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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. They are truly the building blocks of an organism. Virtually every life process depends on it. In the bloodstream, proteins, such as haemoglobin and albumin, transport molecules essential to life, whereas immunoglobulins fight infectious bacteria and viruses. Enzymes and polypeptide hormones direct and regulate metabolism in the body, whereas contractile proteins in muscle permit movement. In bone, the protein forms a framework for the deposition of calcium phosphate crystals, acting like the steel cables in reinforced concrete.
Since mouth is the 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, Ossificans Progressiva, 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. Proteins are the most abundant and functionally diverse molecules in living systems. They are truly the building blocks of an organism. Virtually every life process depends on it. In the bloodstream, proteins, such as haemoglobin and albumin, transport molecules essential to life, whereas immunoglobulins fight infectious bacteria and viruses. Enzymes and polypeptide hormones direct and regulate metabolism in the body, whereas contractile proteins in muscle permit movement. In bone, the protein forms a framework for the deposition of calcium phosphate crystals, acting like the steel cables in reinforced concrete.[1]

Among different types of proteins, collagen is a protein present in the majority of species throughout the animal kingdom, including all vertebrates. In mammals, collagen constitutes approximately 25% of the total protein. It was thought until the 1970s, that collagen is a single protein. But discoveries of new, genetically distinct types of collagen proteins in recent years, has led to knowledge of a vast collagen family rather than a single entity.[1,2]

The term "collagen" was introduced into histological works in the nineteenth century and was derived from the Greek words "kolla" and "genos:' which mean "glue" and "formation.' The earliest observations were related to the ability of collagen to produce glue (gelatin) when tissues, usually hide, were extracted with boiling water. This first property of collagen was known in antiquity **(Bogue 1922)**. In modern times, the first studies on collagen were carried out by chemists involved in leather tanning and gelatin production.[2]

Distribution, Classification and General Structural Features of Collagen

Distribution of collagen within the body refers to the amounts of collagen which occur in certain organs or parts of the body as well as to the tissue and organ localization. The first aspect was investigated in the early years of biochemical research on collagen. The results obtained are still valuable, although the methods used were based only on simple extraction procedures and hydroxyproline determinations. The total amount of collagen is estimated at 25% - 30% of total body proteins. In human skin, collagen constitutes about 75% of total nitrogen content (**Eisele and Eichelberger 1945**).[3]

Collagen	Distribution in the body
I	It is found in tendons, skin, artery walls, cornea, the endomysium surrounding muscle fibres, fibrocartilage, and the organic part of bones and teeth. This is the most abundant collagen of the human body. It is present in scar tissue, the end product when tissue heals by repair.
II	Lung, reticular fibers, vessel wall, hyaline cartilage, makes up 50% of all cartilage protein, vitreous humour of the eye.
III	This is the collagen of granulation tissue, and is produced quickly by young fibroblasts before the tougher type I collagen is synthesized. Reticular fibre. Also found in artery walls, skin, intestines and the uterus
IV	Basement membrane, eye lens. Also serves as part of the filtration system in capillaries and the glomeruli of nephron in the kidney.
V	Most interstitial tissue (assoc. with type I), associated with placenta.
VI	Most interstitial tissue (assoc. with type I) Dermis, placenta, lungs, cartilage, intervertebral disk, and placenta.
VII	Forms anchoring fibrils in dermo-epidermal junctions.
VIII	Endothelial cells.
IX	FACIT collagen, cartilage, assoc. with type II and XI fibrils
X	Hypertrophic and mineralizing cartilage.
XI	Cartilage.
XII	FACIT collagen, interacts with type I containing fibrils, decorin and glycosaminoglycans. Found in tendon, perichondrium, and ligaments.
XIII	Transmembrane collagen, interacts with integrin a1b1, fibronectin and components of basement membranes like nidogen and perlecan. Present in hair follicle, intestine, liver, dermal & epidermal junctions, epidermis, and lungs. MACIT collagen.
XIV	FACIT collagen, also known as undulin.
XV	Associated with collagens close to basement membranes, close structural homologue of XV.
XVI	Many tissues.
XVII	Transmembrane collagen, also known as BP180, a 180 kDa protein. Present in enamel of tooth, epithelia and skin hemidesmosomes.
XVIII	Source of endostatin,
XIX	FACIT collagen. Present in rhabdomyosarcoma cells.
XX	Embryonic skin, tendon, corneal epithelium, and sternal cartilage.
XXI	FACIT collagen
XXII	Tissue junctions, including cartilage synovial fluid hair follicle dermis.
XXIII	MACIT collagen. Limited in tissues mainly in transmembrane and shed forms.
XXIV	Developing cornea and bone.
XXV	MACIT collagen. Present in brain.
XXVI	Testes, ovary.
XXVII	Embryonic cartilage and other developing tissues, cartilage in adults.
XXVIII	Basement membrane around Schwann cells.

Table 1: Types of Collagen and their sites.

Collagen Disorders

a. Ehlers-Danlos Syndrome

The Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous connective tissue disorder. EDS is characterized in its most common form by hyperextensibility of the skin, hypermobility of joints often resulting in dislocations, and tissue fragility exemplified by easy bruising, atrophic scars following superficial injury, and premature rupture of membranes during pregnancy. The recognition of frequent ultrastructural abnormalities of collagen fibrils in EDS patients led to the concept that EDS is a disorder of fibrillar collagen metabolism.[36]
The concept that EDS is a disorder of fibrillar collagen metabolism 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 of disease known to produce EDS:
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 leading to EDS are lysyl-hydroxylase deficiency and procollagen peptidase deficiency.
In the first case, the inability to hydroxylate lysine residues precludes normal intermolecular cross-linking of collagen trimers, and in the second instance, absence of procollagen peptidase prevents normal proteolytic cleavage of the NH2-terminus of procollagen chains. In both circumstances the morphology and strength of the collagen fibril is compromised.

Classification of EDS types:
EDS is classified in the following Table[4] -

TYPE	CLINICAL CHARACTERISTICS
I and II (Classic)	Marked skin hyperextensibility, widened atrophic scars and joint hypermobility. Molluscoid pseudo tumours (calcified haematomas) and periodontitis has been reported.
III (Hypermobility Type)	Joint hypermobility 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.
IV (Vascular Type)	The skin is 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 manifested by spontaneous ecchymosis. Arterial / intestinal / uterine fragility or ruptures are common.
V	It has been described in a single family, is a rare variant and the molecular basis remains unknown.
VI (Kyphoscoliosis Type)	Generalized joint laxity, severe muscle hypotonia and scoliosis at birth. 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 2: Classification of Ehlers-Danlos syndrome.

