Enigmatic insight into collagen

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Abstract
Collagen is a unique, triple helical molecule which forms the major part of extracellular matrix. It is the most abundant protein in the human body, representing 30% of its dry weight. It is the fibrous structural protein that makes up the white fibers (collagen fibers) of skin, tendons, bones, cartilage and all other connective tissues. Collagens are not only essential for the mechanical resistance and resilience of multicellular organisms, but are also signaling molecules defining cellular shape and behavior. The human body has at least 16 types of collagen, but the most prominent types are I, II and III. Collagens are produced by several cell types and are distinguishable by their molecular compositions, morphologic characteristics, distribution, functions and pathogenesis. 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. Various studies have proved that mutations that modify folding of the triple helix result in identifiable genetic disorders. Collagen diseases share certain similarities with autoimmune diseases, because autoantibodies specific to each collagen disease are produced. Therefore, this review highlights the role of collagen in normal health and also the disorders associated with structural and functional defects in collagen.

Key Words: Autoimmune diseases, collagen, triple helical structure

INTRODUCTION
The word collagen is derived from Greek origin: Kolla (glue) and gene. It is the fibrous structural protein that makes up the white fibers (collagen fibers) of skin, tendons, bones, cartilage and all other connective tissues. It is also found widespread in the gelatinous substances of the body. Collagen is the natural protein that constitutes most of the body’s structural support and is the primary substance of connective tissue. Without collagen a human being would be reduced to clump of cells interconnected by few neurons. [1]

HISTORY AND BACKGROUND
The molecular and packing structures of collagen have eluded scientists over decades of research. The first evidence that it possesses a regular structure at the molecular level was presented in the mid-1930s. Since that time many prominent scholars, including Nobel laureates Crick, Pauling, Rich and Yonath and others including Brodsky, Berman and Ramachandran, concentrated on the conformation of the collagen monomer. [2-4] so far the triple-helical “Madras” model provided an essentially correct model of the molecule’s quaternary structure although this model still requires some refinement. [3,5] The packing
structure of collagen has not been defined to the same degree outside of the fibrillar collagen types, although it has been long known to be hexagonal or quasi-hexagonal. As with its monomeric structure, several conflicting models alleged that either the packing arrangement of collagen molecules is “sheet-like” or microfibrillar.

**LIGHT MICROSCOPIC STRUCTURE**

Under light microscope collagen fibers are seen in bundles which are 1–12 microns and which branch and Anastomose with adjacent bundles, but the individual fibers do not branch.

**ELECTRON MICROSCOPIC STRUCTURE**

Under electron microscope, collagen fibrils show characteristic cross striations (dark and light bands) which are due to regular arrangement of collagen molecules within the collagen fibrils. These molecules of collagen are about 300 nm in length and about 1.5 nm in thickness. These are also known as tropocollagen molecules, which are made up of three polypeptide chains called alpha chains that are arranged in the form of triple helix.

The α chains are left-handed helices which wrap around each other into a right-handed, ropelike triple helical rod. Depending on the type of collagen, the molecule may be made up of either three identical α chains or two or three different α chain. The triple helix may be a continuous stretch, or it may be interrupted by non-collagenous segments. Within the triple helical domain, glycine occupies every third position in the repetitive amino acid sequence Gly-X-Y, where X and Y are amino acid other than glycine. Glycine is essential for triple helical conformation because larger amino acid will not fit in the center of the triple helix. Proline frequently occupies the X and Y positions.

Collagen contains two unique amino acids, hydroxyproline and hydroxylsine (Hyl). In vertebrate’s collagens, these amino acids are present in the Y position. The collagen molecule is stabilized through the formation of number of lysine derived intra- and inter-molecular cross–links [Figure 1].

**BIOSYNTHESIS OF COLLAGENS**

Collagen is synthesized mainly by the Mesenchymal cells and their derivatives such as fibroblasts, chondrocytes, osteoblasts, odontoblasts and cementoblasts and other cells such as epithelial cells, endothelial cells, muscle cells and Schwann cells.

