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Abstract:

Contemplating the vast knowledge about life has always been a topic of major interest. Not only does it help us to understand the normal biological mechanisms, it also helps us to grasp the idea of any deviation from that said normality. Proteins are the most abundant and functionally diverse molecules in living systems. One such protein is collagen. Since mouth is mirror of body it is an oral physician's job to perform early diagnosis and management of these conditions, this dissertation aims to provide concise and relevant information about collagen disorders affecting the Head and Neck region.

Keywords: Amelogenesis imperfecta, Collagen, Collagen Disorders, Dentin Dysplasia, Dentinogenesis Imperfecta, Ehlers-Danlos Syndrome, Epidermolysis Bullosa, Fibrodysplasia, Oral Submucous Fibrosis, Marfan Syndrome, Osteogenesis Imperfecta, Scleroderma, Systemic Lupus Erythematosus,

Collagen Disorders

Contemplating the vast knowledge about life has always been a topic of major interest. Not only does it help us to understand the normal biological mechanisms, it also helps us to grasp the idea of any deviation from that said normality. In this living system proteins are the most abundant and functionally diverse molecules. They function as the building blocks of an organism. In the bloodstream, proteins like haemoglobin and albumin, transport molecules essential to life, immunoglobulins fight infectious bacteria and viruses. Metabolism in the body is regulated by enzymes and polypeptide hormones, whereas contractile proteins in muscle allow movement. In bone, the protein forms a framework for calcium phosphate deposition. [1]

Collagen is one of these proteins present in the majority of species throughout the animal kingdom, including all vertebrates. Collagen constitutes approximately 25% of the total protein in mammals. Until the 1970s, it was speculated that collagen is a single protein. But in recent years, discoveries of new, genetically distinct types of collagen proteins, has led to the knowledge of a vast collagen family rather than a single entity.

The term "collagen", introduced in the nineteenth century, was derived from the Greek words "kolla" which means “glue”and "genos:' which mean "formation.” [2]

The total amount of collagen is estimated as 25% - 30% of total body proteins. Collagen constitutes about 75% of total nitrogen content of human skin. [3]

Collagen Disorders

a. Ehlers-Danlos Syndrome

The Ehlers-Danlos syndrome (EDS) is a heterogeneous tissue disorder. EDS shows skin hyperextensibility, joint hypermobility that usually leads to dislocations, and tissue fragility exemplified by simple bruising, atrophic scars following superficial injury, and premature rupture of membranes throughout gestation. The concept that EDS is a disorder of fibrillar collagen metabolism was due to the recognition of frequent ultrastructural abnormalities of scleroprotein fibrils in EDS patients.

Thi concept is well supported by identification of specific defects in the collagen biosynthetic pathway that produce clinically distinct forms of EDS. There are three fundamental mechanisms that are known to produce EDS. They are:

i. deficiency of collagen-processing enzymes,
ii. dominant-negative effects of mutant collagen α-chains, and
iii. haploinsufficiency.

The two known examples of deficient enzyme activity are lysyl-hydroxylase deficiency and procollagen peptidase deficiency.

In the first case, normal intermolecular cross-linking of collagen trimers is hindered due to defective hydroxylate lysine, and in the second instance, normal proteolytic cleavage of the NH2-terminus of procollagen chains is prevented due to absence of procollagen peptidase. The morphology and strength of the collagen fibril is compromised in both cases.

Classification of EDS types:

EDS is classified in the following Table[4]-

TYPE	CLINICAL CHARACTERISTICS
I and II (Classic)	Marked hyperextensibility of skin with widening of atrophic scars and hypermobility of joints. Molluscoid pseudo tumours (calcified haematomas) and periodontitis has also been reported.
III (Hypermobility Type)	Hypermobility of joints is the dominant clinical manifestation. The hyperextensibility and/or smooth velvety skin and bruising tendencies are present but variable in severity. Periodontitis has been reported in some cases
IV (Vascular Type)	The skin appers thin and translucent with visible veins. The facial characteristics are large eyes, thin nose, lobeless ears, short stature, thin scalp hair and also evident is a decrease in subcutaneous tissue of face and extremities. Easy bruising is manifested by spontaneous ecchymosis. Arterial / intestinal / uterine fragility or ruptures are very frequently noticed.

V	It has been described in a single family. It is rare and the molecular basis is still unknown.
VI (Kyphoscoliosis Type)	Generalized laxity of joints. Severe muscle hypotonia and scoliosis at birth is noticed. Tissue fragility, atrophic scars, easy bruising and marfanoid habitus (Marfan-like features), micro cornea and radiologically considerable osteopenia.
VII A and B (Arthrochalasia Type)	Congenital hip dislocation, generalized joint hypermobility with recurrent subluxations, skin hyperextensibility with easy bruising, tissue fragility including atrophic scars; muscle hypotonia; kyphoscoliosis and radiologically mild osteopenia.
VII C (Dermatosparaxis Type)	Severe skin fragility and substantial bruising. Normal wound healing and the scars formation. Skin texture is soft and doughy. The redundancy of facial skin results in an appearance resembling cutis laxa. Large hernias (umbilical, inguinal) may be seen. The oral findings are alterations on the teeth and severe periodontitis.
VIII	Similar to the classical type except that it also presents periodontal friability. This is a rare type of EDS and its existence as an autonomous entity is uncertain.

Table 1: Classification of Ehlers-Danlos syndrome.

