heritable/genetic collagen disorders	*Autoimmune collagen disorders*	*Miscellaneous*
• Ehlers-Danlos syndrome • Osteogenesis imperfecta • Stickler syndrome • Alport syndrome • Epidermolysis bullosa • Marfan syndrome	• Systemic lumpus erythematosus • Systemic sclerosis • Oral submucous fibrosis	• Scurvy

Collagen Disorders Categorization

Heritable/Genetic Collagen Disorders

a. *Ehlers-Dalnos syndrome* (Tenascin – X deficiency syndrome/Lysyl hydroxylase deficiency syndrome)**:** Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous connective tissue disorder characterized by hyperextensibility of the skin, hypermobility of joints and tissue fragility. It was first described by Van Meekeran in 1682 (Table 2). The exact abnormality in biogenesis of the collagens has been identified in four varieties and in case of EDS IV an abnormal gene locus has been determined. In some clinical forms of EDS a mutation in COL1A1 and COL1A2 genes is reported which results in interferences with conversion of procollagen to collagen. This leads to defective crosslinking and a consequent reduction in tensile strength of tendons. Presence of dystrophic scars and a tendency to excessive bleeding manifested by bruises, ecchymoses and hematomas is noticed in EDS. The oral manifestations of EDS include the ability of 50% of these patients to touch the tip of their nose with their tongue (Gorlin sign), a feat that can be achieved by less than 10% of normal people. Mucosal tears are more frequent when touched by instruments and sutures do not hold. The gingiva is fragile and hemorrhage may be difficult to control during surgical procedures. Early onset generalized periodontitis is one of the most noteworthy oral manifestations of the syndrome resulting in the premature loss of deciduous and permanent teeth. Hypoplasia of the enamel is commonly seen. Premolar and molar teeth can present with deep fissures and long cusps. The teeth seem to be fragile and microdontia is sometimes present. Radiographic examination often divulges pulp stones and roots that are short and deformed. A tendency for recurrent subluxation of the temporomandibular joint has also been reported.[16,17]

b. *Osteogenesis imperfecta:* Comprises a heterogeneous group of heritable disorders characterized by impairment of collagen maturation. The disease causes either a decrease in collagen synthesis or the production of structurally defective collagen, hence, all tissues rich in type I collagen may be affected. Except on rare occasions, the disorder arises from heterozygosity for mutations in one of two genes that guide the formation of type I collagen: The COLIAI gene on chromosome 17 and the COLIA2 gene on chromosome 7. The clinical features commonly observed in patients with osteogenesis imperfecta include abnormal bone formation, growth deficiency, bone fragility, blue sclerae, hearing loss, skin thinness, joint laxity and hypermobility and dentinogenesis imperfecta. Abnormal collagenous maturation results in bone with a thin cortex, fine trabeculation and diffuse osteoporosis. Upon fracture, healing will occur but may be associated with exuberant callus formation. [6,18]

c. *Stickler syndrome:* It is a unique autosomal dominant syndrome of premature osteoarthritis, retinal degeneration, hearing loss and orofacial abnormalities described by Gunnar B Stickler in 1965. The disorder (hereditary arthro-ophthalmopathy or Stickler syndrome) is known to be caused by mutations in the COL2A1, COL11A1 and COL11A2 procollagen genes of type 2 and 11 collagen. [19]

d. *Alport syndrome:* Alport syndrome is a generalized inherited disorder of basement membranes, particularly those of glomeruli that involve type IV collagen. The mutations occur in the gene located on the X chromosome. Inherited defect of the classical X-linked Alport syndrome affects the α-5 chain of collagen type IV collagen gene (COL4A5) while the α-3 and α-4 chain of collagen type IV collagen gene (COL4A3 and COL4A4) are responsible for less frequent recessive forms of Alport syndrome. It is characterized by renal impairment, loss of hearing and lens abnormalities, hypertension, hematuria and proteinuria. The damage of collagen IV due to mutations causes dysfunction of bound epithelium and results in organ damage. [20]

e. *Epidermolysis bullosa:* Hereditary epidermolysis bullosa is a group of rare genetically transmitted disorders that have several methods of inheritance with various degrees of severity and expression. It is a multiracial disorder that is characterized by the formation of vesicles and bullae on the skin and mucous membranes. The vesicles may arise spontaneously or from minor trauma. The four types of epidermolysis bullosa are simplex, dystrophic and junctional and hemidesmosomal. Specific mutations in the K5 or K14 genes and genes coding for the laminin has

been responsible for dominant simplex type and junctional form respectively. The dystrophic type is related with mutations in the type VII gene. The hemidesmosomal type is characterized by mutations of genes associated with various hemidesmosomal attachment proteins such as plectin, type XVII collagen and $\alpha 6\alpha 4$ integrin.[21,22]

f. *Marfan syndrome:* It is the most common inherited connective tissue disorder with a reported incidence of one in 10,000 individual and equal distributions between the sexes. It is caused by an autosomal dominant mutation in the gene encoding fibrillin (FBN1, chromosome 15q15–21.3), a glycoprotein that is an integral part of the connective tissue in the body (ligaments, blood vessel, eye lenses). It primarily involves the skeletal, ocular and cardiovascular systems. Typically, patients present with tall stature, ectopia lentis, aortic root dilatation and a positive family history. The diagnosis is made when a patient presents with complications of the syndrome, such as aortic dissection or with involvement of the pulmonary, skin/integument or nervous systems. [23]

