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Collagen in Health and Disease –A Review

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Abstract:- Collagens are a family of extracellular matrix that helps tissues and organs retain their structural integrity. In mammals, it accounts for about 30% of all proteins and forms a building block of body structure. It is predominantly present in the skin, blood vessels, tendons, cartilages, bone, teeth, and cornea. It plays an important role in the healing of wounds and fractures. Excessive collagen in the body leads to fibrosis of various organs. There are certain diseases related to collagen such as Ehlers- danlos syndrome, Osteogenesis imperfecta, Alport syndrome, Scurvy, Oral submucous fibrosis, Marfan's syndrome. Collagen's function in health and disease is discussed in this review article.

Keywords:- *Collagen; Extracellular Matrix; Structure; Fibroblast.*

I. INTRODUCTION

Collagen is a one-of-a-kind natural protein found in the extracellular matrix and connective tissue.[1] They play an important role in maintaining structural integrity and in determining the physical properties of the tissues.[2] It is the single most abundant animal protein in mammals which accounts for about 30% of all proteins forming building blocks of the body structures.[3,4] It is the predominant constituent of skin, blood vessels, tendons, and cartilage as well as the organic component of bones, teeth, and the cornea.[2]

Collagen is essential for wound healing and fracture healing, so conditions that prevent collagen formation can cause wound healing to be delayed. Excess collagen formation causes fibrosis in a variety of organs and tissues.[2] Collagens play critical roles in a variety of diseases, including Osteogenesis imperfecta, Chondrodysplasia, Ehlers-Danlos syndrome, Alport syndrome, Bethlem myopathy, Scurvy, Systemic Lupus erythematosus, Systemic sclerosis, Stickler syndrome, Oral submucous fibrosis, Marfan's syndrome, Epidermolysis bullosa, and Arterial aneurysms, Osteoporosis, and osteoarthrosis and Intervertebral disc disease.[2,5]

II. STRUCTURE OF COLLAGEN

Collagen is a long (approximately 300 nm), rod-like molecule. Its basic structural unit consists of three parallel polypeptide chains arranged in a triple helix, two of which are identical(α1) and the third of which differs to some extent in its chemical composition(α2), flanked by a non-helical region.[5,7]

III. SYNTHESIS OF COLLAGEN

Mesenchymal cells and their derivatives such as fibroblasts, chondrocytes, osteoblasts, odontoblasts, and cementoblasts, as well as other cells such as epithelial cells, endothelial cells, muscle cells, and Schwann cells, synthesize collagen.[1,8]

Fibroblasts are principal cells of connective tissue. It is spindle-shaped which produces and maintains the extracellular matrix and collagen. Collagen, in conjunction with the extracellular matrix, serves as a structural framework for many tissues. It is essential for wound healing and repair. It secretes ground substances and a variety of fibers and hence maintains the structural integrity of connective tissue.[4]

IV. DEGRADATION OF COLLAGEN

Matrix metalloproteinases (MMP-1,8,13), gelatinases (MMP-2,9), metalloelastases (MMP-12), stromelysins (MMP-3, 10, 11), and matrilysin (MMP-7) are the main enzymes involved in collagen degradation.[4]

V. COLLAGEN IN HEALTH

Collagen is often referred to as the body's cement, as it holds everything together. It is essential for health because it determines the structure of the skin, connective tissues, tendons, bones, and cartilage.

A. Skin

Collagen is essential for good skin health. It accounts for roughly 70% of type I collagen, 10% of type III collagen, and trace amounts of type IV, V, VI, and VII collagen. Collagen hydrolysate, which contains collagen, aids in keeping the skin hydrated.[9]

B. Wound Healing

Wound healing is one of the most intricate processes in the human body. Collagen is a protein found in connective tissue that is involved in all phases of wound healing, including hemostasis, inflammation, proliferation, and remodelling. It helps promote wound healing by organizing and accumulating newly formed fibers and granulation tissue in the wound bed, thereby creating a favourable healing environment. Collagen deposition and remodelling occur during healing, which aids in the repair and scar formation processes. There is also an increase in tensile strength of the wound, which is up to 20% of normal skin after 3 weeks and gradually increases to a maximum of 70% of normal skin.