The characteristic features of this syndrome are

1. Joint hypermobility.
2. Skin hyperelasticity and fragility.
3. Deficient healing of wounds.
4. Ecchymosis caused by minor traumas.

Besides the cutaneous and articular anomalies, the patients may show:

- Cardiovascular complications (aneurysms and mitral valve prolapse),
- Gastrointestinal complications (such as hernias and gastrointestinal diverticulosis), and
- Ocular defects.[5]

Oral manifestations of EDS include:

1. The mucous membrane becomes fragile, which may lead to bleeding on instrumentation. Suturing becomes difficult
2. Dentinal aberrations like pulp stones, short and deformed roots.
3. A high incidence of deciduous teeth caries.
4. Spontaneous fractures of teeth.
5. Early onset of generalized periodontitis.
6. A supple tongue. Approximately 50% of those with this syndrome can touch the end of their noses with their tongue (Gorlin's sign), whereas only 8-10% of the normal population can do this.
7. TMJ hypermobility, with increased incidence of dysfunction in some cases.[6,7]

b. Marfan Syndrome

Marfan syndrome (MFS) is an autosomal dominant, heterogenous, connective tissue disorder. It affects the skeletal, ocular and cardiovascular systems. This condition was first described in 1896 by the French pediatrician Antoine Bernard-Jean Marfan.

Fibrillar collagens are major structural components of connective tissue. The hypothesis has long been proved that Marfan syndrome is a disorder of fibrillar collagen.[8] It is caused mainly by mutations in the gene *FBN1*. This gene encodes fibrillin-1, a glycoprotein that is the main constituent of the microfibrils of the extracellular matrix. Reduced or abnormal fibrillin-1 causes tissue weakness, increased transforming growth factor β signalling and loss of cell–matrix interactions. Among the many different clinical manifestations of Marfan syndrome, cardiovascular involvement deserves special consideration, owing to its impact on prognosis. However, the diagnosis of patients with Marfan syndrome should be made according to Ghent-2 criteria. Genetic testing can be of use in the diagnosis of selected cases. Several genes that are suspected to be defective in Marfan syndrome, are located on the long arm of chromosome 2. These genes include COL3A1 and COL5A2 and COL6A3.[9]

Orofacial features of Marfan syndrome include[10]–

i. Dolichocephaly,

ii. Malar hypoplasia,

iii. Long and narrow face,

iv. Frontal bossing,

v. Prominent supraorbital ridges,

vi. Maxillary and mandibular retrognathia,

vii. Skeletal malocclusion,

viii. TMJ hypermobility,

viii. High arched palate,

ix. Dental crowding, and posterior open bite**.**

x. Developmental abnormalities of the teeth may also be noticed (supernumerary teeth).

xi. Enamel defects, dentinogenesis imperfecta, dysplasia of teeth and cysts formation in the jaws have been reported in few cases.

xii. Periodontal problems may occur due to difficulty of effective brushing because of the higharched palate and mouth breathing which particularly affects the anterior region.

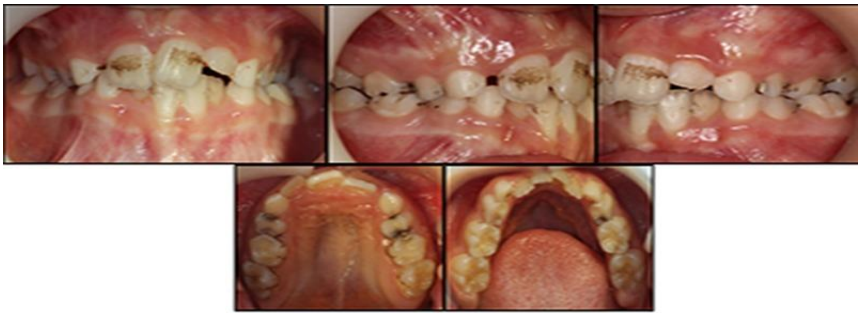


Fig 2: Intraoral pictures of a patient with Marfan syndrome.

Diagnostic Criteria of Marfan Syndrome according to Ghent -2 nosology[11]:

In the absence of family history:

1. Aortic root diameter (Z-score ≥2) and ectopia lentis = MFS*
2. Aortic root diameter (Z-score ≥2) and causal *FBN1* mutation = MFS
3. Aortic root diameter (Z-score ≥2) and systemic score ≥7 points = MFS*
4. Ectopia lentis and causal *FBN1* mutation with known aortic root dilatation = MFS

In the presence of family history:

5. Ectopia lentis and family history of MFS (as defined above) = MFS
6. Systemic score ≥7 points and family history of MFS (as defined above) = MFS*
7. Aortic root diameter (Z-score ≥2 above 20 years old, ≥3 below 20 years) and family history of MFS (as defined above) = MFS*

*Caveat: without discriminating features of Shprintzen–Goldberg syndrome, Loeys–Dietz syndrome or vascular form of Ehlers–Danlos syndrome

AND after *TGFBR1/2*, collagen biochemistry, *COL3A1* testing if indicated.