Clinical Features of Ehlers-Danlos syndrome:

The characteristic features of this syndrome are

1. Hypermobility of the joints.
2. Hyperelasticity, fragility and softness of the skin.
3. Deficient healing of wounds.
4. Ecchymosis caused by minor traumas.

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

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

Beighton's Scale for Assessment of Joint Hypermobility[4]:

SL NO.	CHARACTERISTICS	MAXIMUM SCORE
1	Passive dorsiflexion of each little finger beyond 90 °	02 (01 for each side)
2	Passive apposition of each thumb to the flexor aspect of the forearm.	02 (01 for each side)
3	Hyperextension of each elbow beyond 10°	02 (01 for each side)
4	Hyperextension of each knee beyond 10°	02 (01 for each side)
5	Forward flexion of the trunk, with knees straight, so that the palms of the hands rested easily on the floor.	01

Table 3: Beighton's Scale for Assessment of Joint Hypermobility

Oral manifestations of EDS include:

1. The mucous membrane is fragile, which may bleed on instrumentation and which sutures cannot hold. [7]
2. Dentinal aberrations like pulp stones, short and deformed roots.
3. A high incidence of caries in the deciduous teeth. [8]
4. Spontaneous fractures of teeth have been reported.
5. Early onset of generalized periodontitis is one of the most significant oral manifestations of the syndrome.[9, 10]
6. Hyperelasticity, fragility and softness of the skin.
7. A supple tongue. Approximately 50% of those with this syndrome can touch the end of their noses with their tongue (Gorlin's sign), as compared to 8-10% in the normal population who can do this.
8. Hyper mobility of the TMJ, with increased incidence of dysfunction may be seen in some cases. [5]

b. Marfan Syndrome

The Marfan syndrome (MFS) is an autosomal dominant, heterogenous, connective tissue disorder with pleiotropic manifestations affecting skeletal, ocular and cardiovascular systems. This condition was first described in 1896 by the French pediatrician Antoine Bernard-Jean Marfan. Because the fibrillar collagens are major structural components of connective tissue, the hypothesis has long been set forth that the Marfan syndrome is a disorder of fibrillar collagen.[11] Marfan syndrome is a connective-tissue disease inherited in an autosomal dominant manner and 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. Most mutations are unique and affect a single amino-acid of the protein. Reduced or abnormal fibrillin-1 leads to tissue weakness, increased transforming growth factor β signalling, loss of cell–matrix interactions, and, finally, to the different phenotypic manifestations of Marfan syndrome. 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 criteria and requires a comprehensive clinical assessment of multiple organ systems. Genetic testing can be useful in the diagnosis of selected cases.[12] Several genes, suspected to be defective in Marfan syndrome, are located on the long arm of chromosome 2. These genes include a cluster of two genes coding for fibrillar collagens COL3A1 and COL5A2, and a third member of the collagen gene family: COL6A3.

Organ system	Requirement for classification of organ system as meeting a major criterion	Requirement for classification of organ system as being 'involved'
Skeletal system	At least four of the following features: 1. Pectus carinatum 2. Pectus excavatum requiring surgery 3. Reduced upper to lower segment ratio or increased arm-span to height ratio (>1.05) 4. Positive wrist and thumb signs 5. Scoliosis (>20°) or spondylolithesis 6. Reduced extension of the elbows (<170°) 7. Medial displacement of the medial malleolus causing pes planus 8. Protrusio acetabulae of any degree	At least two features contributing to major criterion, or one feature from that list and two of the following minor criteria: 1. Pectus excavatum of moderate severity 2. Joint hypermobility 3. Highly arched palate with dental crowding 4. Characteristic facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fisures)
Ocular system	Ectopia lentis	At least two of the following minor criteria: 1. Abnormally flat cornea 2. Increased axial length of globe 3. Hypoplastic iris or hypoplastic ciliary muscle, causing decreased miosis
Cardiovascular system	At least one of the following features: 1. Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva 2. Dissection of the ascending aorta	At least one of the following minor criteria: 1. Mitral valve prolapse with or without regurgitation 2. Dilatation of the pulmonary artery, in the absence of valvular or peripheral stenosis or any other obvious cause, in individuals younger than 40 years of age 3. Calcification of the mitral annulus in individuals younger than 40 years of age 4. Dilatation or dissection of the descending thoracic or abdominal aorta annulus in individuals younger than 50 years of age
Pulmonary system	None	At least one of the following minor criteria: 1. Spontaneous pneumothorax 2. Apical blebs
Integumentary system	None	At least one of the following minor criteria: 1. Stretch marks not associated with marked weight changes, pregnancy or repetitive stress 2. Recurrent or incisional herniae
Dura	Lumbosacral dural ectasia by CT or MRI	None

*For a diagnosis of Marfan syndrome in patients with no family background of this disease, two different organ systems must be classified as meeting the major criteria and there should be data suggesting at least the 'involvement' of a third system. In patients with a family history of Marfan syndrome, only one major criterion need be met, along with data suggesting the involvement of a second system.

Fig 4: Ghent-1 nosology (diagnostic Criteria of Marfan Syndrome).

Furthermore, genes for elastin (ELN) and fibronectin (FN) are also located in this area of chromosome 2.[13]

Orofacial features of Marfan syndrome include –

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. hypermobility of the temporomandibular joint.

Furthermore, the patients need to have orthodontic treatment because of having

viii. high arched palate,

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

Uteja et al. stated that it is important for the patients with Marfan syndrome to initiate the orthodontic treatment at an early age to limit the need for surgical procedures. **Westlig et al.** found that 50% of the patients with Marfan syndrome had high and deep palates.

x. Developmental abnormalities of the teeth may also be evident among which the supernumerary teeth is the most common.

xi. More rarely; enamel defects, dentinogenesis imperfecta, dysplasia of teeth and cysts formation in the jaws have been reported.

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

Parents' awareness and their knowledge of the patient's special needs are very important. Regular dental visits, oral hygiene motivation and preventive management may help to avoid having complex and invasive treatments. [14]

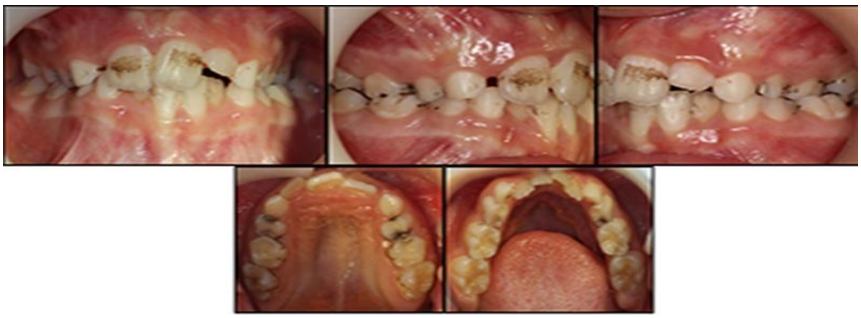


Fig 5: Intraoral pictures of a patient with Marfan syndrome.

