International Journal of Research in Health and Allied Sciences

Journal home page: www.ijrhas.com

Official Publication of "Society for Scientific Research and Studies" [Regd.]

ISSN: 2455-7803 Index Copernicus value [ICV] = 68.10;

REVIEW ARTICLE

Collagen Disorders: A Review

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ABSTRACT:
Collagen is the largest and most abundant protein in the body, making up about 65% of our total protein. It is a fibrous protein, found mainly in the skin, bones, muscles, cartilage, tendons, ligaments where it forms a scaffold to provide strength and structure. As collagen forms building block of body structures, any defect in collagen results in disorders. This review highlights the role of collagen in disorders associated with structural and functional defects in collagen.
Keywords: Collagen, Extracellular matrix, Genetics, Disorders

Received: 4 April, 2020 Accepted: 28 April, 2020

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This article may be cited as: K Smitha, Jose M, Nayak S. Collagen Disorders: A Review. Int J Res Health Allied Sci 2020; 6(3):121-130.

INTRODUCTION:

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. 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 and provides rigidity, elasticity and strength.[1] Collagen contributes to the stability of tissues and organs and maintain their structural integrity. A balanced synthesis, regulation and degradation of collagen ensure a good health. It is unavoidable that the undesirable effects of molecular changes in the structure of this fibrous protein may affect many systems of the human body, from the central nervous system to the musculoskeletal and cardiovascular systems leading to collagen disorders.[2]

CATEGORIZATION OF COLLAGEN DISORDERS

Heritable/genetic collagen disorders	Autoimmune collagen disorders	Miscellaneous
Ehlers – Danlos syndrome	Systemic lupus erythematosus	Scurvy
Osteogenesis Imperfecta	Systemic sclerosis	
Stickler syndrome	Oral submucous fibrosis	
Alport syndrome		
Epidermolysis Bullosa		
Marfan syndrome		

HERITABLE/ GENETIC COLLAGEN DISORDERS:

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. Ehlers-Danlos syndrome is a rare hereditary disease of the connective tissue which can present oral manifestations.[3] Ehlers-Danlos syndrome (EDS) is a hereditary collagen disease presenting primarily as dermatological and joint disorders. [4]

Epidemiology and Diagnosis

The prevalence of the condition varies between 1:10,000 and 1:150,000 depending on the author. The diagnosis of EDS depends primarily on clinical findings and family history, as it is an autosomal dominant hereditary disorder which presents in several ways.[5]

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 interference with conversion of procollagen to collagen.[1]

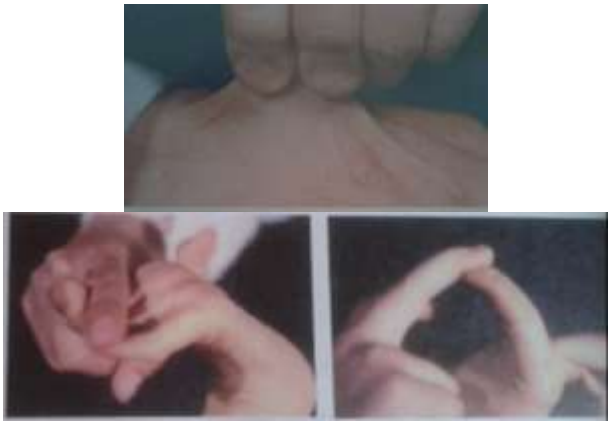
Characteristics of EDS

The classic signs of EDS are Joint hypermobility, Hyperelasticity of skin, which is soft, thin and fragile, the presence of dystrophic scars, tendency to excessive bleeding manifested by bruises, ecchymoses and hematomas. [6]

Clinical Manifestations of EDS

Extraoral

The extraoral manifestations of EDS are the presence of scarring on the chin and forehead, a history of repeated luxations of the TMJ, epicanthus, hypertelorism, a narrow curved nose, sparse hair and hyperelasticity of the skin.



The typical lax skin and joint hypermobility

Intraoral

Oral examination can help diagnose EDS. The classic intraoral signs of EDS can point to the eventual diagnosis of the condition.