Scoring of systemic features of MFS

1. Wrist and thumb sign – 3 points (wrist or thumb sign – 1 point)
2. Pectus carinatum deformity – 2 points (pectus excavatum or chest asymmetry – point)
3. Hindfoot deformity – 2 points (plain pes planus – 1 point)
4. Protrusio acetabuli – 2 points
5. Reduced upper segment/lower body segment ratio and increased arm/height and no severe scoliosis – 1 point
6. Scoliosis or thoracolumbar kyphosis – 1 point
7. Reduced elbow extension – 1 point
8. Facial features (3/5) – 1 point (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
9. Pneumothorax – 2 points
10. Skin striae – 1 point
11. Myopia >3 diopters – 1 point
12. Mitral valve prolapse (all types) – 1 point
13. Dural ectasia – 2 points

Fig 3: Ghent -2 nosology (Revised Diagnostic criteria of Marfan Syndrome)

Clinical Pictures-

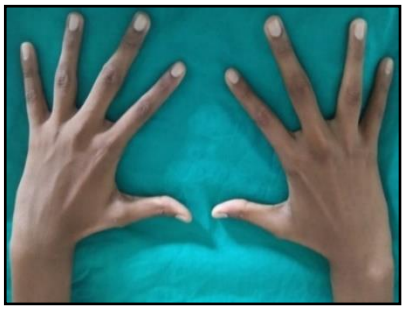


Fig 4: Arachnodactyly

Fig 5: Positive Walker-Murdoch sign

Fig 6: Positive Steinberg sign

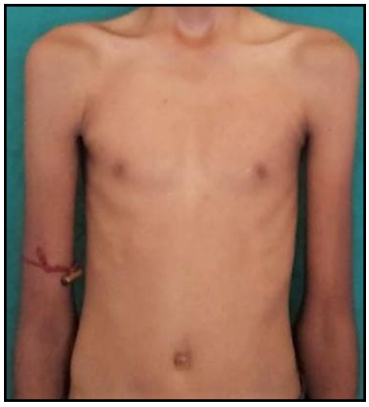


Fig 7: Depressed sternum or pectus excavatum

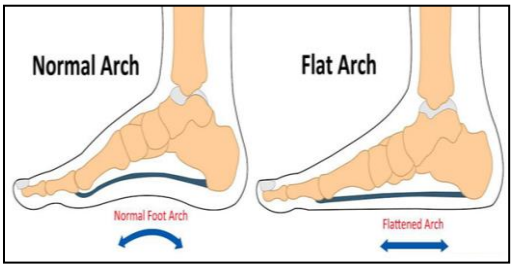


Fig 8: Pes Planus

c. Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a heterogeneous genetic disorder of connective tissue. It is known as "brittle bone disease". It is a dominant autosomal disorder characterized by bone fragility and abnormalities of connective tissue.

Sillence et al. (1979) identified four types of OI (Table 9)[12] on the basis of clinical, radiologic and genetic criteria.

OI type	Inheritance	Clinical characteristics
I	Autosomal Dominant	Normal stature, little or no deformity, blue sclerae, hearing loss.
II	Autosomal Dominant (new mutation)	Lethal in perinatal period, beaded ribs, long bone fractures.
III	Autosomal Dominant Autosomal Recessive (rare)	Progressively deforming., short stature, multiple fractures, triangular facies, hearing loss.
IV	Autosomal Dominant	Moderately severe, variable short stature, dentinogenesis imperfecta, osteoporosis. Bowing of long bones.

Table 9: Classification of OI phenotype according to Sillence et al. (1979)

Biochemical and molecular genetic studies have shown that the vast majority of affected individuals have mutations in either the COL1A1 or COL1A2 genes that encode the chains of type I procollagen. Although type I collagen is the major structural protein of both bone and skin, the mutations in type I collagen genes cause a bone disease.[13]

Clinical Pictures-

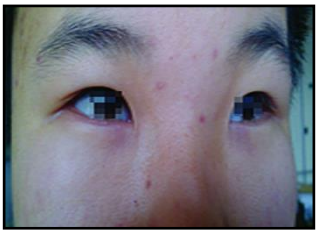


Fig 10: Blue sclera.

Fig 11: Hypermobility of joints.

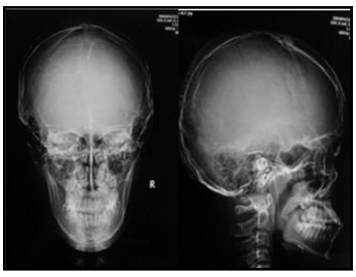


Fig 12: Skull radiograph showing diffuse low bone density

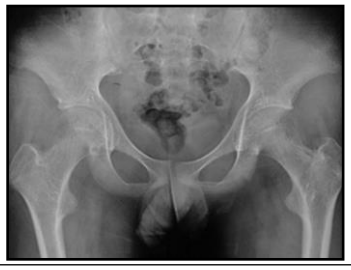


Fig 13: Triradiate pelvis and acetabular protrusion

d. Epidermolysis Bullosa

Epidermolysis bullosa (EB) refers to a group of heterogenous heritable disorders characterized by formation of blisters at sites of minor friction or trauma.

It is classified into four main types according to the layer of skin in which blistering occurs: epidermolysis bullosa simplex (intraepidermal), junctional epidermolysis bullosa (within the lamina lucida of the basement membrane), dystrophic epidermolysis bullosa (below the basement membrane), and Kindler epidermolysis bullosa (mixed skin cleavage pattern). [14]

Epidermolysis bullosa simplex (EBS) is characterized by intraepidermal blistering. Electron microscopy shows breakdown of the basal cells, whose remnants can sometimes be seen on the blister floor. With few exceptions, patients with EB simplex follow a benign clinical course, and mucosal involvement is uncommon.