**COLLAGEN SYNTHESIS AND ASSEMBLY**

Collagen synthesis and assembly into fibers occurs via series of:
1. Intracellular events
2. Extracellular events.

**Intracellular events**

Pre-procollagen synthesis occurs at rough endoplasmic reticulum (RER) and is directed by mRNAs that encode different types of α chain. Hydroxylation of specific proline and lysine residues of the forming polypeptide chain occur within the RER which is catalyzed by specific hydroxylases that require Vitamin C as a cofactor. Attachment of sugar (glycosylation) to specific Hyl residue also occurs within RER. Procollagen triple – helix formation takes places in the RER and is regulated by propeptides. The three α – chains align and coil into triple helix. The addition of carbohydrate occurs in the Golgi complex and the oligosaccharides chains are completed. Secretion of procollagen occurs by exocytosis.

**Extracellular events**

Cleavage of procollagen is catalyzed by procollagen peptidases, which remove most of the propeptide sequences at the ends of each α-chain, yielding tropocollagen.

Self-assembly of tropocollagen occurs as insoluble tropocollagen molecules aggregate near the cell surface. Fibrils characteristic of Types I, II, III, V, VII collagen are produced which have a transverse banding periodicity of 67 nm in Types I, II, III collagen. The periodicity varies with different types of collagen. Cross-linking occurs between adjacent tropocollagen molecules and involves the formation of lysine and Hyl which imparts tensile strength to collagen fibrils.

[Figure 1: Molecular structure of collagen. (Courtesy: Klug W.S, Cummings M.R. Concepts of Genetics. 5th edition 1997; p. 49-55)]
Table 1: Types of collagen

| Type | Gene name | Chains | Characteristic features | Tissue distribution | Major function |
|------|-----------|--------|-------------------------|--------------------|---------------|
| I    | Col1A1    | α1(I) 3| Most abundant collagen  | Abundant in skin, bone dentin cementum, tendons, ligaments and most connective tissue | Provides tensile strength to connective tissue |
|      | Col1A2    | α1(I) 2|                         |                    |               |
| II   | Col2A1    | α1(II) 3| Forms heterofibrils with colix | Cartilage, vitreous humor, intervertebral disk | Provides tensile strength to connective tissue |
| III  | Col3A1    | α1(III) 3| Abundant in elastic tissue | Embryonic connective tissue, pulp, skin, blood vessels, lymphoid tissue | Provides tensile strength to connective tissue |
| V    | Col5A1    | α1(V) 2| Forms the core of Type I fibrils. | Basal lamina, blood vessels, ligaments, skin, dentin, periodontal tissues | Provides tensile strength to connective tissue |
|      | Col5A2    | α2(V) 2|                         |                    |               |
|      | Col5A3    | α3XII 3|                         |                    |               |
| XI   | Col1A1    | α1XII 3| Forms core of Type II fibrils | Cartilage, vitreous humor, placenta | Provides tensile strength, controlling lateral growth of Type II fibrils |
|      | Col1A2    | α2XII 3|                         |                    |               |
|      | α3XII 3   |        |                         |                    |               |
| XXIV | Col24A1   | α1(XXIV) 3| Displays structural features unique to invertebrates fibrillar collagen | Bone cornea | Regulation of Type I fibrinogenesis |
|      |          |        | Presence of triple helix imperfection | Cartilage, eye ear, lungs | Association of Type II fibrils |
| VI   | COL6A1, A2, A3 | α1(VI) 3| Highly disulfide crosslinked | Ligaments, skin, placenta, cartilage | Bridging between cells and matrix |
|      |          | α2(VI) 3|                         |                    |               |
|      |          | α3(VI) 3|                         |                    |               |
| XII  | COL13A1   | α1(XIII) 3| Single transmembrane domain | Epidermis, hair follicle, cell surface Neurons | Cell matrix, cell to cell adhesion |
|      | COL25A1   | α1(XVII) 3| Extracellular domain deposited in β amyloid plaques | Epithelial and endothelial basement membranes | Neuron adhesion |
|      |          | α1(V) 3| Contains antiangiogenic factor | Cartilage, vitreous humor | Stabilizes skeletal muscle cells and microvessels |
|      | COL9A1    | α1(I) 3| Interacts with glycosaminoglycans in cartilage | Cartilage, eye ear, lungs | Attaches functional groups to surface of Type II fibrils |
|      | COL14A1   | α1(XIV) 3| Associated with Type I | Widespread in many connective tissue | Modulates fibril interactions |
|      | COL26A1   | α1(XVI) 3| Disulfide bonds are made into N-terminal noncoaggregation domain | Developing and adult testis and ovary | Unknown |
|      | COL4A1    | α1(IV) 2| Interaction with Type IV, laminin, nondogend, integrin | Basal laminae | Structural network of basal lamina together with proteoglycans and laminin, nondogend, integrin |
|      |          |        |                         |                    | Calcium binding |
|      | COLBA1    | α1(VIII) 2| Cornea, endothelium | Epithelium (skin, mucosa) | Strengthen epithelial-connective tissue junction |
|      | COL10A1   | α1(X) 3| Hypertrophic zone of cartilage growth plate | Epithelium (skin, mucosa) | Strengthen epithelial-connective tissue junction |
|      | COL7A1    | α1(VII) 3| Forms bundles made of dimers anchored in anchoring plaques and basal lamina | Epithelium (skin, mucosa) | Strengthen epithelial-connective tissue junction |