Diagnostic Criteria of Marfan Syndrome according to Ghent -2 nosology [15]:

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

Clinical Pictures-

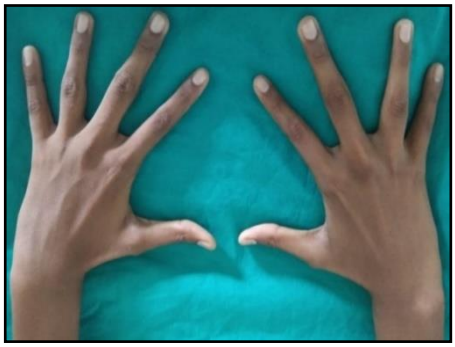


Fig 7: Arachnodactyly

Fig 8: Positive Walker-Murdoch sign

Fig 9: Positive Steinberg sign

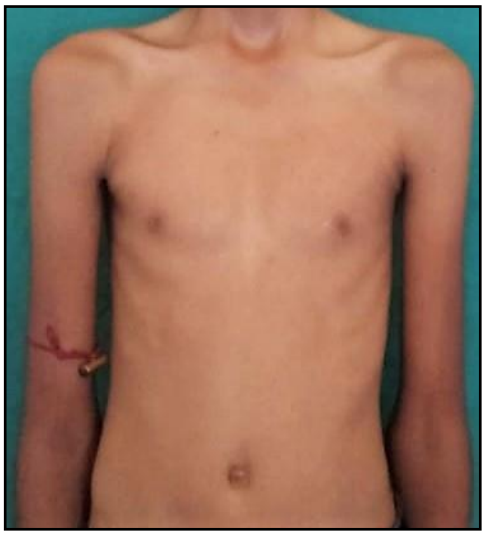


Fig 10: Depressed sternum or pectus excavatum

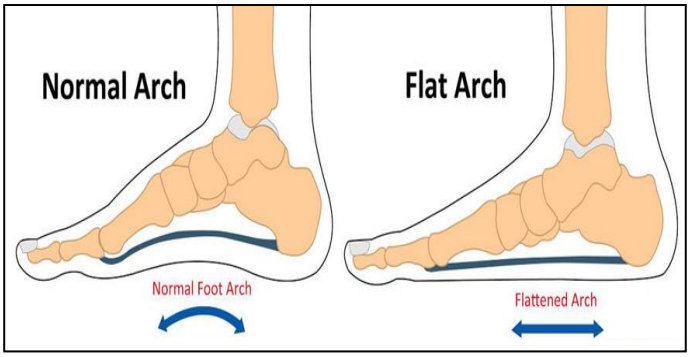


Fig 11: Pes Planus

c. Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a heterogeneous genetic disorder of connective tissue, commonly known as "brittle bone disease", is a dominant autosomal disorder characterized by bone fragility and abnormalities of connective tissue. OI is associated with a wide spectrum of phenotypes varying from mild to severe and lethal conditions. Since most mutations identified in OI are dominant negative, the gene therapy requires a fundamentally different approach from that used for genetic-recessive disorders.[16]

On the basis of clinical, radiologic and genetic criteria, **Sillence et al. (1979)** identified four types of OI (Table 10.3).[16,17]

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 12: 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.[16]

Two genes, COL1A1 located on chromosome 17, and COL1A2 located on chromosome 7, encode the proα1(I) and proα2(I) chains of type I procollagen, respectively **(Kielty et al., 1993)**. These genes are composed of about 50 exons scattered over 18 kb (for α1(I)) and 38 kb (for α2(I)) of chromosomal material. Most of the exons consist of 54 or 108 base pairs, and the final coding mRNAs in the cytoplasm range in size from 5.5 to 7.2 kb. Fibril-forming collagens such as type I collagen are synthesized into larger precursors, known as procollagens, which contain globular N-terminal and C-terminal propeptides. Two proα1 and a single proα2 chains first associate by hydrophobic and electrostatic interactions among the C-propeptides. [16]

Clinical Pictures-

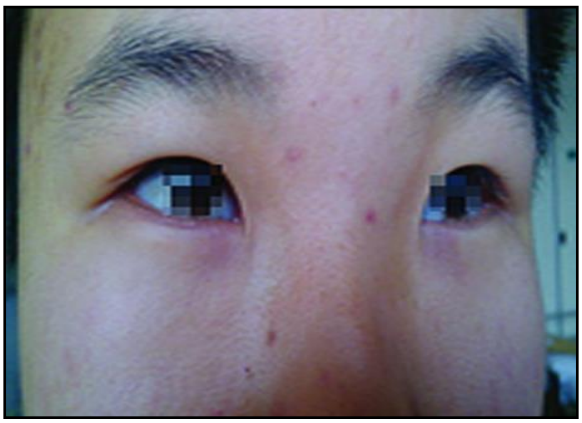


Fig 13: Blue sclera.

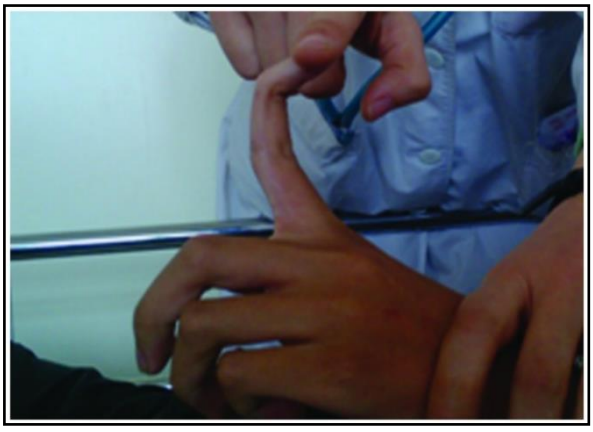


Fig 14: Hypermobility of joints.