Mucosa

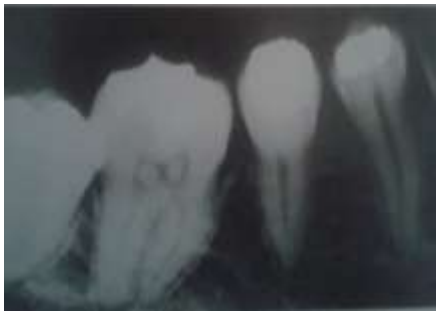
As fragile as the skin, the mucosa tears easily when touched by instruments. Sutures do not hold.[7]

Periodontal Tissues

The fragility of the gingiva can be detected following treatments such as prophylaxis, periodontal surgery or extraction. Hemorrhage may be difficult to control during surgical procedures. Early-onset generalized periodontitis is one of the most significant oral manifestations of the syndrome. This can lead to the premature loss of deciduous and permanent teeth.[8]

The 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 reveals pulp stones and roots that are short and deformed. Microscopic-level anomalies of the various dental tissues are described in detail by Barabas and Pope. One case of type III EDS with multiple supernumerary teeth has been reported in the literature.[9]



Radiograph shows the short roots and characteristic pulp stones in the molar

The Tongue
The tongue is very supple. Approximately 50% of those with the syndrome can touch the end of their nose with their tongue **(Gorlin's sign),** compared to 8-10% of the population.

The Palate
The palate is commonly vaulted.[10] A tendency for recurrent subluxation of the temporomandibular joint has also been reported.

Differential diagnosis
The differential diagnosis of EDS includes

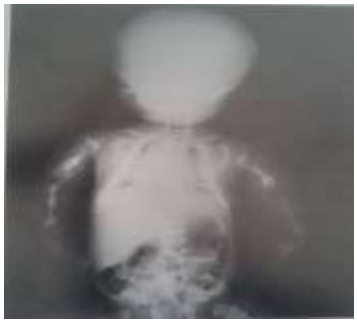
- Marfan's syndrome,
- Generalized familial joint hypermobility syndrome,
- Cutis laxa,
- Pseudoxanthoma elasticum
- Larsen's syndrome.

OSTEOGENESIS IMPERFECTA:
Osteogenesis imperfecta is an inherited disorder of the connective tissue which is commonly known to have an autosomal dominant pattern of inheritance. However, autosomal recessive and non hereditary types are also known to occur. 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.[11]
Type I collagen fibers are found in bones, organ capsules, fascia, cornea, sclera, tendons, meninges, and dermis. Structurally, this protein is composed of a left-handed helix formed by intertwining of pro-a1 and pro-a2 chains. Mutations in the loci coding for these chains (COL1AI on band 17q21 and COL1A2 on band 7q22.1 respectively) cause osteogenesis imperfecta. Qualitative defects (abnormal collagen I molecule) and quantitative defects (decrease in production of normal collagen I molecules) both exist in its causation.
Four types of osteogenesis imperfecta exist.

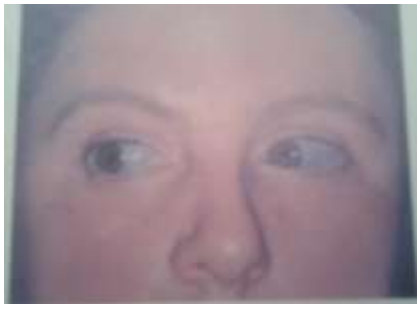
- **Type I** is autosomal dominant,
- **Type II** is autosomal dominant with new mutation,
- **Type III** is autosomal dominant with new mutation (rarely recessive forms also are observed),
- **Type IV** which is autosomal dominant.

Researchers have defined three more types of osteogenesis imperfecta **(type V, type VI, and type VII),** but the genetic causes have not yet been identified.

