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Cutaneous Manifestations of Common Connective Tissue Diseases: Focus on the Skin of Colour

Amadi Ekechi Stella[1*] & Lakhani, Som[2]
[1]Lecturer, Rivers State University / Tutor, University of South Wales
[2]Professor and Head, Department of Dermatology,Parul University/ Tutor, University of South Wales

ABSTRACT
Connective tissue diseases are those diseases that affect the tissues that serve as a frame work for other tissues to formed on and bridge the matrix of different tissues. They are not as rare as once thought in those of skin of colour. Connective tissue diseases commonly present with cutaneous signs and symptoms. This review article focuses on the ways which cutaneous characteristics of connective tissue diseases differ and resemble that of the lighter skin pigments which are seen in Caucasians. Knowledge of the varying ways in which CTDs present in skin of colour enhances early diagnosis, treatment and secondary prevention

Keywords: *Connective tissue disease, Cutaneous, Skin of colour*

***Corresponding Author**
Amadi Ekechi Stella
Lecturer, Rivers State University, Nigeria / Tutor, University of South Wales, United Kingdom

INTRODUCTION

Connective tissues are components of the human body that bridge one part to the other. Examples of these are bone, cartilage, tendon and muscle with collagen and elastin forming a major part of the cellular matrix[1]. Connective tissue diseases (CTDs) are those in which there is distortion or disruption in the normal functioning of these tissues. This distortion can manifest in the skin with varying clinical pathologies[1-3]. They are also known as collagen vascular diseases and consist of a heterogeneous group of diseases[4,5]. The term skin of color identifies persons of similar ethnic groups who have in common similar cutaneous characteristics and disorders, as well as reaction patterns to those disorders. These persons have darker skin hues and fall into four of the five groups as defined by the 2010 United States Census which include African, Asian, Native American, Native Pacific Islander and Caucasian. This article intends to contribute to knowledge by reviewing articles that provide a better perspective on the clinical manifestations of CTDs on the skin of colour which may present clinically in a different manner[6].

Classification

There are over four hundred CTDs; however a simplified classification divides them into heritable causes, autoimmune disorders and others. Examples of the heritable conditions are Marfan's syndrome (MfS), osteogenesis imperfecta (OI), epidermolysis bullosa(EB) and Ehlers -Danlos(EDS)[2-5]. Autoimmune conditions include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), systemic sclerosis (SSc),mixed connective tissue disease (MTCD), dermatomyositis(DM) and scurvy, a nutritional CTD[2-5].

Epidemiology

CTDs occur worldwide. The prevalence and incidence of connective tissue disorders varies from region to region and is dependent on the study method used, duration of study, the population being studied and the classification criteria[7,8]. Connective tissue disorders affect all age groups, but incidence is higher among women than men for most of the distinct disease with estimates as high as 12:1 for SLE[8]. In the elderly, the prevalence of CTDs is on the increase due to longer life expectancy and more tolerable effective therapy[9]. RA affects about 1% of the adult population in North Europe and North America[8]. The cumulative prevalence in Black- Caribbeans was about 2.9/1000 and was lower comparatively to that seen in the Caucasian population in the same region[10,11]. The crude prevalence in Africa was estimated to be 0.036%[12]. In India, estimated prevalence rate of RA is 0.5%–0.75%[13] the estimated prevalence of rheumatoid arthritis amongst the Chinese is about 0.042%[14], affecting about 5 million persons as 2013. SSc is an uncommon disease with estimated prevalence to be 1-2 cases per10, 000[15]. A meta-analysis done for the global prevalence and incidence showed the prevalence of SSc ranged from 3.1 to 144.5 per 100,000 person-years, with a

pooled prevalence of 17.6 per 100,000 person-years.The pooled prevalence among men was 6.0per 100,000 person-years and among women it was 28.0 per 100,000 person-years. The prevalence was noted to be lowest amongst Asians.The pooled incidence of SSc was 1.4 per 100,000 person-years. Stratification by sex indicated a pooled incidence of 0.5 per 100,000 person-years in men and 2.3 per 100,000 person-years in women[16].