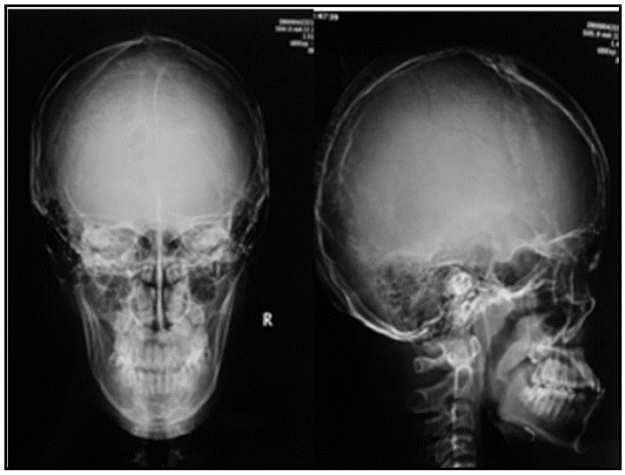


Fig 15: Skull radiograph showing diffuse low bone density

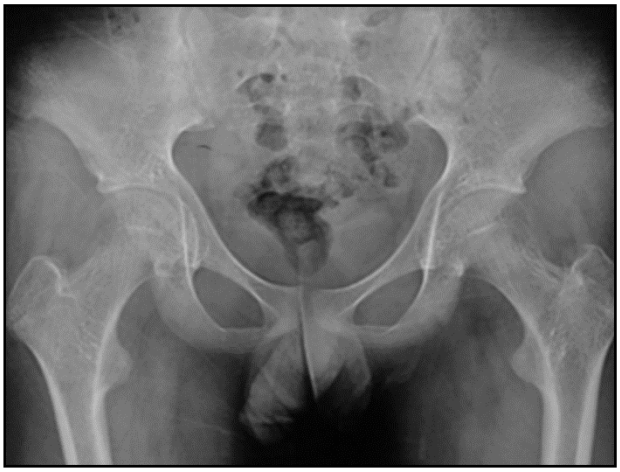


Fig 16: Triradiate pelvis and acetabular protrusion

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 clinically and genetically very heterogeneous, being 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).[18]

The basement membrane zone consists of several distinct morphological components. In **Epidermolysis bullosa simplex (EBS)**, just below the basal cell plasma membrane is the lamina lucida, an electron-lucent zone containing bullous pemphigoid antigen and laminin. Located below the lamina lucida is the lamina densa, an electron-dense zone that contains type IV collagen. Deep to this is the dermis, a connective tissue layer made up primarily of collagen and elastin.

The most superficial type of EB is epidermolysis bullosa simplex. It 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.[19]

In **junctional EB (JEB)**, blisters form at the lamina lucida, at a plane between bullous pemphigoid antigen and laminin. It was formerly 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. Complete ablation of type XVII collagen or integrin a6b4 results in junctional cleavage below the plasma membrane. Huber et al. reported a patient with a predominant simplex type of cleavage owing to a large deletion in the cytoplasmic domain of COL17A1. Unexpectedly, the intraepidermal blister formation in our patient was caused by mutations in the extracellular domain of type XVII collagen instead of the cytoplasmic domain. The initial blister formation initiated very peripherally in the cytoplasm above the hemidesmosome in the basal cell.[18,19]

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-

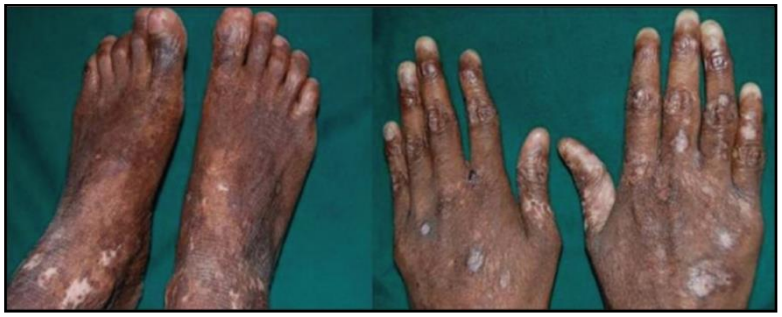


Fig 17: Complete dystrophy of toe and finger nails.

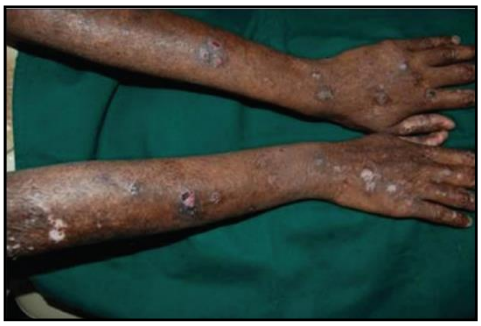


Fig 18: Hypo- or hyper-pigmented healed scar marks and ulcerations present on upper arm.

Type VII collagen is synthesised primarily by epidermal keratinocytes, which are probably the major source of this protein in human skin in vivo, although dermal fibroblasts are also capable of expressing the gene. During the intracellular processing of the protein, three proα1(VII) chains associate and fold into a homo-trimeric type VII collagen monomer. After secretion, type VII collagen molecules form antiparallel dimers with overlapping carboxy-terminal ends, and this association is stabilised by intermolecular disulphide bonds. During this process, part of NC2 is proteolytically removed. Subsequently, several type VII collagen dimer molecules laterally assemble into anchoring fibrils, which extend from the lower part of the dermo–epidermal basement membrane to the upper papillary dermis, thus providing critical integrity to the association of the epidermis with the underlying dermis. It has been postulated that the NC1 of type VII collagen at both ends of the anchoring fibrils bind to the basement membrane zone macromolecules, such as laminin 5 and type IV collagen, within the lamina densa and entrap the interstitial collagen fibres consisting primarily of type I, III and V collagens. Thus, the anchoring fibrils secure the association of the epidermal basement membrane with the underlying papillary dermis.[18,20]

Oral manifestations-

- Milia are frequently observed on the skin of individuals with EB and these can occur intra-orally as well.
- It is well-known that individuals with certain forms of EB are at increased risk for developing squamous cell carcinomas and this is clearly the case in severe generalized recessive dystrophic EB. While carcinomas occur with far greater frequency on the skin in individuals with EB, they can occur intra-orally. Individuals with severe generalized recessive dystrophic EB are at increased risk of oral squamous cell carcinoma formation and should therefore be extra vigilant in monitoring changes in oral ulcerations such as the development of raised, indurated borders.
- Type VII collagen is not expressed by ameloblasts and the enamel appears to generally form normally in individuals with the EB. Despite having relatively normal tooth formation the prevalence of dental caries and resulting dental morbidity in severe generalized recessive dystrophic EB can be severe.
- The tremendous 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. In the presence of marked oral blistering affected individuals frequently 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. Taken together these factors produce an extremely high risk for dental caries in individuals with severe generalized recessive dystrophic EB that can be challenging to prevent and difficult to treat.

Many severely affected individuals have tremendous difficulty performing normal oral hygiene due to their extreme soft tissue fragility and even the use of anticariogenic mouth rinses can be unpleasant due to the presence of alcohol or strong flavouring agents.[21]

e. Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressive (FOP), also known as myositis ossificans, is a rare autosomal dominant disorder with an incidence of one in two million births with no sexual, racial, or regional predisposition. Most patients are scattered around the world except in instances of familial inheritance.[22,23]

Fibrodysplasia ossificans progressive (FOP) is characterized by :

i. congenital bilateral hallux valgus malformations and

ii. early-onset heterotopic ossification.