The excessive production of collagen can lead to abnormal scar formation that impedes wound healing. In elderly individuals, wound healing is delayed due to the impairment in collagen synthesis and increase in collagen degradation. The increase in fibroblasts and collagen during healing suggests that there could be a link between the number of fibroblasts, the amount of collagen, and the tensile strength of a scar.[10]

C. Bone

Bone is a complex rigid organ that provides a structural framework for the body. It protects various organs of the body and enables mobility. It consists of both organic and inorganic components out of which 22 to 25% is an organic component. Organic component mainly constitutes 94-98% of type I collagen and 2-5% of cells. The hydroxyapatite and flexible collagen present in bone makes it harder than cartilage and also the combination of collagen mesh and water acts as a cushion during muscle movement .[11]

D. Cartilage, Tendon, Ligaments

Collagen serves as the structural framework for cartilage and is responsible for its shape as well as the majority of its biochemical properties such as resistance to pressure, torsion, and tension. Type II collagen is a key component of cartilage. Tendons and ligaments are made up of elongated fibrils of collagen.[12]

E. Muscles

In muscle tissues, collagen is a significant component of the endomysium. It makes up 1-2 percent of muscle tissue and makes up 6% of the weight of heavy tendinous muscle.[13] It supports the vessels and nerves mechanically. It also ensures that the muscle has a passive elastic response. To transmit power, the tendon, and intramuscular connective tissue work closely with the contractile elements of the skeletal muscle. The tension formed in one part of the muscle can be transferred to the other part of the muscle through a shear connection.

F. Dental Tissues

i) Dentin

Dentin is a mineralized hard tissue forming the main bulk of the tooth. The mature dentin is composed of approximately 70% inorganic material, 20% organic material, and 10% water by weight. Calcium hydroxyapatite crystals and non-crystalline amorphous calcium phosphate make up the majority of inorganic content. The organic material is made up of fibrils embedded in an amorphous ground substance containing 30% collagen (mainly type I with small amounts of types III and V). It also has fractional lipid and non-collagenous matrix protein inclusions.[14]

ii)Pulp

The dental pulp is a non-mineralized elastic mesenchymal connective tissue found in the center of the teeth. It is the only vascularized tissue encased in highly mineralized structures such as enamel, dentin, and cementum, and it keeps the tooth as a viable organ in a state of homeostasis. Collagen fibres and ground substances make up the extracellular compartment of the pulp or matrix. It is made up of young collagen fibres with a diameter of 10-12mm. They can be found in bundles or dispersed in the coronal or radicular pulp. Collagen types I and III make up the majority of the fibres.[14]

iii) Cementum

Cement is primarily composed of Type I collagen, which accounts for 90% of the organic matrix. It also contains Type III collagen, which is present in higher amounts during mineralized tissue growth, repair, and regeneration. When compared to other collagen forms, it has a lower crosslinking collagen. The cementum's Type XII collagen binds to Type I collagen as well as non-collagenous matrix proteins. Types V, VI, and XIV collagens are also present in trace quantities.[15]

iv) Periodontal ligament

The periodontal ligament is a soft, specialized fibrous connective tissue present in the periodontal ligament space which connects the cementum to the alveolar bone. It is derived from the dental follicle and it is in continuation with the connective tissue of the gingiva and apical foramen which is further in continuation with dental pulp. It consists of 53-74% of collagen and oxytalan fibers. The collagen fibers present in the periodontal ligament are called principal fibers. These fibres are arranged in fibre bundles that are distinct from one another. Collagen types I, III, and XII are the most common fibres. Individual fibrils with a smaller average diameter than tendon collagen fibrils are also present. The periodontal ligament can adapt to functional changes; when there is an increase in functional demand, the periodontal ligament's width can increase by up to 50%, and the fibre bundles thicken significantly.[15]

G. Basement Membrane

The lamina densa is made up of type IV collagen-coated with heparan sulphate, a glycosaminoglycan, and anchoring fibrils are made up of type VII collagen that runs from the lamina densa to the connective tissue.[16]

VI. HERITABLE/GENETIC COLLAGEN DISORDERS

A. Ehlers-Danlos Syndrome (Tenascin – X deficiency syndrome/Lysyl hydroxylase deficiency syndrome)

It is a category of connective tissue disorders caused by genetic mutations. Hypermobility of joints, hyperextensibility of skin, and tissue fragility are the manifestations of EHD.[4] It is divided into thirteen subtypes.

B. Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) (brittle bone disease) is a group of hereditary disorders affecting the connective tissue. OI can occur by both inheritance and spontaneous genetic mutation and has been linked to over 150 genetic mutations. It is mainly caused by mutations in COLA1 and COLA2 genes that encode type I procollagen. The occurrence is estimated to be 1 in every 20,000 live births. The hallmark characteristic of OI is a weak, easily fractured bone. Ankylosis of the ossicles and osteosclerosis cause the classic clinical

triad of bone fragility, blue sclera, and deafness. It also affects bone quality and mass. There are 4 types of Osteogenesis Imperfecta. Type I is a mild form that has an autosomal dominant inheritance. Type II collagen is considered the most severe type. This form of OI causes people to die within the first year of their lives. Type III, which is an extreme and increasingly deforming type caused by a new mutation, is seen in 15% of patients. Similar to type I, type IV is a moderately extreme form of the condition. In general, skeletal and extraskeletal clinical characteristics can be distinguished. Excess/atypical fractures, short stature, scoliosis, and basilar skull deformities are all skeletal characteristics. Extraskeletal manifestations include hearing loss which is a mixture of conductive and hearing loss and seen in 50% of adults by 50 years and 5% of children with OI. Dentinogenesis imperfecta is a condition in which the dentin becomes irregular, resulting in the appearance of small deformed teeth that are opalescent due to a higher ratio of translucent enamel to opaque dentin. It is one of the most common dental defects, along with malocclusion. The colour of the sclera may be blue or grey.[17]

C. Stickler Syndrome

It is a group of genetic disorders characterized by defective collagen production also called hereditary progressive arthro ophthalmopathy. Mutations in the procollagen genes COL2A1, COL11A1, and COL11A2 of Type 2 and 11 collagen are believed to cause it.[4,18] It is usually diagnosed during infancy and childhood. Clinical features include ocular, auditory, skeletal, and orofacial abnormalities which include a prominent eye, a small nose with a scooped out facial appearance, and a receding chin as described by Gunnar B Stickler in 1965.

D. Alport Syndrome

It is a genetically heterogeneous disease involving basement membranes of the kidney. It is caused by the mutations occurring in the gene which is located on the X chromosome. It affects around 1 in 5,000-10,000 children. Classical X-linked Alport syndrome affects the α-5 chain of collagen Type IV collagen gene (COL4A3, COL4A4, COL4A5). These genes provide instructions for making one component of a protein which is Type IV collagen. These play an important role in kidneys mainly glomeruli. The mutation in these genes causes abnormalities in Type IV collagen finally leading to kidney failure. It is characterized by glomerulonephritis, renal failure, hearing loss, lens abnormalities, hypertension, haematuria, and proteinuria.[1]

E. Marfan's Syndrome

It is the most common genetic disorder affecting connective tissue, with a confirmed occurrence of one in 10,000 people and equal gender distributions. It has an autosomal dominant mode of transmission where there is a mutation in the gene encoding fibrillin (FBN1, chromosome 15q15–21.3), which is a glycoprotein that forms an integral part of the connective tissue in the body.[19] Since connective tissue is present all over the body, it can have an impact on a variety of organs and systems, including the heart, blood vessels, joints, skin, and bones. Marfan syndrome patients are tall and thin, with a long and narrow face, elongated fingers and toes, loose joints, an arm span that is greater than their body height, crowded teeth, a bent back, a sunken stomach, or a protruded chest. Aortic dilatation that progresses with aortic valve collapse, mitral valve prolapse and failure, lens dislocation and myopia, arachnodactyly, chest deformations, and nervous system and lung defects are some of the other signs.[20]

F. Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a heterogeneous group of inherited disorders characterized by fragility and blistering of the skin and mucous membrane, with extracutaneous manifestations. The blisters can arise spontaneously or occur from minor trauma, heat, rubbing, or scratching. In severe cases, blisters can occur inside the body. It is classified into four types depending on the level of separation of tissue within the epidermal-dermal basement membrane zone. They are simplex, dystrophic and junctional, and hemidesmosomal types.[2] Mutations in the K5 or K14 gene, which codes for laminin, cause the simplex and junctional forms, while mutations in the type VII gene cause the dystrophic form. Mutations in genes associated with hemidesmosome attachment proteins such as plectin, type XVII collagen, and 64α4 integrin cause the hemidesmosomal type.[2]

G. Systemic Lupus Erythematosus

Systemic lupus erythematosus is a chronic autoimmune disease that affects the connective tissue such as cartilage and lining of blood vessels disease mediated by pathogenic immune complexes.[1] It can be of either cutaneous or systemic forms with varied prevalence. The signs and symptoms may vary among the affected individuals. It can affect many organs including skin, joints, kidneys, lungs, and hematopoietic system. Generalized findings include fever, weight loss, pain or swelling in the joints of hand, feet, wrist, and knees, fatigue and malaise along with renal, pulmonary, and butterfly rashes which develop over the malar area and nose.[4] Oral lesions include ulcerations which is painful, hyperkeratosis, periodontal disease, xerostomia, and candidiasis.

H. Oral Submucous Fibrosis

Oral submucous fibrosis (OSMF) is an oral precancerous condition characterized by submucosal tissue inflammation and progressive fibrosis. OSMF was first reported in India in 1953 by Joshi and he coined the term Submucous fibrosis of palate and faucial pillars. It is commonly seen in the south east Asians and Indian population with the highest rate of incidence seen in the Indian population. OSMF has been specifically linked to the chewing of areca nut/quid or pan masala while chewing or smoking tobacco did not increase the likelihood of OSMF. It is often associated with a juxta-epithelial inflammatory reaction accompanied by fibroelastic changes of the lamina propria with epithelial atrophy, leading to pronounced rigidity and stiffness of the oral mucosa, causing trismus and inability to feed, despite the fact that it is rarely preceded by or associated with vesical formation.[21]

I. Scurvy

Scurvy is a clinical syndrome that results from vitamin C deficiency. The symptoms are manifested 8 to 12 weeks of inadequate food intake which is presented as irritability and

anorexia. Slow wound healing, gingival swelling with tooth loss, mucocutaneous petechiae, ecchymosis, and hyperkeratosis are all dermatologic findings after these initial symptoms. Capillary fragility is unable to endure the gravity-dependent hydrostatic pressure, resulting in localised perifollicular haemorrhages in the lower extremities, which is known as "woody edoema." Some signs and symptoms include a scorbutic rosary at the costochondral junction, sternal depression, hemarthrosis, and subperiosteal haemorrhages. Flame haemorrhages cotton-wool streaks, and retrobulbar bleeding into optic nerves, resulting in atrophy and papilledema, are all ocular forms of haemorrhage. Anasarca, hemolysis, jaundice, and convulsions are seen in the late stages of the disease, which may be life-threatening.[22]

J. Systemic sclerosis

Systemic sclerosis (SSc) is a chronic, autoimmune multisystem connective tissue disease characterized by microangiopathy leading to inflammation and fibrosis involving skin and internal organs. SSc is a rare rheumatological disease that affects more women than men (7:1). Based on the degree of skin involvement, SSc is divided into minimal and diffuse cutaneous types. Initial vascular injury in genetically susceptible individuals, leading to functional and structural vascular changes, inflammation, and autoimmunity are all part of the pathogenic mechanism. The inflammatory and immune responses activate and maintain fibroblast differentiation and activation, resulting in pathological fibrogenesis and excessive collagen and other cellular matrix components. Raynaud's syndrome is characterised by episodic vasoconstriction in the fingertips, toes, tip of the nose, and ear lobes. The characteristic of systemic sclerosis is the thickening of the skin, which begins with pitting edema and progresses to tightening and hardening of the skin. Resorption of bone at the angle of the mandible is also normal. Collagen deposits in the lingual and esophageal submucosa, resulting in a stiff, hypomobile (board-like) tongue and an inelastic oesophagus, causing dysphagia.[4]