In **junctional EB (JEB)**, blisters form at the lamina lucida, at a plane between bullous pemphigoid antigen and laminin. It was previously thought that patients with junctional EB never lived past infancy, but careful clinical observations have led to recognition of different subtypes that vary in prognosis, and that some patients can survive to adulthood. [15]

In **dystrophic EB (DEB)**, blisters occur in the dermis, below the lamina densa. This type is characterized by scarring, which can be severe and mutilating, and formation of milia. Immunofluorescent techniques can be used to visualize various constituents of the basement membrane zone on light microscopy.

Clinical Pictures-

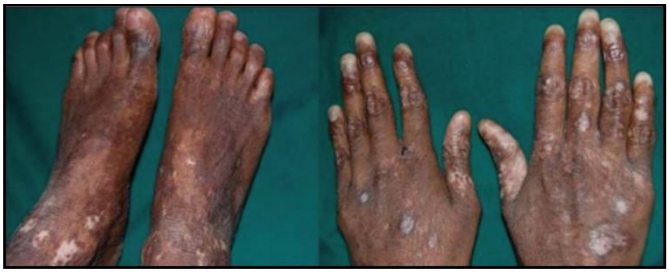


Fig 14: Complete dystrophy of toe and finger nails.

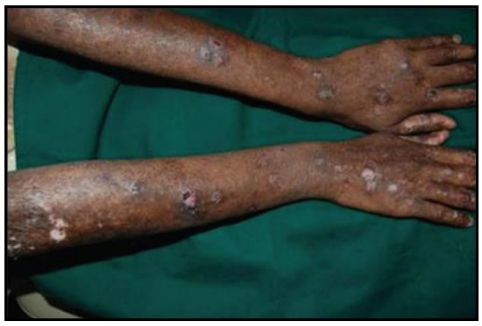


Fig 15: Hypo- or hyper-pigmented healed scar marks and ulcerations present on upper arm.

Oral manifestations-

- Milia are frequently observed on the skin of individuals with EB and these can occur intra-orally as well.
- Certain forms of EB have an increased risk for developing squamous cell carcinoma. While carcinomas occur with far greater frequency on the skin in individuals with EB, they can occur intra-orally as well. Physician should be extra vigilant in monitoring changes in oral ulcerations with raised, indurated borders.
- Enamel is normal as type VII collagen is not expressed by ameloblasts. Despite having relatively normal tooth formation the prevalence of dental caries and resulting dental morbidity in severe generalized recessive dystrophic EB can be severe.
- Oral soft tissue involvement results in the need to consume relatively soft diets that are frequently high in calories to meet the nutritional needs of the individual. Marked oral blistering causes individuals to eat slowly and with increased frequency.
- The loss of normal tongue mobility and obliteration of the oral vestibule decrease the normal food clearance causing additional prolongation of the dental surfaces to potentially cariogenic substrates.

- Many affected individuals have difficulty in performing normal oral hygiene due to severe soft tissue fragility and even the use of anticariogenic mouth rinses can be unpleasant due to the presence of alcohol or strong flavouring agents. [16]

e. Scleroderma

Scleroderma (Sc) presents with progressive fibrosis of the skin and of various internal organs, notably, the lungs, heart and gastrointestinal tract.

The extracellular matrix (ECM) is a complex structure that is composed of a large number of distinct molecules. It has become clear that the ECM is simply not an inert structural scaffold for endothelial cells, fibroblasts, and other mesenchymal cells, as was previously believed. Rather, there is a dynamic and reciprocal interaction between the structural components of the ECM and the cellular elements that is contained within it. These interactions control various aspects of cell behaviour, including chemotaxis, migration and adhesion, proliferation, differentiation, apoptosis, and the biosynthetic activities of fibroblasts and other mesenchymal cells. The structural composition of the ECM is profoundly altered in affected systemic scleroderma tissues. These alterations are most dramatically showed by the changes observed in the skin. Histologic examination of affected systemic scleroderma skin shows a marked increase in the dermis thickness with accumulation of dense and tightly packed collagen fibers replacing the loose dermal and subcutaneous adipose tissue. Increased collagen content in systemic scleroderma (SSc) skin and elevated production of newly synthesized collagens by skin biopsies in organ cultures have been consistently demonstrated. Excessive accumulation of collagen in the dermis and subcutaneous tissue also has been demonstrated in clinically uninvolved skin of patients, which suggests that the biosynthetic activation of fibroblasts is a very early event in the pathogenesis of tissue fibrosis in SSc. The marked accumulation of collagen does not appear to be accompanied by changes in the relative proportions of the various collagen types present in the affected indicating that there is a coordinated up-regulation of several collagen genes in SSc tissues.[17]

f. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that is extremely heterogeneous in its presentation. This can cause significant challenges for the physicians to diagnose and treat such patients. SLE arises from a combination of genetic, epigenetic and environmental factors. Pathologically, the disease is primarily driven by loss of immune tolerance and abnormal B- and T-cell function. Major organ involvement may lead to significant morbidity and mortality.

Numerous investigations into the pathogenesis of systemic lupus erythematosus (SLE), is focused on immunity to collagen. Despite the fact that the exact role that collagen autoimmunity plays in these disorders has yet to be discovered, there have been other reports that indicate the presence of autoantibodies against endothelial cells in vascular diseases. However, all these studies failed to determine and characterize the antigenic sites and specific epitopes present on the surface of the endothelial cells.