Heterotopic ossification (HO) is often associated with disability, such as skeletal deformities (trunk, limb, and facial deformity), chronic pain, growth defects, and stiffness. The average life expectancy of patients with FOP is no more than 40 years. The specific pathogenesis of FOP is not yet clear, and the early phenotype of the disease is easily confused with other diseases, including tumors, fibromas, and bursitis, resulting in its misdiagnosis.

The "classic" clinical presentation of FOP with a mutation of the ACVR1/ALK2 gene (R260H, c.617G>A) induces structural changes in the GS domain. Eighty percent of patients with this mutation may have a congenital big toe (hallux valgus deformity), and some may exhibit soft tissue swelling leading to the formation of abnormal bone in the first decade of life. More than 90% of "classic" patients have a tumor in the tibia and more than 80% have a vertebral deformity (16). However, 1.5% of patients with this mutation also have a thumb deformity just like those with G356D (G328 R/W/E) mutations, and some patients with R260H will have cataracts, delayed growth, or other atypical symptoms.[24]

FOP should be suspected in individuals with the following clinical and radiographic findings.[25]

Clinical findings:

- Congenital hallux valgus deformity that is most often bilateral
- Progressive heterotopic ossification (extraosseous bone formation) that may manifest as a palpable mass. Ossification is either spontaneous or in response to soft-tissue trauma, including iatrogenic trauma from vaccinations or surgical procedures.
- Painful, recurrent soft-tissue swellings (flare-ups) that may precede localized heterotopic ossification. This may occur in the form of scalp nodules in infancy, which may be an early or presenting feature.
- Limb reduction defects that may affect the fingers in atypical or non-classic FOP and may be mistaken for a brachydactyly syndrome in individuals who have not yet developed heterotopic ossifications

Imaging findings:

- Prenatal ultrasound may identify a hallux valgus deformity as early as 23 weeks' gestation.
- Radiographs of the halluces demonstrate short, malformed first metatarsals and a single dysplastic phalanx.
- Radiographs of affected areas demonstrate heterotopic ossification (extraosseous bone formation).

f. Scleroderma

Scleroderma (Sc) presents with progressive fibrosis of the skin and of various internal organs, notably, the lungs, heart and gastrointestinal tract, is the pathologic hallmark of systemic sclerosis. The fibrotic process results in disruption of the normal architecture of the affected organs, and ultimately leads to their dysfunction and failure.

The extracellular matrix (ECM) is a remarkably complex structure composed of a large number of distinct molecules. It has become apparent that the ECM is not simply an inert structural scaffold for endothelial cells, fibroblasts, and other mesenchymal cells, as was believed for a long time. Rather, there is a dynamic and reciprocal interaction between the structural components of the ECM and the cellular elements contained within it. These interactions modulate 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 illustrated by the changes observed in the skin. Histologic examination of affected systemic scleroderma skin shows a remarkable increase in the thickness of the dermis with marked 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, suggesting 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 coordinate up-regulation of several different collagen genes in SSc tissues.[26]

g. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that is highly heterogeneous in its presentation. This can pose significant challenges for physicians responsible for the diagnosis and treatment of 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.

Classification criteria for SLE have been developed largely for research purposes; however, these are also widely used in clinical practice. Antinuclear antibodies are the hallmark serological feature, occurring in over 95% of patients with SLE at some point during their disease. [27]

Numerous investigations into the pathogenesis of connective tissue disorders such as systemic lupus erythematosus (SLE), have focused on immunity to collagen. Autoimmunity to collagen has also been reported in thromboangiitis obliterans, relapsing polychondritis, and blistering skin diseases. Despite the fact that the exact role that collagen autoimmunity plays in these disorders has yet to be elucidated, there have been other reports indicating 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. Since it is well established that the pericellular exocytoskeleton and basement membrane of vascular endothelial cells are comprised of distinct connective tissue matrix components, including collagen types IV, V, and laminin, and the possibility that these endothelial cell antibodies may initiate and/or perpetuate endothelial damage, indicated the need to study the humoral immune response against distinct well-defined basement membrane and pericellular connective tissue components.

Antibodies to endothelial cells or endothelial cell-associated antigens have been reported in a variety of connective tissue diseases. Data suggest an association between anti-endothelial antibodies and SLE. The specific epitope(s) present on the surface of the endothelial cell that reacts with these antibodies has not been elucidated. Various investigations have studied endothelial cell-derived factor VIII-related proteins, but less on extracellular matrix components. The elevated von Willebrand factor antigen has been detected in the plasma of patients with SLE; markedly elevated levels appear to indicate a poor prognosis.

The factor VIII related antigen, an endothelial cell product, has also been shown to be markedly elevated in systemic necrotizing arteritis.

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 data together with the present data 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.[28]

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.[29]

h. Amelogenesis imperfecta (AI)

It is a genetic condition showing enamel abnormalities in both primary and permanent teeth (**Smith *et al.*, 2017**). AI exhibits a prevalence as high as 1 in 700 in some populations (**Smith *et al.*, 2017**). Tooth discolouration and changes in enamel appearance are common observations.
Clinical characteristics can be classified into
i. hypoplastic,
ii. hypocalcified, and
iii. hypomatured.
Each type is contributed by different mechanisms. Hypoplastic AI is caused by the failure at secretory stage during enamel formation, while hypocalcified AI is caused by inadequate calcium ion transportation (**Smith *et al.*, 2017**). Defection in enamel matrix protein removal results in the remaining of protein in mature enamel, causing hypomaturation type of AI (**Smith *et al.*, 2017**).[30,31]
A study by **Kim et al. 2006** evaluated 24 AI families and found disease-causing mutations in 6 of the families. They sequenced all of the AI disease-causing genes known at the time (*AMELX, ENAM, KLK4,* and *MMP20)* and 3 other candidate genes *(AMBN, DLX3 and TUFT1).* Mutations in *AMELX, ENAM,* and *MMP20* were identified. After further studies mutation in several genes have been identified to cause AI including AMELX, MMP20, ENAM, FAM83H, WDR72, KLK4, COL17A, and C4orf26 which contribute to different clinical phenotypes.[31]