REGULATION OF COLLAGEN BIOSYNTHESIS

Regulation of collagen production occurs at gene transcription level, collagen gene expression is regulated in a cell and tissue-specific manner during both normal development and homeostasis. Regulation of transcription rate is mediated primarily through promoters and enhancer element. In the Type I collagen gene, promoter and enhancer sequence are present in the first introns of COL1A2 gene. In Type IV collagen, the pair of genes for COL4A1 and COL4A2 is arranged in a unique head-to-head arrangement separated by a short 130 bp segment, with the binding site for SP1 at its center. The intervening sequence interacts with enhancer and negative regulatory elements located in COL4A1 and COL4A2 genes, respectively, thus regulating the expression of both the genes. The magnitude of collagen synthesis is dependent on the levels of the mRNA for its alpha chains. Collagen synthesis is regulated post translationally by the extent of prolyl hydroxylation, and it is also influenced by a variety of growth factors, hormones, cytokines and lymphokines. Transforming growth factor-beta (TGF-β) have a positive influence and TGF-α have a negative influence on production of collagen.[16,17]

DEGRADATION AND REMODELLING OF COLLAGEN

It is primarily mediated by collagenases and several other enzymes which belong to a family of enzymes called matrix metalloproteinases (MMPs). Based on their substrate specificity Woessner et al. 1991, Mignatti et al. 1996 have classified them into the following types:

1. Collagenases
2. Gelatinases
3. Stromelysins.
It is produced by a variety of human epithelial and mesenchymal cells including keratinocytes, fibroblasts and macrophages. It can hydrolyze Type I, II, III, VI, VIII and X collagen and gelatine (Birkedal-Hansen et al. 1993). It hydrolyzes Type III collagen molecules faster when compared to Type I.