Clinical features:
The chief clinical characteristic of osteogenesis imperfect is the extreme fragility and porosity of the bones, with an attendant proneness to fracture. The fractures heal readily, but the new bone is of a similar imperfect quality.
The age of onset of symptoms varies depending on the type of OI with fractures Type I and type IV occurring during infancy and type II in utero. Type III- half the cases present fracture in utero, and other half in the neonatal period. Other clinical features of osteogenesis imperfecta is the occurrence of pale blue sclera, hearing loss, skin thinness, joint laxity and hypermobility and dentinogenesis imperfect.[11,12]



Radiograph shows multiple fractures



Typical blue sclera

STICKLER SYNDROME:
It is a unique **autosomal dominant** syndrome of premature osteoarthritis, retinal degeneration, hearing loss, and orofacial abnormalities. First described by Gunnar B Stickler in 1965.[13] The disorder (hereditary arthro-ophthalmopathy, or Stickler syndrome) is now known to be caused by mutations in the COL2A1, COL11A1, and COL11A2 procollagen genes of type 2 and 11 collagen . Incidence is estimated at around 1/10,000, and Stickler syndrome may be the most common autosomal dominant connective tissue dysplasia in North America.[14]
Type 2 collagen is a homotrimer of three COL2A1 gene products, whereas Type 11 collagen is a heterotrimer containing one each of the COL2A1, COL11A1, and COL11A2 gene products.[15] Both type 2 and 11 collagens are members of the fibrillar collagens, which

are primarily expressed in cartilage, vitreous, and nucleus pulposus.

Most patients with Stickler syndrome are thought to have premature stop mutations in their COL2A1 gene, leading to the classic Stickler phenotype (type 1 Stickler syndrome)[16] and a COL2A1 mutation has been identified in the original family reported by Stickler COL11A2 is not expressed in the vitreous, leading to a phenotype with systemic manifestations of Stickler syndrome but normal eye findings (nonocular or type 2 Stickler syndromes) Finally, a few families have been described with mutations in their COL11A1 gene. These patients display the classic phenotype, but subtle differences in the vitreoretinal abnormalities may be present. This variant is now referred to as type 3 Stickler syndrome.[17]

Most patients are recognized in childhood if they present with cleft palate or severe ocular findings or have a positive family history. Approximately one fourth have an open cleft palate, and other patients have more subtle clefting (bifid uvula or submucous clefts) Pierre- Robin sequence (the constellation of cleft palate, glossoptosis, and severe micrognathia, which can result in neonatal feeding problems and potentially lifethreatening respiratory obstruction) may be present. Other common facial features include malar hypoplasia, a flattening or widening of the nasal bridge, and micro/retrognathia.

ALPORT SYNDROME:

Alport syndrome (AS) is a generalized inherited disorder of basement membranes, particularly those of glomeruli that involve type IV collagen. The mutation occurs in a gene located on the X chromosome. The normal allele on the other X chromosome in females partially compensates for the genetic disorder. The inherited defect of the classical X-linked AS affects the α5 chain of the type IV collagen gene (COL4A5), which has been mapped to chromosome Xq22, while inherited mutations in α3 and α4 chains of type IV collagen (COL4A3 and COL4A4), which map to chromosome 2, are responsible for the less frequent recessive form of AS.[18]

MARFAN SYNDROME:

Marfan syndrome is the most common inherited connective tissue disorder, with a reported incidence of 1 in 10,000 individuals and equal distribution between the sexes.[19] 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 (eg, ligaments, blood vessel, eye lenses). Although the genetic and biochemical bases of the condition have been identified, the disease continues to be underdiagnosed.[20]

Clinical presentation

Most patients who have Marfan syndrome are usually diagnosed incidentally when they present for a routine physical examination for various reasons, such as a pre-employment physical or screening examination prior to participation in sports. Marfan syndrome primarily involves the skeletal, ocular, and cardiovascular systems. Typically, patients with Marfan syndrome present with tall stature, ectopia lentis, aortic root dilatation, and a positive family history. Less frequently, 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. Presentation of the disease varies greatly, even among family members.

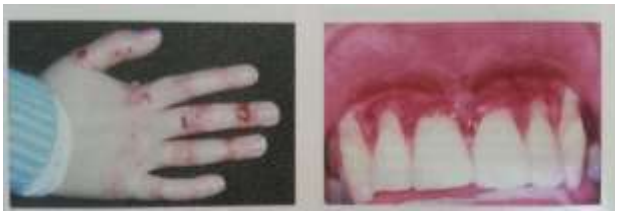
Skeletal manifestations are the cardinal signs of Marfan syndrome and usually gain the attention of a physician. The most common features include tall stature with the lower segment of the body greater than the upper segment and long, slender limbs,or dolichostenomelia; thin body habitus with increased arm span-to-height ratio; long, slender fingers, or arachnodactyly , deformities of the chest, such as pectus carinatum or pectus excavatum; scoliosis; and highly arched palate with crowded teeth and dental malocclusion. Other less common manifestations include hypermobility of joints, flat foot (pes planus), reduced extension of elbows (< 170 degrees), and elongated face (dolichocephalia).[21]

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.