Clinical pictures-

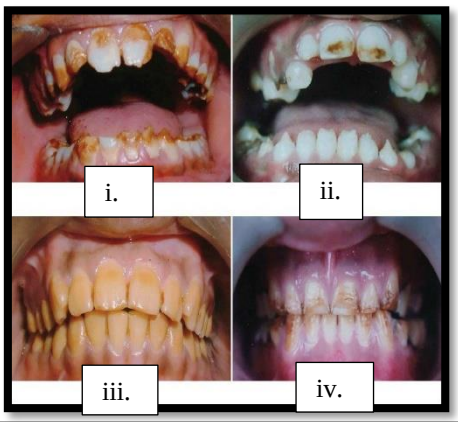


Fig 19: Clinical photos showing Amelogenesis Imperfecta. (i-iv)

i. 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. Histologically, the dentin has a dysplastic appearance with irregular dentinal tubules and areas lacking dentin tubules. Because of the defect in dentin, enamel is easily broken off, exposing the underlying dentin, leading to accelerated attrition. According to Shields, DI is classified into three main groups. [32,33]

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). In some cases, DI may be the most penetrant clinical finding. 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. These genes encode for the α-1 and α-2 polypeptide chains of collagen type I. These polypeptides chains are the basic building blocks of the collagen molecules, and therefore any alterations in the structural integrity of the molecules may trigger abnormal collagen fibril formation. Genetic mutations causing DI type I are often linked to the substitution of the glycine (Gly) residue present in the α-1 and/or α-2 polypeptide chains by other larger residues such as serine.[34]

DI Type II

The presence of DI without 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 seen in syndromic DI type I. Penetrance is almost complete and de novo mutations are rare. A few families with DI type II have also had hearing loss, but it is not clear how the mutation in *DSPP* causes the hearing loss.[32]

DI Type III

DI type III was initially described in the Brandywine, triracial isolate in southern Maryland. The phenotype can be traced to a sea captain from Liverpool who came to Maryland in 1732. This isolate has the highest reported frequency of dental defects in the world, with approximately 6% having DI. 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.[32, 35]

Clinical Pictures-

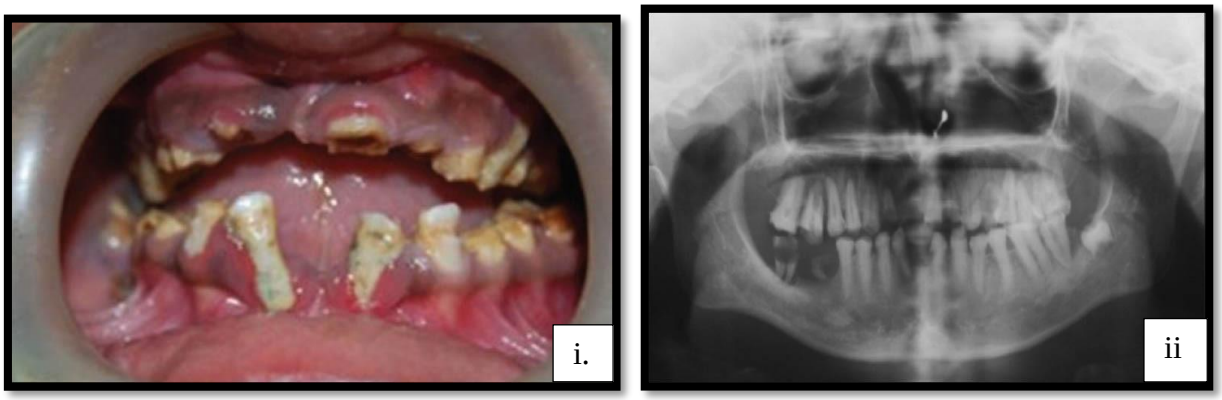


Fig 20: Dentinogenesis imperfecta type I (i)intraoral and (ii)radiographical pictures.

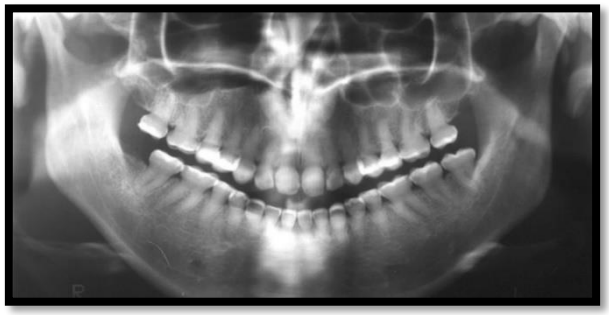


Fig 21: Dentinogenesis imperfecta type II radiographical picture.

j. 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.[36]

In type I, both the deciduous and permanent dentitions are affected. 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, atubular area and irregular organisation. [37]

The pathogenesis of DD is still unknown in the dental literature. Logan *et al* proposed that it is the dentinal papilla that is responsible for the abnormalities in root development. They suggested that multiple degenerative foci within the papilla become calcified, leading to reduced growth and final obliteration of the pulp space. Wesley *et al* proposed that the condition is caused by an abnormal interaction of odontoblasts with ameloblasts leading to abnormal differentiation and/or function of these odontoblasts. There is no specific treatment for this rare genetic disorder affecting the dentin development of the teeth. 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 due to the short roots and presence of associated periapical radiolucencies.[38]

Clinical Pictures-

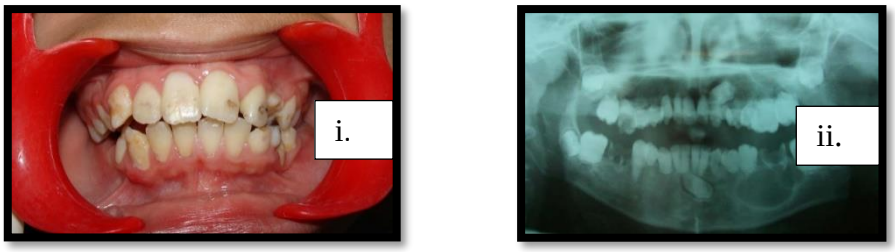


Fig 22: Dentin dysplasia type I (i) intraoral and (ii) radiographical pictures.

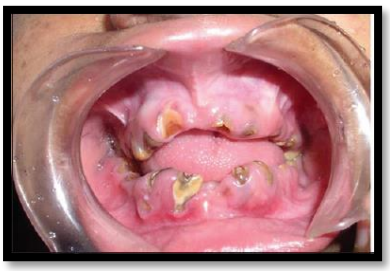


Fig 23: Dentin dysplasia type II intraoral picture.

k. 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. Oral submucous fibrosis is a precancerous condition in which there is excessive deposition of collagen in connective tissue. 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; which leads to stiffness of the oral mucosa, causing trismus and inability to eat.[39]

The fibro-elastic changes seen 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. Though, Schwartz was the first person to describe the disease as a fibrosing condition for which he coined the term “atrophia idiopathica tropica mucosae oris”, however the disease was later renamed as “oral submucous fibrosis” by Joshi and is most widely accepted.

