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Review Article

Review of Collagen in Health and Disease (Part II Collagen in Diseases)

[1]Praveena Kulkarni, [2]Venkatesh Kulkarni

[1]Assistant Professor and [2]Professor , Department of Oral Pathology & Microbiology, Bharati Vidyapeeth Deemed to be University Dental College & Hospital, Pune.

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ABSTRACT

Collagen is the most abundant protein in the human body. It possesses triple helical protein molecule which forms the major part of the extracellular matrix. It forms integral part of skin, connective tissues, tendons, bones and cartilage. Also collagen is integral part of dental tissues such as enamel, dentin, pulp and periodontal ligaments. Thus, 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 highlights the various pathological aspect of collagen.

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

Address for Correspondence: Dr. Praveena Kulkarni, Assistant Professor, Department of Oral Pathology & Microbiology, Bharati Vidyapeeth Deemed to be University Dental College & Hospital, Pune, India; Email: drshrikantwinner@gmail.com

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INTRODUCTION

As collagen is integral part of body and its various organs. It comprises a family of proteins rather than single type of protein and are distinguishable by their molecular compositions, morphologic characteristics, distribution, functions and pathologies. It is present in the skin, bone, cartilage, smooth muscle and basal lamina. It providesrigidity, elasticity and strength.[1]As already physiological aspects reviewed. This review highlights the various pathological aspect of collagen.

Collagen Disorders Categorization
1. Heritable/Genetic Collagen Disorders.
2. Autoimmune Collagen Disorders.
3. Miscellaneous.

1. Heritable/Genetic Collagen Disorders

a. Ehlers-Dalnos syndrome (Tenascin – X deficiencysyndrome/Lysylhydroxylase deficiency syndrome):[2,3]
Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous connective tissue disorder characterized by hyper extensibility of the skin, hyper mobility of joints and tissue fragility.
The exact abnormality in biogenesis of the collagens has been identified in four varieties and in case of EDS an abnormal gene locus has been determined. In some clinical forms of EDS a mutation in genes, such mutations in genes resulted 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 tendencyto 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.

b. Osteogenesis imperfecta: [4,5]
Osteogenesis imperfect acomprises 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.

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 inbone with a thin cortex, fine trabeculation and diffuseosteoporosis. Upon fracture, healing will occur but maybe associated with exuberant callus formation.

c. Stickler syndrome:[6]
It is a unique autosomal dominant syndrome of premature osteoarthritis, retinal degeneration, hearing loss and orofacial abnormalities. The disorder (hereditary arthroophthalmopathyor Stickler syndrome) is known to be caused by mutations in the COL2A1, COL11A1 and COL11A2 procollagen genes of type 2 and 11 collagen.

d. Alport syndrome:[7]
Alport syndrome is a generalized inherited disorder of basement membranes, particularly those of glomeruli that involve type IV collagen. Themutations occur in the gene located on the X chromosome. It is characterized by renal impairment, loss of hearing andlens abnormalities, hypertension, hematuria and proteinuria.The damage of collagen IV due to mutations causes dysfunction of bound epithelium and results in organ damage.

e. Epidermolysisbullosa:[8]
Hereditary epidermolysisbullosais 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 bullaeon the skin and mucous membranes. The vesicles may arise spontaneously or from minor trauma. The four types of epidermolysisbullosa 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,

f. Marfan syndrome [9]

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 mutationin the gene encoding fibrillin (FBN1, chromosome15q15–21.3), a glycoprotein that is an integral part of the connective tissue in the body (ligaments, blood vessel, eyelenses). It primarily involves the skeletal, ocular and cardiovascular systems. Typically, patients present with tall stature, ectopialentis, 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.

Autoimmune Collagen Disorders

A. Systemic Lupus Erythematosus[10,11]

Lupus erythematosus is a multifactorial autoimmune collagen vascular or connective tissue disease, which may affect the oralmucosa 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 arexerostomia, stomatodynia, candidiasis, periodontal diseaseand dysgeusia.

b. Systemic sclerosis (progressive systemic sclerosis; scleroderma; hide-bound disease)[10,12]

Progressive systemic sclerosis is a disorder of the connective tissue tha tillustrates fibrosis of the skin, blood vessels, visceralorgans 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´sphenomenon 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 produces a firm, hypo mobile (board-like) tongue and an inelastic esophagus, thus resulting in dysphagia.

c. Oral submucous fibrosis:[13,14]

It is a chronic, premalignant condition of the oral mucosa which was first described by Schwartz 1952. Various studies suggested that it is an autoimmune disease. The presence of various autoantibodies in varyingtiters is reported in several studies confirming autoimmunebasis to the disease.[15]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.[16] 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 juxtaepithelial inflammatory reaction followed by fibroelastic change in the lamina propria and associated epithelialatrophy. 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.

Miscellaneous

Scurvy[17]

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. Othe rmetabolic 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, 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.

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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