COLLAGENASE 2/POLYMORPHONUCLEAR LEUKOCYTE COLLAGENASE/MATRIX METALLOPROTEINASES-8

It hydrolyzes both Type I and Type III collagen. It degrades Type I faster than Type III collagen. It is found only in the specific granules of polymorphonuclear (PMN) neutrophil cells.
Surgical hemostats
Collagen is a natural hemostat and a wide variety of collagen-based products are used in surgery and dentistry to control excessive bleeding or hemorrhage.\cite{27}

Collagen stents and vascular graft coatings
Expandable, intra-arterial stents are widely used for treating coronary artery diseases. In addition to mechanical dilation, biopolymer-coated stents may provide supplementary functions such as local drug delivery, gene transfer, reduction of operative blood loss and facilitation of endothelial cell in-growth.\cite{28}

SPECIAL STAINS FOR DETECTION OF COLLAGEN
Trichrome stains are employed which utilizes a number of techniques for the selective demonstration of collagen fibers in various connective tissues [Table 2].

EFFECTS OF DRUGS ON COLLAGEN
Phenytoin sodium
It is believed to stimulate the high-affinity phenotype of fibroblast. Exposure of the gingiva fibroblast to phenytoin increases the level of translatable collagen mRNA; thus, there is an increased steady state level of collagen mRNA and not a decrease in collagen degradation.\cite{29}

Cyclosporin
Bartold has reported a stimulatory effect on DNA synthesis which increases the synthesis of collagen. It also negates the inhibitory effect of lipopolysaccharides indicating a possible observed relationship between areas of prominent gingival overgrowth and dental plaque.\cite{30}

Calcium channel blocker
Lucas et al. have shown that nifedipine induced hyperplasia is due to an increase in the ground substance. Gingival overgrowth may also be related to calcium-dependent inhibitory effect on T-cells and subsequent immunosuppression. Blockade of intracellular calcium uptake by the fibroblast alters both their secretory properties as well as the synthesis of collagenases.\cite{31}

COLLAGEN DISORDERS
Three types of alterations can affect collagen and lead to tissue changes in these disorders: A defect in the structure of collagen, molecular defect in processing enzymes, mechanisms affecting the expression of collagen gene as in acquired defects [Table 3].

Osteogenesis imperfecta
It comprises a heterogeneous group of heritable disorders characterized by impaired collagen maturation. Except on rare occasions, the disorder arises from heterozygosity for mutation in one of the two genes that guide the formation of Type 1 collagen: The COL1A1 gene on chromosome 17 and the COL1A2 gene on chromosome 7. The clinical features observed are abnormal bone formation, growth deficiency, bone fragility, blue sclera, hearing loss, joint laxity, hypermobility and dentinogenesis imperfecta and osteoporosis. On fracture, healing occurs with exuberant callus formation.\cite{32-36}

Ehler–Danlos syndrome
It is a name given to a group of more than ten different inherited disorders all involving a genetic defect in collagen and connective tissue synthesis and structures. This syndrome is clinically heterogeneous, the underlying collagen abnormality is different for each type. In some forms of Ehler–Danlos syndrome (EDS), a mutation in COL1A1 and COL1A2 genes is reported which results in interferences with the conversion of procollagen to collagen. This leads to defective crosslinking and consequent reduction in tensile strength of tendons. EDS is characterized by hypermobility of joints, hyperextensibility and fragility of skin and blood vessels, the presence of dystrophic scars and tendency to bleed excessively, manifested by bruises, ecchymosis and hematomas. Oral manifestation includes fragile gingiva, periodontitis, premature loss of deciduous and permanent teeth. Hypoplasia of enamel, recurrent subluxation of temporomandibular joint has also been reported.\cite{32,37-40}

Alport syndrome
It is a generalized inherited disorder of basement membranes. The mutations occur in gene located on X chromosome. Classical X-linked Alport syndrome affects the \(\alpha-5\) chain of
collagen Type IV collagen gene (COL4A5). While the α-3 and α-4 chain of collagen Type IV collagen (COL4 A3 and COL4 A4) are responsible for less frequent recessive forms. It is characterized by renal implants, loss of hearing and lens abnormality, hypertension, hematuria and proteinuria.[32]