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. Among OSMF patients in China, 62.3% have the habit of chewing arecal nuts. Certain studies also reported that habits such as chewing and smoking tobacco and drinking alcohol increase the risk of OSMF. A study in Taiwan indicated that a high proportion of betel quid chewers are also tobacco smokers (86%) or alcohol drinkers (74%). 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.[40]

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 and majority of the cases occur between 20 to 40 years age group. Unfortunately, even after cessation of the causative habit, all clinical and histologic features of the disease will remain.

The changes in OSMF are mainly due to increased collagen deposition in connective tissue, subsequent to which there are changes in epithelium.[40]

Etiopathogenesis

It is a high risk precancerous condition characterised by chronic, progressive scarring of the oral mucosa. It is seen primarily in the Indian subcontinent, South- East Asia, Taiwan, southern China, Polynesia and Micronesia. The condition affects more than 5 million people in India alone. Cases among Asian communities in North America, Europe and Africa also have been reported. The aetiology is linked to the use of betel quid (paan) and related products- a habit among up to 20% of the world’s population. The quid consists of a betel leaf wrapped around a mixture of areca nut (from the Areca catechu palm tree), slaked lime, possibly tobacco and sometimes sweeteners and spices. The slaked lime releases alkaloids from the areca nut to produce a feeling of euphoria in the user. Villagers habitually chew betel quid from an early age, frequently for 16-24 hours a day.
The incidence of OSMF has been increasing especially among young person due to growing popularity of commercially freeze- dried betel quid substitutes (such as pan masala, gutkha and mawa), conveniently packaged in portable sachets.
These products maintain a higher concentration of areca nut and may cause OSMF more rapidly than conventionally prepared betel quid. The fibrosis appears to be induced by areca nut, whereas the epithelial alterations and carcinogenesis appear to result mainly from tobacco.
Furthermore 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 is hypothesized to involve 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, there are considerable amounts of copper 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 for varying depths in to the muscle layer. There are two different types of collagen organization in the normal oral mucosa. The upper connective stroma (lamina propria) contains a loose reticular network mainly composed of collagen types III and IV while collagen type I predominates in the deeper stroma. Collagen I and III are major fibrillar components of the normal oral mucosa present in a ratio of 4:1 in the submucosa. Collagen fiber organization and fiber size vary topographically in the oral mucosa. For instance, in the buccal and gingival mucosa, collagen fiber bundles are thicker, less wavy, and of larger diameter in the deeper layers. They tend to be thinner, more wavy, and of smaller diameter towards the surface (near the epithelial junction). This difference is absent in the palate and rugae areas where the mucosa tends to be tightly adherent to underlying bone. In the palate and rugal regions, the fibril diameter generally remains constant. Moreover, in contrast 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.[41]

Studies using standard light microscopy supplemented with special stains for collagen reported findings suggesting altered collagen. Electron microscopic (EM)/scanning electron microscopic (SEM) studies did not shed much light on the nature of collagen apart from identification of submicroscopic damage to collagen ends.

The prevalence rate of OSMF rate in India is 0.2%-0.5% which has increased in recent times due to increase in the consumption of areca nut and areca nut containing products. The malignant rate transformation of OSMF was found to be 2.3% -7.6%.15

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

a. stomatitis and burning sensation,

b. later on vertical fibrous bands occurs on oral mucosa and

c. excessive fibrosis leads to restricted mouth opening.

Severe fibrosis can even affect the soft palate, pharynx, oesophagus and uvula. The uvula can be shrunken and deviated.

Clinical features

OSMF often manifests in young adult betel quid users. Reported gender predilection varies by population. Typical chief complaints include inability to open mouth and a generalised oral burning sensation (stomatopyrosis) with intolerance to spicy foods. An interincisal distance of less than 20mm is considered severe.
The most frequently affected locations in OSMF are the buccal mucosa and the retromolar areas. It also commonly involves the soft palate, palatal fauces, uvula, tongue and labial mucosa. It is generally believed that OSMF originates from the posterior part of oral cavity and subsequently involves the anterior locations.
Bhonsle RB et al. (1987) in their study on the regional variations pointed out that such an observation would depend more on whether the areca nut juice and the quid is swallowed or spat out rather than reflecting upon the general pathogenesis. These investigations found that; in Pune, the soft palate, palatal fauces, and the retromolar areas were significantly more often affected. Further in this area the buccal mucosa involvement was restricted to its posterior 1/3rd
and the fibrous bands were continuous with the retromolar region, palatal fauces and the soft palate. The tongue however was not involved in this region. In sharp contrast, in Ernakulam, the soft palate, palatal fauces and uvula were less commonly involved and the tongue was more affected. In addition the involvement of buccal mucosa was more generalised.
The symptoms and clinical features of OSMF have been described in detail in various literature. Except for excess pigmentation or occasional loss of pigmentation of the vermillion border in some instances, this disease does not show any discernible extra oral features.[42]
Pindborg JJ and Sirsat SM (1966) sumrised that the onset of the disease is insidious and is often 2-5 years duration. The most common initial symptom is burning sensation of the oral mucosa, aggravated by spicy food. Vesiculations, excessive salivation, ulceration, pigmentation changes, recurrent stomatis, defective gustatory sensation and dryness of the mouth have also been indicated as early symptoms. Gradual stiffening of the oral mucosa occurs a few years after the initial symptoms appear. This leads to the inability to open the mouth. When fibrosis extends to the pharynx and oesophagus, the patient may experiences 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.[43]
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 $1/5^{th}$ of the cases petechiae may occur however these petechiae are not due to any systemic disorder.

Sarode CS and Sarode SG (2013) have reported that the burning sensation in OSMF is due to fibrosis of minor salivary glands. All minor salivary glands are a major source of Membrane Associated Mucin (MAM) especially at their local areas. MAM plays a very important role in protection and lubrication of oral mucosa. The MAM attaches to the 'microplicae' (ridge like folds present on the surface of superficial cells of oral epithelium) with the help of membrane
anchored 'mucous binding proteins'. This MAM then acts as a scaffold for the formation of highly hydrated and viscous gel called Salivary Mucous Gel (SMG). In addition, lactoperoxidase and trefoil factor 3 may be identified in the formation of SMG. Fibrosis and hyalinization in and around minor salivary glands due to OSMF leads to reduction in the secretion of saliva.

This SMG barrier loss may cause the following consequences:

a. Hampers the 'protective diffusion membrane' function of SMG causing less protection against irritation from food substances e.g. spicy and hot food. This mechanism could be mainly responsible for the burning sensation of the oral cavity.

b. Less protection for superficial cells of the oral epithelium causing their rapid exfoliation even by normal physiologic friction. It is reported in the literature that proliferative activity of oral epithelium in OSMF is high which ideally is supposed to cause epithelial hyperplasia.