Epidermolysis bullosa (EB) is classified into the **four** major subtypes depending on the level of skin cleavage within the epidermal keratinocyte or basement membrane zone. Tissue separation occurs within the intraepidermal cytoplasm of the basal keratinocyte, through the lamina lucida, or in sublamina densa regions of the basal lamina (basement membrane)

Simplex EB
Junctional EB
Dystrophic EB
Hemidesmosomal EB

Transmission electron microscopy (TEM) is an effective method for determining the level of tissue separation and hemidesmosome (HD) and anchoring fibril morphology.[22] 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 α6 α4 integrin.[1]

AUTOIMMUNE COLLAGEN DISORDERS

SYSTEMIC LUPUS ERYTHEMATOSUS

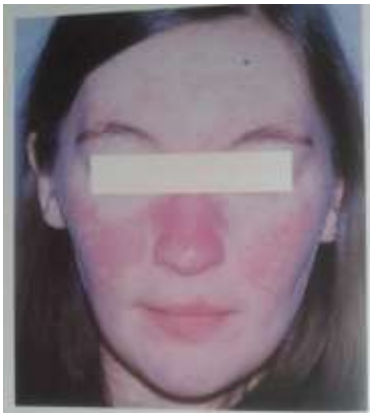
Lupus erythematosus (LE) is a multifactorial autoimmune collagen vascular or connective tissue disease, which may affect the oral mucosa in either its cutaneous and systemic forms, with varied prevalence.
Classically, LE has been subdivided into
Systemic lupus erythematosus (SLE) is a multiorgan disease with variable prognosis
cutaneous lupus erythematosus (CLE) is a more benign condition – limited to skin and/or mucosal surfaces.[23, 24]

The prevalence of mucosal involvement in LE patients is debatable. Some authors suggest that oral lesions are present in 9–45% of patients with the systemic form of the disease and in 3–20% in those with CLE.[25, 26]

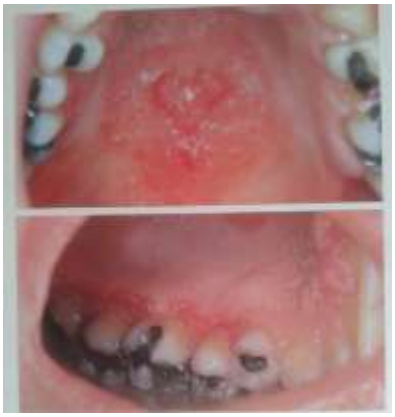
Systemic lupus erythematosus – Is a serious multisystem disease with a variety of cutaneous and oral manifestations. There is an increase in the activity of the humoral limb (B lymphocytes) of the immune system in conjunction with abnormal function of the T lymphocytes. Although the precise cause is unknown.

Pathogenesis
Hereditary predisposition, viral infection, sex hormones and other factors are thought to interact in complex ways to cause immune abnormality and SLE. However, the pathogenesis has not been identified. It is known that antinuclear antibodies, anti-DNA antibodies and anti-Sm antibodies are produced and destroy tissues directly (type II allergy) or form immunocomplexes to destroy tissues by complement cascades (type III allergy), which results in inflammation in the systemic internal organs.[27]

Clinical features
Women are affected nearly 8 to 10 times more frequently than men The average at diagnosis is 31 years. 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. Sunlight often makes the lesions worse. 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. Involvement of the vermilion zone of the lower lip (lupus cheilitis) is sometimes seen. Other oral complaints are xerostomia, stomatodynia, candidiasis, periodontal disease and dysgeusia.[28,29]



Typical butterfly rash in a young woman



Palatal lesion

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.[1] Scleroderma or Progressive systemic sclerosi; a rare