K. Knobloch syndrome

Knobloch syndrome is a rare condition characterized by severe vision problems and a skull defect. Knobloch syndrome has been shown to result from mutations in the COL18A1 gene.[2] Typical eye abnormalities, including high myopia, cataracts, dislocated lens, vitreoretinal degeneration, and retinal detachment, with occipital skull defects, which can range from occipital encephalocele to occult cutis aplasia.

L. Bethlem myopathy

Bethlem myopathy is a rare and slowly progressive form of muscular dystrophy, mainly affecting skeletal muscles and connective tissues. It is caused by a mutation in the genes COL6A1, COL6A2, and COL6A3 that encode the type VI collagen.[2] Onset of the disease is usually in early childhood. It begins as a slowly progressive generalized muscle weakness and joint stiffness. Fingers, wrists, elbows, and ankles are also affected by contractures. Signs and symptoms can appear before birth (with reduced foetal movements), shortly after birth (with low muscle tone or torticollis), in early childhood (with delayed motor skills, muscle weakness, and contractures), or adulthood (with delayed motor skills, muscle weakness, and contractures) (with weakness or finger contractures). Many people with Bethlem myopathy over the age of 50 need mobility aids (such as a cane, crutches, or wheelchair) for outdoor mobility due to the disease's progression. Extreme muscle weakness can sometimes lead to respiratory problems later in life.

VII. APPLICATIONS OF COLLAGEN

In vivo and in vitro, collagen-based biomaterials can be used for a variety of purposes. Collagen is a primary resource in medical applications because of its excellent biocompatibility and protection due to biodegradability. Collagen's use in biomedical applications stems primarily from its ability to shape fibres with increased strength and flexibility due to self-aggregation and cross-linking. Collagen's elasticity and ability to repair are two of their most significant characteristics.

Collagen is mostly used in dentistry as a guided tissue regeneration membrane, allowing for the selective repopulation of periodontal ligament cells. It has a chemotactic effect on regenerative cells and, due to its ability to create space, it can aid fibroblast migration and attachment. Collagen enhances the handling properties of Bone Graft Substitutes such as beta-tricalcium phosphate, hydroxyapatite, bioactive glass, and other osteoconductive materials and promotes cell ingrowth, which is essential for tissue regeneration. Collagen also has hemostatic properties, which aid in blood clotting and tissue repair. The platelets adhere to each other and clump together, forming a thrombus. It is also used as an agent for local drug delivery which includes collagen shields in ophthalmology; sponges for burns/wounds; mini pellets and tablets for protein delivery; gel formulation in combination with liposomes for sustained drug delivery; a controlling material for transdermal delivery; nanoparticles for gene delivery; and basic matrices for cell culture systems. Collagen is also used as dermal fillers to minimize the appearance of wrinkles, as vascular closure devices to provide immediate sealing of arterial punctures, and are an alternative to manual compression.[23]

VIII. CONCLUSION

All connective tissues contained in the interstitial tissue of all parenchymal organs contain collagens, which are essential structural elements. The thorough analysis of the structure and stability of collagen triple helices has been made, due to high-resolution crystal structures and modern biophysical approaches, simplifying the process of synthesizing long collagen triple helices and fibrils. Collagens have applications in biomedicine and nanotechnology. Collagenous biomaterials have been linked to their elastic and repairable nature, ability to promote periodontal tissue regeneration and restoration of aesthetics and function.

Collagen disorders are caused by an inborn metabolic error involving irregular collagen structure or metabolism and is considered as incurable. As a result, further research and

studies have to be conducted in this area to provide the best treatment for patients suffering with collagen disorders.

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