**Stickler syndrome**
It is an autosomal dominant syndrome of premature osteoarthritis, retinal degeneration, hearing loss and orofacial abnormalities. It is caused by a mutation in COL2A1, COL11A1 and COL11A2 procollagen genes of Type 2 and 11 collagen.[32,39]

**Marfan syndrome**
It includes a spectrum of disorders caused by a heritable genetic defect of connective tissue that has an autosomal dominant mode of transmission. The defect is on FBN1 gene on chromosome 15, bands q15-q23, which codes for the connective tissue protein, fibrillin. In general, patients present with tall stature, ectopia lentis and aortic root dilatation. The diagnosis is made when a patient presents with complications of the syndrome, such as aortic dissection or with the involvement of pulmonary, skin/integument or nervous system.[32,39]

**AUTOIMMUNE COLLAGEN DISORDERS**

**Systemic lupus erythematosus**
Systemic lupus erythematosus is a prototypical human autoimmune, collagen vascular or connective tissue disease mediated by pathogenic immune complexes. Generalized findings include fever, weight loss, arthritis, fatigue and malaise. It is also characterized by butterfly rash along with renal, pulmonary and gastrointestinal involvement. Oral lesions include ulceration, pain, erythematic, hyperkeratosis, periodontal disease, xerostomia and candidiasis.[34,41]

**Systemic sclerosis**
It is a chronic disease characterized by diffuse sclerosis of skin, gastrointestinal tract, heart muscle, lungs and kidney. The pathological findings state those fibroblasts are activated to form an excessive amount of collagen and other components of the cellular matrix. The clinical findings include thickening of the skin, starting with pitting edema and over several months pitting edema is replaced by tightening and hardening of skin because of its firm fixation to deep connective tissue. This contracture of skin gives a mask like appearance to the face. The mouth aperture is constricted and radial furrows appear, giving a pursed look. The vermilion border is reduced and the lips become immovable making entry to the oral cavity difficult. The oral mucosa is pale and is rigid on palpation. When the tongue is affected, it loses its mobility and papillary pattern and becomes shrunken in later stages. Another characteristic change is a flattening of the palatal rugae. Widening of the periodontal ligament is also seen in this disease.[34,42-44]

**Oral submucous fibrosis**
Oral submucous fibrosis (OSMF) is a chronic, progressive, scarring disease; that predominantly affects people of Southeast Asian origin. This condition was described first by Schwartz (1952). The presence of various autoantibodies in varying titers in several studies have confirm the autoimmune basis of the disease.[32] Genetic susceptibility is associated with OSMF because of raised frequency of HLA - A10, -B7 and - DR3 are found in OSMF patients compared to normal subjects.[33] The disease is considered as a consequence of disturbances in homeostatic equilibrium between synthesis and degradation of extracellular matrix, wherein collagen forms a major component, that can be recognized as a collagen-metabolic disorder. It is characterized by a juxta-epithelial inflammatory reaction followed by a fibroelastic change in lamina propria and associated epithelial atrophy. This leads to 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 the abnormal accumulation of collagen in subepithelial layers, resulting in dense bands in the mouth.[32,44,45]

**Scurvy**
Prolong deficiency of Vitamin C results in scurvy. There is defective formation of collagen in connective tissues because of failure of hydroxylation of proline to hydroxyproline which is a characteristic amino acid of collagen. There is also increased permeability of capillaries (hemorrhage), anemia due to erythropoiesis and defective collagen formation. Clinical features include lassitude, anorexia, painful limbs and enlargement of the costochondral junction, folliculosis, hemorrhage, epistaxis, anemia and delayed wound healing. Oral signs may be cardinal: Fetid odor and loosened teeth, gingiva are boggy, ulcerated and bleed with the interdental and marginal gingiva becoming bright red, smooth, swollen and shiny.[32]

A list of collagen disorders and manifestations is summarized in Table 4.