Autoimmune Collagen Disorders

a. *Systemic lupus erythematosus:* Lupus erythematosus is a multifactorial autoimmune collagen vascular or connective tissue disease, which may affect the oral mucosa in either its cutaneous and systemic forms with varied prevalence. Common findings include fever, weight loss, arthritis, fatigue and general malaise. A characteristic rash, having the pattern of a butterfly, develops over the malar area and nose. Cardiac involvement is also common with pericarditis. Warty vegetations affecting the heart valves (Libman-Sacks endocarditis) are also observed. Oral lesions include ulceration, pain, erythema and hyperkeratosis may be present. Other oral complaints are xerostomia, stomatodynia, candidiasis, periodontal disease and dysgeusia. [21,24]

b. *Systemic sclerosis (progressive systemic sclerosis; scleroderma; hide-bound disease):* Progressive systemic sclerosis is a disorder of the connective tissue that illustrates fibrosis of the skin, blood vessels, visceral organs and mucosa. The exact mechanism of the fibrotic changes is unknown, but hyperplastic changes of collagen have been documented. The pathological findings signify that fibroblasts are activated to produce excessive amounts of collagen and other components of the cellular matrix. The most apparent symptom is the involvement of the skin together with the quality of its mobility, particularly in the distal portions of the extremities. Cutaneous manifestations include thickening of skin, starting with pitting edema and over several months pitting edema is replaced by tightening and hardening of skin. Raynaud´s phenomenon is usually the first symptom. The oral manifestations include classic facial skin hardening and limited opening of the oral orifice with characteristic furrows radiating from the mouth resulting in a classic mask-like and appearance purse string appearance respectively. Bone resorption at the angle of the mandible is also a common feature. Deposition of collagen in the lingual and esophageal submucosa, producing a firm, hypomobile (board-like) tongue and an inelastic esophagus, thus resulting in dysphagia.[21,25]

c. *Oral submucous fibrosis:* It is a chronic, premalignant condition of the oral mucosa which was first described by Schwartz 1952. Recently it is thought to be an autoimmune disease. The presence of various autoantibodies in varying titers is reported in several studies confirming autoimmune basis to the disease.[26] Tilakratne WM et al in 2006 reported that although the data on various HLA types, raised autoantibodies and the detection of immune complexes tend to indicate an autoimmune basis for the disease substantial number of cases and matched controls may be required to verify these findings.[27] This disease is considered to be a consequence of disturbances in the homeostatic equilibrium between synthesis and degradation of extracellular matrix, wherein collagen forms a major component, thus can be recognized as a collagen-metabolic disorder. It is characterized by a juxta epithelial inflammatory reaction followed by fibroelastic change in the lamina propria and associated epithelial atrophy. This leads to a restricted mouth opening, resulting in trismus leading to restriction of food consumption, difficulty in maintaining oral health, as well as impairs the ability to speak. The fibroelastic changes are almost entirely due to abnormal accumulation of collagen in the subepithelial layers, resulting in dense fibrous bands in the mouth. [28, 29]

Miscellaneous

Scurvy: A deficiency of vitamin C is known as scurvy. Key function of ascorbic acid is its involvement in the synthesis of collagen fibers from proline via hydroxyproline. Other metabolic reactions for which vitamin C is required are the hydroxylation of lysine into hydroxylysine in collagen. In individuals who suffer from a deficiency of this vitamin, the α-chains of the tropocollagen molecules are unable to form stable helices and the tropocollagen molecules are incapable of aggregating into fibrils. It first affects connective tissues with a high turnover of collagen, such as the periodontal ligament and gingiva. Avitaminosis C is associated with the failure of wound healing or the rupture of capillaries due to intrinsic intercellular weakness with lack of connective tissue support of the capillary walls. Among the presenting features

of scurvy, oral signs may be cardinal: Fetid odor and loosened teeth, gingivae are boggy, ulcerated and bleed with the interdental and marginal gingiva becoming bright red, smooth, swollen and shiny.[30]

CONCLUSION

Collagens are the major structural element of all connective tissues and are also found in the interstitial tissue of virtually all parenchymal organs, where they contribute to the stability of tissues and organs and maintain their structural integrity. An inborn error of metabolism involving abnormal structure or metabolism of collagen results in collagen disorders. Despite the increasing knowledge about the structure and synthesis of collagen, the genetic and molecular bases of the collagen disorders are considered as incurable. Hence, future research and studies are required in this field in order to provide the best treatment modalities to the patients with collagen disorders.

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ABOUT THE AUTHORS

Simarpreet V Sandhu (Corresponding Author)

Professor and Head, Department of Oral and Maxillofacial Pathology Genesis Institute of Dental Sciences and Research, Ferozepur, Punjab India, e-mail: s_vrk@yahoo.com

Shruti Gupta

Junior Resident, Department of Oral and Maxillofacial Pathology, Genesis Institute of Dental Sciences and Research, Ferozepur, Punjab, India

Himanta Bansal

Associate Professor, Department of Oral and Maxillofacial Pathology Genesis Institute of Dental Sciences and Research, Ferozepur, Punjab India

Kartesh Singla

Junior Resident, Department of Oral and Maxillofacial Pathology, Genesis Institute of Dental Sciences and Research, Ferozepur, Punjab, India