Antibodies to collagen type IV have been found in a variety of connective tissue diseases such as SLE, and mixed connective tissue disease. With the destruction of the endothelium in SLE, there may be exposure to the integral components of basement membranes, and thus induction of humoral and cell-mediated immunity to type IV collagen may result. Once an antibody response to the collagen has been initiated, a self-perpetuating cycle may occur leading to complement activation, immune complex formation, and antibody-dependent cell-mediated cytoxicity. On the other hand, it does not appear likely that autoantibodies to collagen type IV induce such a heterogeneous group of diseases such as SLE; nevertheless, autoreactivity to collagen type IV may have a role in perpetuation of disease. These clearly indicate that the autoreactivity against endothelial cells observed in patients with vascular disorders is not only related to a humoral immune response against endothelial cell collagen types IV and V, but also potentially contributes to the perpetuation of further vascular damage.[18,19]

Oral Manifestations –

Oral lesions in SLE manifest in a variety of forms, such as

mucosal ulceration, mouth burns, xerostomia, salivary gland diseases, temporomandibular joint disease, periodontal disease, dysgeusia, white lesions, oedema, bleeding and petechiae.[20]

g. Amelogenesis imperfecta (AI)

Amelogenesis imperfecta (AI) is a genetic condition that shows enamel abnormalities in both primary and permanent dentition. Tooth discolouration and changes in enamel appearance are frequently observed.
Clinical characteristics can be classified into
i. hypoplastic,
ii. hypocalcified, and
iii. hypomatured.
Each type is contributed by different mechanisms. Hypoplastic AI is caused due to the failure at secretory stage during enamel formation, while hypocalcified AI is caused by inadequate calcium ion transportation. Defect in enamel matrix protein removal results in the remaining of protein in mature enamel, causing hypomaturation type of AI.[21,22]
A study by **Kim et al. 2006** found disease-causing mutations in AI. They are AMELX, ENAM, KLK4, MMP20, AMBN, DLX3 and TUFT1.[22]
After further studies mutation in several other genes have been identified such as FAM83H, WDR72, KLK4, COL17A which contribute to different clinical phenotypes.

Clinical pictures-

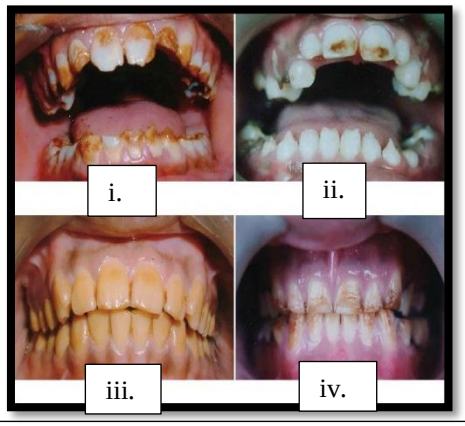


Fig 16: Clinical photos showing Amelogenesis Imperfecta. (i-iv)

h. Dentinogenesis Imperfecta (DI):

The first classification of DI was originally proposed by Shields in 1973 and was further commented by Wiktop in 1975. In DI, both the deciduous and permanent teeth are clinically affected, appearing blue-gray or amber brown and opalescent, although the deciduous teeth are often more severely affected. Radiographically, bulbous crowns, narrow roots, and small or obliterated pulp chambers and root canals are seen. Because of the defective dentin, enamel is easily broken off, exposing the underlying dentin, leading to accelerated attrition. According to Shields, DI is classified into three main groups.[23]

DI Type I

Individuals with DI type I have a syndromic form of DI. In addition to having DI, they also have osteogenesis imperfecta (OI), an autosomal dominant disorder of bone fragility. OI is further classified into collagenous and non-collagenous forms. All four collagenous OI subtypes can have DI as a feature. DI is more common in types III and IV. DI only occurs in cases of OI due to dominant negative effects (such as missense mutations). Approximately 90% of individuals with OI types I–IV have an identifiable mutation in COL1A1 *or* COL1A2, the two genes that encode the chains of type I procollagen.[24]

DI Type II

DI without any other etiologically related clinical findings (i.e. non-syndromic DI) is classified as DI type II. The clinical and radiographic tooth phenotype is indistinguishable from that in syndromic DI type I.[25]

DI Type III

DI type III was initially described in the Brandywine, triracial isolate in southern Maryland. In addition to the abnormalities in tooth colour and size seen in DI type II, very large pulp chambers and multiple pulp exposures are seen in deciduous teeth in approximately 2% of the Brandywine cohort. Enamel pitting has also been reported in some members of the Brandywine cohort. These large pulp chambers led to the designation DI type III. But not all affected family members demonstrate large pulp chambers. Asymptomatic radiolucencies are sometimes seen in teeth with significant attrition.[24,26]

Clinical Pictures-

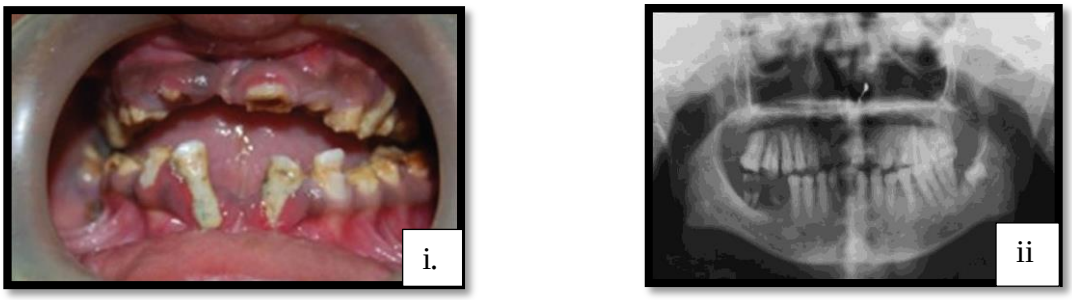


Fig 17: Dentinogenesis imperfecta type I (i)intraoral and (ii)radiographical pictures.