In addition to the above-mentioned disorders, excessive deposition of collagen occurs in Scleroderma.

**CONCLUSION**

Collagen is the most common protein in the animal world. It is 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. In spite of
Underlying cause
Protrusion of the brain tissue and degeneration of the retina
Lassitude, anorexia, painful limbs and enlargement of
Premature osteoarthritis, retinal degeneration, hearing loss and
Tiptoe walking, joint laxity, contractures of fingers and legs,
Mutation in COL1A1 and COL1A2
Mutation in the collagen XVIII gene
Mutations in gene located on X
Failure of hydroxylation of proline to hydroxyproline
Clinical features
Mutation in COL2A1, COL11A1 and COL11A2
Hypermobility of joints, hyperextensibility and fragility of skin
Mutation in the COL1A1 gene on chromosome 17
Mutations in genes encoding collagen VI (COL6A1)
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Conflicts of interest
There are no conflicts of interest.

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| Collagen disorder        | Underlying cause                                                                 | Clinical features                                                                 |
|--------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Osteogenesis imperfecta  | Mutation in the COL1A1 gene on chromosome 17 and the COL1A2 gene on chromosome 7 | Abnormal bone formation, growth deficiency, bone fragility, blue sclera, hearing loss, joint laxity, hypermobility and dentinogenesis imperfecta and osteoporosis |
| Ehlers-Danlos syndrome   | Mutation in COL1A1 and COL1A2                                                    | Hypermobility of joints, hyperextensibility and fragility of skin and blood vessels, presence of dystrophic scars and tendency to excessive bleeding manifested by bruises, ecchymosis and hematomas |
| Alport syndrome          | Mutations in gene located on X chromosome - collagen gene (COL4A5)               | Renal implants, loss of hearing and lens abnormality, hypertension, hematuria and proteinuria |
| Stickler syndrome        | Mutation in COL2A1, COL11A1 and COL11A2                                          | Premature osteoarthritis, retinal degeneration, hearing loss and orofacial abnormalities |
| Marfan syndrome          | Defect is on FBN1 gene on chromosome 15, bands q15-q23                          | Tall stature, ectopia lentis, and aortic root dilatation. Aortic dissection, involvement of pulmonary, skin/integument or nervous system |
| SLE                      | Autoimmune disorder. Deficiencies of classical pathway complement components (C1q, C2, and C4) Mutation in signal transducer and activator of transcription (STAT4) gene | Butterfly rash along with renal, pulmonary and gastrointestinal involvement Oral lesions include ulceration, pain, erythematic, hyperkeratosis, periodontal disease, xerostomia and candidiasis |
| Scurvy                   | Failure of hydroxylation of proline to hydroxyproline                           | Lassitude, anorexia, painful limbs and enlargement of costochondral junction, folliculosis, hemorrhage, epistaxis, anemia and delayed wound healing Oral signs: Fetal odor and loosened teeth, gingiva are boggy, ulcerated and bleed with gingiva becoming bright red, smooth, swollen and shiny Blisters on skin and mucous membranes, deformity or loss of finger nails and toe nails, scattering alopecia, milia, poorly formed enamel, dysphagia |
| Dystrophic epidermolysis bullosa | Collagen fibrils that attach dermis to epidermis break down                      | Protrusion of the brain tissue and degeneration of the retina Tiptoe walking, joint laxity, contractures of fingers and legs, muscle weakness |
| Knobloch syndrome        | Mutation in the collagen XVIII gene                                               |                                                                                   |
| Bethlem myopathy         | Mutations in genes encoding collagen VI (COL6A1)                                 |                                                                                   |

S.L.E: Systemic lupus erythematosus

the increasing knowledge about the structure, synthesis and genetic bases of collagen, collagen disorders are considered as incurable. Thus, the field of collagen research still remains to be further explored.

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Conflicts of interest
There are no conflicts of interest.

Table 4: Collagen disorders and manifestations
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