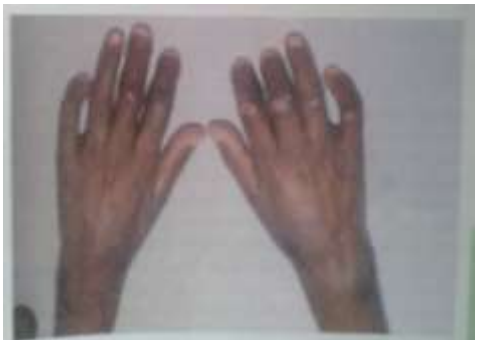
condition, was first characterized as a single condition in 1752 by Curzio of Naples.[30] It generally affects woman between 30 and 50 years of age, with and has a low prevalence 130 : million.[31]

The exact mechanism of the fibrotic changes is unknown, but hyperplastic changes of collagen have been documented.[32] Also, inflammatory changes and globulin deposits were found in blood vessel walls, which apparently explain the basis for altered collagen. The pathological findings indicate that fibroblasts are activated to produce excessive amounts of collagen and other components of the cellular matrix. Moreover, an autoimmune mechanism can be involved because patients with systemic sclerosis show high levels of highly specific and non-specific circulating autoantibodies, i.e., against DNA topoisomerase, centromeric protein B, RNA polymerases II, laminin S and vimentin.[33] Whether these genetic alterations are clinically or pathogenetically relevant remains to be seen.

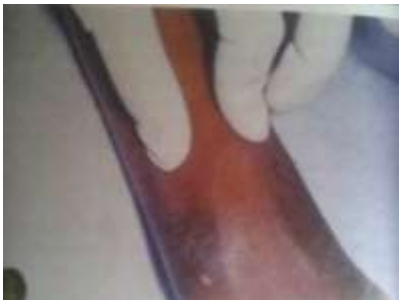
The high prevalence of autoantibodies in serological markers suggests that immune activation of scleroderma is localized and targets skin. Complicated cytokine Cascades seem to be involved in the development of this disorder.

Clinical features

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. An early indicator of systemic sclerosis is **Raynaud´s phenomenon**, a vasoconstrictive event triggered by emotional distress or exposure to cold, characterized by a painful digital ischemia, which results in local resorption of terminal phalanges (**acro-osteolysis**). Survival of scleroderma patients is determined by the severity of visceral involvement.[34] Cutaneous manifestations include thickening of skin, starting with pitting edema is replaced by tightening and hardening of skin.

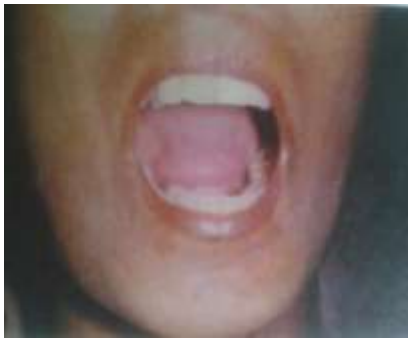


Scleroderma of the hand

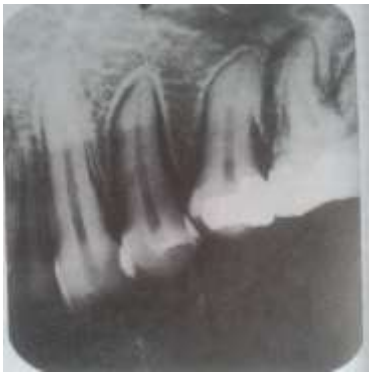


With extreme fixation of the skin to the subjacent connective tissue

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.[35]



Difficulty in mouth opening due to involvement of perioral skin



The extreme widening of the periodontal ligament is obvious in the radiograph

ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis is a precancerous condition first described by Schwartz in 1952 & named it as "Atrophica idiopathica mucosae oris"

In 1953 Joshi named it as "Oral submucous fibrosis". Meaning of Oral submucous fibrosis is Oral – Mouth , Submucous – Below the mucosa of the mouth,Fibrosis – Hardening and scarring.

This condition predominantly affects people of South East Asian origin. WHO defined OSF as a slowly progressing disease characterized by formation of fibrous bands which form a blanched oral mucosa resulting in severe restriction of movement of mouth.

Pindborg defined OSF as an insidious chronic disease affecting any part of the oral cavity & sometimes the pharynx. Occasionally preceded with vesicle formation, always associated with juxtra-epithelial inflammatory reaction followed by fibro elastic change of lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat.