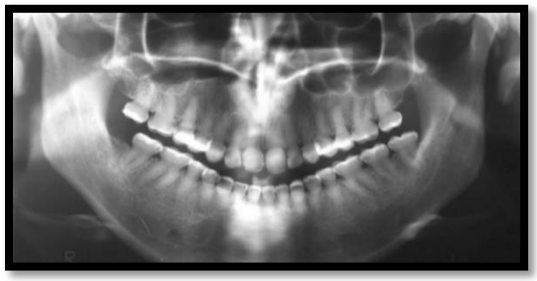


Fig 18: Dentinogenesis imperfecta type II radiographical picture.

i. Dentin Dysplasia (DD)

Both the radicular (Type I) and the coronal (Type II) dysplasias have been well characterized. The major radiographic findings in DD Type I include defective root formation, pulpal obliteration of the primary teeth, crescent-shaped remnants of pulp chambers with denticles in the permanent dentition and periapical radiolucent areas of unknown etiology. Type II DD shares some common features with DD Type I in the primary dentition, but the permanent teeth in Type II exhibit thistle-tube-shaped pulps with denticles.

Both the deciduous and permanent dentitions are affected in type I. The crowns of the teeth appear clinically normal in morphology but defects in dentin formation and pulp obliteration are present. There are four subtypes for this abnormality. In type 1a, there is no pulp chamber and root formation, and there are frequent periradicular radiolucencies; type 1b has a single small horizontally oriented and crescent shaped pulp, and roots are only a few millimetres in length and there are frequent periapical radiolucencies; in type 1c, there are two horizontal or

vertical and crescent shaped pulpal remnants surrounding a central island of dentine and with significant but shortened root length and variable periapical radiolucencies; in type 1d, there is a visible pulp chamber and canal with near-normal root length, and large pulp stones that are located in the coronal portion of the canal and create a localised bulging in the canal, as well as root constriction of the pulp canal apical to the stone and few peri-apical radiolucencies. Histologically, the enamel and the immediately subjacent dentin appear normal. Deeper layers of dentin show an atypical tubular pattern with an amorphous, non-tubular area and irregular organisation.[27]

The pathogenesis of DD is still unknown. Logan *et al* proposed that the dentinal papilla is responsible for the abnormalities in root development. They suggested that multiple degenerative foci within the papilla become calcified which leads to reduced growth and final obliteration of the pulp space. Wesley *et al* proposed that the condition is due to an abnormal interaction of odontoblasts with ameloblasts leading to abnormal differentiation and/or function of these odontoblasts. There is no treatment for this rare genetic, only procedures to avoid the premature loss of hyper-mobile teeth and to stimulate the normal development of the occlusion can be undertaken because the affected teeth have a very unfavourable prognosis.[28]

Clinical Pictures-

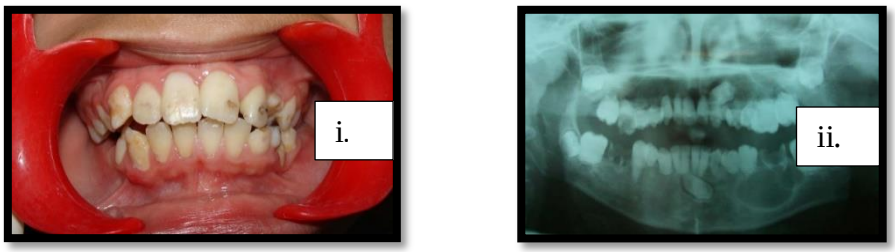


Fig 19: Dentin dysplasia type I (i) intraoral and (ii) radiographical pictures.

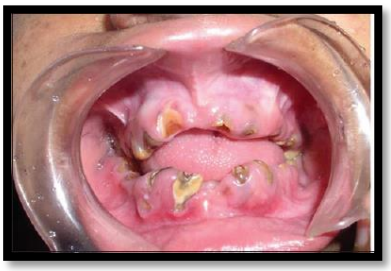


Fig 20: Dentin dysplasia type II intraoral picture.

j. Oral Submucous Fibrosis

Oral Submucous Fibrosis (OSMF) was first described by Schwartz in 1952, where it was classified as an idiopathic disorder by the term atrophia idiopathica (tropica) mucosae oris. Though, Schwartz was the first person to describe the disease as a fibrosing condition, the disease was later renamed as "oral submucous fibrosis" by Joshi and is most widely accepted.