Moreover, decreased 'protective diffusion membrane function' of SMG leads to easy diffusion of spicy food elements towards intra-epithelial nerve endings causing more burning sensation.

Visual analogue scale (VAS) has been used many a times in the available literature for measuring the burning sensation in OSMF. It was first used by **Hayes** and **Patterson in 1921** as a psychometric tool. Basically, the VAS consists of a continuous horizontal line, usually of 10 cm in printed length, and two descriptive phrases at the two extremities. The scale is commonly ranged from 0 (left, least extreme) to 10 (right, most extreme).

In OSMF it has been used in many studies like **Agrawal N et al. (2014), Hazarey VK et al. (2015)** and **Singh U (2016).**[113,114,115]

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.

Different classification of OSMF is give in the following table.

Clinical classification	Histopathological classification	Clinical and histopathological
Desa J.V (1957)	Pindborg J.J. and Sirsat S.M. (1966)	Khanna J.N. and Andrade N.N. (1995)
Wahi P.N. and Kapur V.L. *et al.* (1966)	Utsonumiya H. *et al.* (2005)	
Ahuja S.S. and Agarwal G.D. (1971)	Kumar K. (2007)	
Bhatt A.P. and Dholakia H.M. (1977)		
Gupta D.S. and Golhar B.L. (1980)		
Pindborg J.J (1989)		
Katharia S.K. *et al.* (1992)		
Bailoor D.N. (1993)		
Racher S.K. (1993)		
Lai D.R. *et al.* (1995)		
Maher R. *et al.* (1996)		
Haider S.M. *et al.* (2000)		
Ranganathan K. *et al.* (2001)		
Rajendran R. (2003)		
Bose T. and Balan A. (2007)		
Kumar K. *et al.* (2007)		
Mehrotra D. *et al.* (2009)		
More C.B. *et al.* (2011)		
Kerr A.R. *et al.* (2011)		
Patil S. and Maheshwari S. (2014)		
Prakash R. *et al.* (2014)		

Table 24: Different classification, staging, and grading systems of OSMF

Different classifications have been given by different researchers for better clinical study of OSMF based on its clinical features and histopathology.

These classifications have helped in better study and treatment planning for this potentially malignant condition.

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 stage 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:

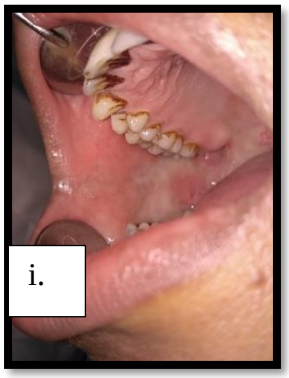
o Ml: Interincisal mouth opening up to or greater than 35 mm.

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:



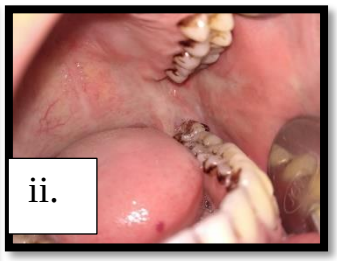


Fig 25: i and ii showing Oral submucous fibrosis of left and right buccal mucosa.

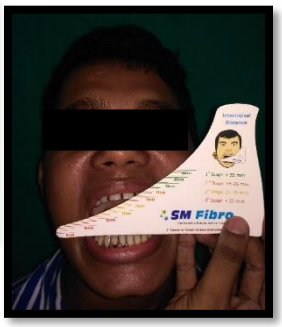


Fig 26: Reduced mouth opening.

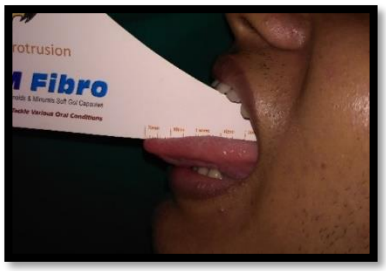


Fig 27: Decreased tongue protrusion.

Treatment:

Treatment includes drug therapy for OSMF which causes anti-inflammation and degradation of the extracellular matrix. Corticosteroids comprise a class of steroid hormones produced in the vertebrate adrenal cortex. Many of them have been synthesized. The glucocorticoids and mineralocorticoid participate in numerous physiological and biochemical processes. Glucocorticoids block inflammation mediators and impede the inflammatory reaction. They 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. They are usually 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. These enzymes are now a days used in cases where excessive fibrosis occurs like in OSMF, keloid, hypertrophic scar etc. 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.

Pentoxifylline is a xanthine derivative primarily used to mitigate muscle pain. It competitively and non-selectively inhibits phosphodiesterase, suppresses TNF-α production in lipopolysaccharide (LPS)-stimulated human monocytes, blocks leukotriene synthesis, and diminishes the inflammatory reaction. Pentoxifylline improved mouth opening and reduced the burning sensation in OSMF. It also facilitated swallowing and speech. Colchicine has been used as early as 1500 BC to treat joint swelling. It was approved for medical use in 1961. It is extracted from the autumn crocus and decreases inflammation by inhibiting neutrophil activation and migration to the inflammation site and by suppressing IL-1 β activation. The efficacy of colchicine in OSMF treatment was first reported in 2013. Patients with OSMF took 0.5 mg oral colchicine twice daily and received injections of 1500 IU hyaluronidase into each buccal mucosal lesion once weekly. By the second week, the burning sensation was alleviated, mouth opening increased, and histological parameters were reduced. The aforementioned dosages combined with 0.5 mL lignocaine hydrochloride once weekly improved mouth opening and reduced the burning sensation in patients with grade II OSF after 12 weeks.

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. The symptoms and signs are secured by history and physical examination.

2. The symptoms and physical signs considered relevant to the problem at hand are interpreted in terms of physiology and anatomy—that is, one identifies the disorder(s) of function and the anatomic structure(s) that are implicated.

3. These analyses permit 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.

4. From the anatomic diagnosis and other medical data—particularly the mode and speed of onset, evolution, and course of the illness, the involvement of organs, the relevant past and family histories, and the laboratory findings - one deduces the pathologic diagnosis and, when the mechanism and causation of the disease can be determined, the etiologic diagnosis.

This may include the rapidly increasing number of molecular and genetic etiologies if they have been worked out for a particular process.

5. Finally, the physician should assess the degree of disability and determine whether it is temporary or permanent (functional diagnosis); this is important in managing the patient's illness and judging the potential for restoration of function.

It goes without saying that all of these are put into writing in the service of effective treatment, an ever-increasing prospect in collagen disorders.
Even though intellectual processing is utilized in solving a particular clinical problem, the fundamental steps in diagnosis always involve the accurate detection of symptoms and signs and their correct corelation in terms of the disorder.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 need to be treated with special cares during dental treatment.

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