OSF as an autoimmune disorder

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.[36]

A recent study has revealed higher haplotype frequencies in pairs HLA B51/Cw7 and B62/Cw7 in OSF patients. Two new HLA DRB1 alleles were identified by sequencing-based typing and named as HLA DRB1-0903 and DRB1-1145.[37] The association of HLA and OSF does not appear consistently as one study showed that there was no demonstrable specific pattern of HLA antigen frequencies in chewers with or without the disease.[38] 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.[39]

Pathogenesis:

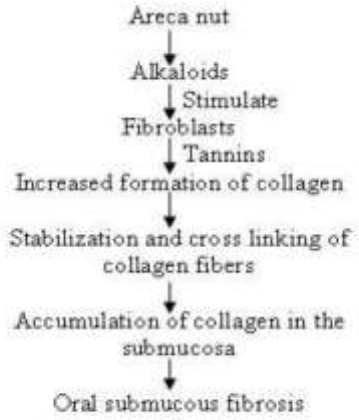
I Collagen accumulation:

Oral submucous fibrosis results from increased production of collagen by fibroblasts. In addition to this there is decreased breakdown leading to accumulation of excessive amount of collagen.

a) Increased Collagen Production:

Under the influence of areca nut, fibroblasts differentiated into phenotypes that produce more collagen. The alkaloids present in areca nut, arecadine and arecoline are responsible for this. Arecoline gets converted in to arecadine which is the active metabolite. There is dose dependent increase in production of collagen by fibroblasts under influence of these factors.

Various cytokines are increased in oral submucous fibrosis. These are: Transforming growth factorβ (TGF-β), Platelet derived growth factor (PDFG) and Basic fibroblast growth factor (bFGF). These are fibrogenic growth factors that stimulate collagen production. Another cytokine that has anticollagen effect is Interfran-α (IFN-α). This is decreased in Oral submucous fibrosis. Thus overall there is stimulation of collagen synthesis through different mechanisms (Haque et al, 1998).



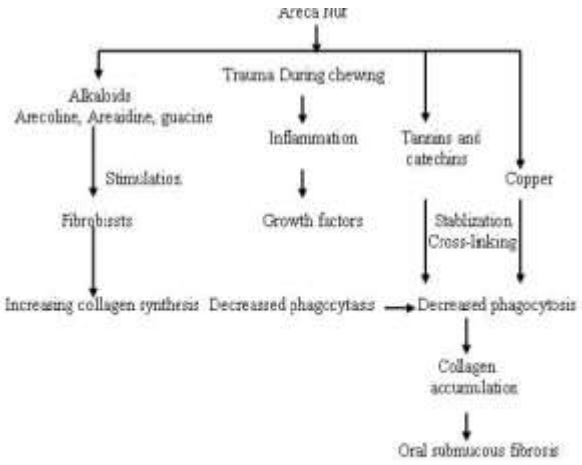
Flow chart 1: Role of areca alkaloids in OSF (Ghom & Mhaske, 2008).

b) Stabilization of collagen structure and decreased collagen breakdown:

One of the mechanisms that can lead to increased fibrosis is by reduced degradation of collagen by forming a more stable collagen structure. Betel nut contains tannin. Tannin has ability to stabilize collagen by cross-linking it. With the progression of the disease type III collagen is almost completely replaced by type I (Utsunomiya et al, 2005). Type I collagen is more resistant to degradation than type III. An important finding from these studies is the identification of excess α-1 chains relative to α-2, suggesting an alteration of collagen molecules during the progression of the disease. Although, the biological function of this trimer is not known, it is regarded as more resistant to degradation than the normal collagen molecule (Tsai et al, 1999).

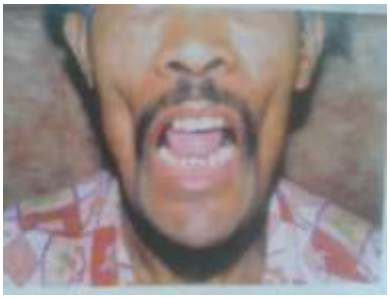
Another component of betel nut that aids this cross-linking is copper. It is a constituent of enzyme lysyl oxidase. This enzyme also causes cross-linking and makes collagen resistant to degradation by collagenase. Due to action of tannin and copper, collagen that is produced in OSF is highly resistant to remodeling and phagocytosis (Tsai et al, 1999). It is fibroblast that brings about remodelling and phagocytosis of collagen. As in Oral submucous fibrosis, these fibroblasts are affected and phenotypically changed, they cannot degrade collagen. Studies on the effects of arecoline on

both normal and oral submucous fibrosis fibroblasts in culture revealed an elevated rate of collagen synthesis by OSF fibroblasts as compared to normal fibroblasts.