Excessive deposition of collagen in connective tissue is found in OSMF. It is an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. It is always associated with juxta-epithelial inflammatory reaction followed by fibro-elastic change in lamina propria and epithelial atrophy; that leads to stiffness of the oral mucosa, causing trismus and difficulty in eating.[29]

The fibro-elastic changes are due to excessive collagen deposition resulting in dense fibrous bands. OSMF occurs predominantly in people of Indian subcontinent and South Asian ethnicity. Initially the disease was mainly found among natives of Indian subcontinent; later it was reported from many South-East Asian populations as well.

Causative factors of OSMF include autoimmunity, vitamin B, C, and iron deficiencies, chewing betel nut, consumption of spicy foods, human papilloma virus (HPV) infection, and genetic mutations. Epidemiological studies have shown that chewing betel nut is one of the most significant risk factors for OSMF. Chewing betel nut and tobacco together substantially increases the incidence of OSMF. Other studies confirmed that drinking alcohol and chewing betel nut have an additive effect on OSMF induction.[30] Areca nut is the main etiologic factor of OSMF and is a main ingredient in commercially available preparations such as pan masala and gutkha. As uses of these substances are increasing, prevalence of OSMF is on the rise among younger population. Unfortunately, all clinical and histologic features of the disease will remain even after cessation of the causative habit.[31]

Etiopathogenesis

It is a precancerous condition characterised by chronic, progressive scarring of the oral mucosa. Based upon human leucocyte antigen (HLA) associations and circulating immune complexes and auto-antibodies, a possible underlying autoimmune mechanism with a genetic predisposition has been proposed in some cases. The pathogenesis of OSMF involves the disruption of collagen metabolism by the components of areca nut. Alkaloids stimulates fibroblasts to produce collagen, whereas flavonoids inhibit collagenase (an enzyme that catalyses collagen breakdown). In addition, considerable amounts of copper are found in areca nut products. Copper upregulates lysyl oxidase, which is an enzyme involved in collagen cross linking; this process renders collagen fibrils resistant to degradation by collagenase.
Collagen forms the structural network of the connective tissue component of the oral mucosal and is present in a fibrillar form. Collagen in the normal mucosa extends from the lamina propria which extends to multiple depths into the muscle layer. Two different types of collagen organization are found in the normal oral mucosa. The upper connective stroma (lamina propria) contains a loose reticular network composed mostly of collagen types III and IV while collagen type I predominates in the deeper stroma. Collagen fiber organization and fiber size vary topographically in the oral mucosa. For example, collagen fiber bundles are thinner, wavier, and of smaller diameter towards the surface (near the epithelial junction) but gets thicker, less wavy, and of larger diameter in the deeper layers. This difference is absent in the palate and rugae areas where the mucosa is tightly adherent to underlying bone. In the palate and rugal regions, the fibril diameter generally remains constant. Moreover, opposed to extraoral skin, the collagenous network of intraoral submucosa does not contain elastic fibers and directly connects the lamina propria with the periosteum of jaws and hard palate.

Studies using standard light microscopy supplemented with special stains for collagen reported findings suggesting altered collagen.

The prevalence rate of OSMF rate in India is 0.2%-0.5% but due to increase in the consumption of areca nut and areca nut containing products it has increased in recent times. The malignant rate transformation of OSMF is 2.3% -7.6%.

Clinical features:
This condition affects oral mucosa and at times pharyngeal mucosa and occurs insidiously, usually diffusely initially appearing with

a. Burning sensation and stomatitis

b. Vertical fibrous bands occur on oral mucosa during later stages, and

c. Restricted mouth opening due to excessive fibrosis. An interincisal distance of less than 20mm is considered severe. Severe fibrosis can even affect the soft palate, pharynx, oesophagus and uvula. The uvula can be shrunken and deviated.[32]
When fibrosis extends to the pharynx and oesophagus, the patient may experience difficulty in swallowing the food. Referred pain in the ears, deafness, and nasal voice have also been observed. The earliest and most common clinical sign is blanching which imparts a marblelike appearance to the oral mucosa. Blanching may be localised, diffused or in the form of a lace like network.[33]
Pindborg JJ et al. (1980) have suggested that blanching represents an early form of the disease and the histological features of blanched areas are consistent with the concept of blanching being an early form of OSMF. As the disease progresses, the mucosa becomes stiff and vertical fibrous bands appears therein. Involvement of the lips is characterised by the presence of circular fibrous bands around rima oris. In severe involvement of the lips they may become leathery. In palate the bands radiate from the pterygomandibular raphae to the anterior faucial pillars. The faucial pillars become thick and short and the tonsils may be pressed between

the fibrosed faucial pillars. When the soft palate is affected, its mobility is restricted, the uvula when involved is shrunken and is often bud-like. The affected tongue in OSMF is devoid of papillae and in extreme cases it is stiff. Its protrusion may be markedly impaired. The floor of the mouth is blanched, leathery and the gingiva is fibrotic and devoid of its normal stippled appearance.

Bhonsle RB et al. (1981) did a study to find the association of reddish blue spots with OSMF; their study contained 40 patients of OSMF. They took biopsy samples from suspected areas and found that in some cases the subepithelial small round spaces found histopathologically was located deep to the epithelium and was lined by endothelial cells which they interpreted as dialated, thin-walled vascular channels. The lamina propria showed a varying degree of hyalinized collagen interspersed with areas of edema. A moderate inflammatory cell infiltrate consisting predominantly of lymphocytes was present in the lamina propria. These vascular changes associated with reddish blue spots in their study was interpreted as vascular changes due to petechiae. They described that in 1/5th of the cases petechiae may occur however these petechiae are not due to any systemic disorder.