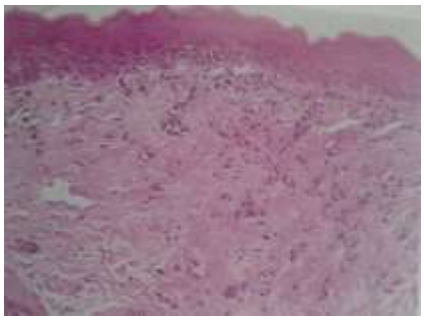


Flow chart 2: Role of areca nut in oral submucous fibrosis (Ghom & Mhaske, 2008)

Oral submucous fibrosis is characterized by a juxtra 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 subepithelial layers, resulting in dense fibrous bands in the mouth. [40]



Advanced OSF



Histologic picture of OSF

MISCELLANEOUS

SCURVY

A deficiency of vitamin C (ascorbic acid) is known as scurvy. A major function of ascorbic acid is its involvement in the synthesis of collagen fibres from proline via hydroxyproline.[41]

Other metabolic reactions for which vitamin C is required are the hydroxylation of lysine into hydroxylysine in collagen, the conversion of folic acid to the active form of folinic acid *in ViVO* the formation of steroids by the adrenal gland.[42]

At the tissue structural level vitamin C is involved with the synthesis of intercellular substances and the collagen fibres of the various forms of connective tissues in which collagen forms a part, for example organ capsular/trabecular, tendinous and fascial tissue, the matrix of calcified tissue such as bone and teeth, and the endothelial cells of the entire vascular tree, including the capillaries.[43]

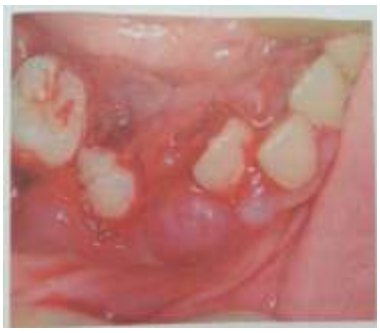
In a normal adult man of 70 kg mass and with a vitamin C reserve of 1500 mg, general scurvy will manifest when the vitamin C reserve is reduced to 300 mg. This can be caused by a reduction of 45 mg vitamin C per day for 60 days on a vitamin C-free diet.

In man a quantity of vitamin C of less than 10 mg/d in the diet is insufficient to sustain health and will consistently produce scurvy. [44]

In an adult man the recommended dietary allowance of vitamin C for health is 60 *mg!*d, nearly double the daily metabolic requirement and enough to maintain normal blood levels of vitamin C (0,75/0,8 mg/dl). Intakes of over 100 mg/d increase blood concentrations of vitamin C to 1,5mg/dl, the renal threshold level for ascorbic acid in the glomerulus; any excess vitamin C in the blood is excreted in the urine.[45]

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 gingival. A vitaminosis 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 odour, and loosened teeth with 'swollen, tender, spongy bleeding - putrid gums.[46]

In fully developed scurvy the gingivae are boggy, ulcerated and bleed with the interdental and marginal gingiva becoming bright red, smooth, swollen and shiny.



Scurvy- hemorrhagic gingival enlargement (scorbutic gingivitis) Because of capillary fragility

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. In recent years, despite the increasing information obtained about the structure and synthesis of collagen, the genetic and molecular bases of the collagen disorders, which are still accepted as untreatable or incurable clinical syndromes, remain undetermined. In addition to having the opportunity to understand numerous molecular disorders, progressive biochemical tests, molecular findings and also the technological resources will facilitate an explanation of the systematic and physiopathologic processes. Hence, future research and molecular studies are required in this field in order to provide the best treatment modalities to the patients with collagen disorders.

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