Ekanayaka PR and Tilakaratne MW (2013) reported that it is conventionally accepted that atrophic epithelium in OSMF is a result of decreased vascularity in the underlying connective tissue stroma. The consequent lack of tissue perfusion is believed to trigger the ischemic atrophy of epithelium and thereby making it vulnerable to the effects of oral carcinogens.

Clinical staging:

- Stage 1 (SI): Stomatitis and/or blanching of oral mucosa.
- Stage 2 (S2): Presence of palpable fibrous bands in buccal inucosa and/or oropharynx, with /without stomatitis.
- Stage 3 (S3): Presence of palpable fibrous bands in buccal inucosa and/or oropharynx, and in any other parts of oral cavity, with/without stomatitis.
- Stage 4 (S4) as follows: A. Any one of the above stages along with other potentially malignant disorders, e.g. oral leukoplakia, oral erythroplakia, etc.

B. Any one of the above stage along with oral carcinoma.

Functional staging:

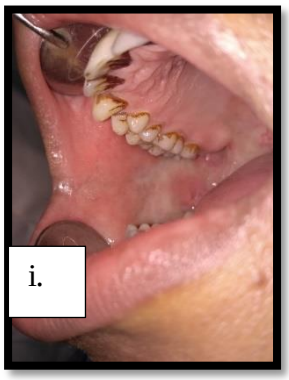
o Ml: Interincisal mouth opening up to or greater than 35 mm.

o M2: Interincisal mouth opening between 25 and 35 mm.

o M3: Interincisal mouth opening between 15 and 25 mm.

o M4: Interincisal mouth opening less than 15 mm.

Clinical Pictures:



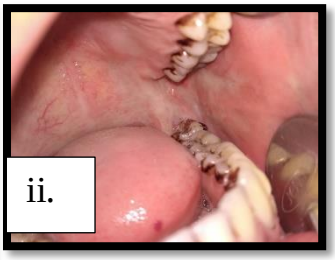


Fig 21 i and ii showing Oral submucous fibrosis of left and right buccal mucosa.

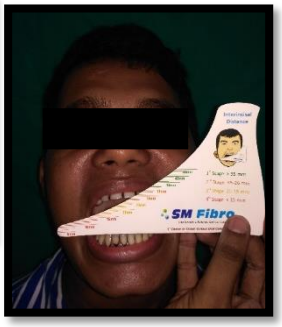


Fig 22: Reduced mouth opening.

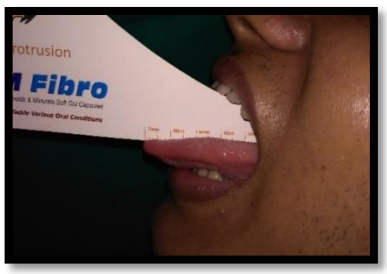


Fig 23: Decreased tongue protrusion.

Treatment:

Treatment of OSMF includes drug therapy which causes anti-inflammation and degradation of the extracellular matrix. Glucocorticoids block inflammation mediators and impede the inflammatory reaction and also block fibroblast proliferation and collagen deposition. Dexamethasone, methylprednisolone, and betamethasone are synthetic drugs with glucocorticoid-like effects. Intralesional injection of synthetic corticosteroids significantly improves mouth opening and alleviates the burning sensation in OSMF. Hyaluronidase and chymotrypsin are proteolytic enzymes that degrade extracellular matrices such as hyaluronan and collagen. Usually, these two drugs are co-administered with corticosteroids in OSMF treatment. Hyaluronidases are a class of enzymes which breaks hyaluronic acid thereby reducing the thickness and viscosity of intracellular cementing substance. In OSMF hyaluronidase causes breakage and dissolution of fibrous bands and provides relief in this condition. Hyaluronic acid helps in formation of collagen and OSMF has excessive collagen production; so this process is also reduced by the usage of hyaluronidase. It has been postulated that hyaluronidase provides better results in patients with restricted mouth opening.

Conclusion

Life in itself remains the biggest mystery of the human kind. Even after countless scientists and their research, only a small part of it has come to light. Asking boundless questions regarding the human biology and endless seeking of their answers has lead us to a point where medical field is using that knowledge to alleviate the quality of life.

Collagens are in a way the base of almost every biological entity. So, any disorders of them leads to a variety of multiple different diseases with their own unique clinical features and manifestations.

This is why the importance of the clinical method stands out more clearly in the study of collagen disorders than in certain other fields. In most cases, the clinical method consists of an orderly series of steps, as follows:

1. Thorough history taking and physical examination to correctly note the symptoms and signs.

2. The symptoms and physical signs considered relevant to the problem at hand identifies the disorder(s) of function and the anatomic structure(s) that are implicated.

3. These analyses allow the physician to localize the disease process, i.e., to identify the part or parts of the body involved.

Often one recognizes a characteristic clustering of symptoms and signs, constituting a syndrome. The formulation of symptoms and signs in syndromic terms is particularly helpful in ascertaining the locus and nature of the disease.

All of these are put into writing in for effective treatment, an ever-increasing prospect in collagen disorders. A large number of these collagen disorders also have their manifestations in the oral and maxillofacial region. Oral diagnosticians come across abnormalities in the dentition, soft tissues and occlusion caused by these disorders during the intra-oral and extra-oral examination. Also, patients with these conditions have to be treated with special cares during dental treatment.

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