DM is a rare disease with an estimated prevalence of 5.5 cases per million of the idiopathic inflammatory subset of dermatomyositis. In dark skinned persons of African descent, DM may be under diagnosed due to the more subtle discolouration of their skin[17]. In DM women are twice more commonly affected in Caucasians but the reverse is the case in Asians[17]. It has two peaks of incidence at the young age group of 5- 10 years and in adults at the age of 50 years[18]. SLE and SS have a female: male ratio as high as 9:1[19,20]. This ratio could be higher up to 20 times more in selected populations such as Greece Caucasian women for those with primary SS[21]. It has been observed that locality and ethnicity can affect the manifestation of primary Sjorgren's syndrome. Primary Sjogren's syndrome was diagnosed an average of seven years earlier in blacks/African-Americans compared with white patients. The female-to-male ratio was highest in Asians (27:1) and lowest in blacks/African-Americans (7:1)[22]. In SSc, the F: M ratio was 3:1[15,16]. African Americans have been noted to present at a younger age and with worse disease outcomes with scleroderma when compared to whites[23,24]. In a study done in Port Harcourt, Nigeria, Systemic lupus erythematosus (SLE) constituted about 91%, rheumatoid arthritis 6% and systemic sclerosis constituted about 3% of the cases of autoimmune diseases within a one year period and the F:M ratio was 14:1[25]. Marfan's syndrome occurs in about 1 in 5000-10000 individuals, there is no gender, geographic or racial predilection[25]. Pseudoxanthoma elasticum(PXE) occurs in 1 in 25000-100000 persons and is more common in young females and can be found in all races[5,26,27], while the combined incidence of different types of ED is 1:5000 and in OI is 1: 12000.Scurvy is a common nutritional disorder due to vitamin C deficiency amongst children particularly in developing countries and even can be a scarce nutrient for those stranded on the sea or during war[27]. EB occurs in about1in 50000 in the United States of America (USA) [28]. Generally it has been observed by rheumatologists that the incidence and prevalence of CTDs are low when compared to other inflammatory rheumatic diseases such as spondyloarthropathies[29].

Pathogenesis/Pathophysiology

The basic mechanisms involved in most CTDs are diverse and poorly understood but have been linked to immunological and vascular induced damage which includes autoimmunity against connective tissues [19, 20, 29]. This could be triggered by environmental factors such as viruses and bacteria as seen in SLE and SS and also influenced by genetic factors such as the involvement of the HLA system. The influence of sex hormones has been shown to be implicated in the aetiology of some types of CTDs but there is no conclusive evidence that it is the sole cause in the pathogenesis of CTDs in both sexes[19,20]. Defective immune regulatory mechanisms like clearance of apoptotic cells and immune complexes, B cell suppression, and immune tolerance have been implicated in SLE[19]. There is also upward regulation of antigenic process viaT2 helper which stimulates B cell hyperactivity which promotes production of auto antibodies[19]. Inflammatory cells such as cytokines and interleukins have been implicated in the pathogenesis of DM. It is considered as a humoural disorder with antibodies stimulating C3b and C4b components against capillaries, arterioles and skin cells. Complements C5b-9 MAC is also known to be deposited and is required in getting the cell for destruction in antibody-mediated disease. B cells and CD4 (helper) cells are also present in abundance in the inflammatory reaction associated with the blood vessels[17,18]. Different factors, including genetic, environmental, vascular, auto immunologic, and micro chimeric factors are involved in systemic sclerosis pathogenesis[30,31]. The pathogenesis of SSc has been attributed to the interaction of three major mechanisms which are innate/adaptive immune system dysfunction leading to the production of auto antibodies and cell mediated autoimmunity; micro vasular endothelial cell/small vessel fibro proliferative vasculopathy and fibroblast dysfunction generating excessive accumulation of collagen and other matrix components in skin and internal organs[32]. Due to the alterations in the endothelial lining of blood vessels there is a chain of stimulated changes that involve several inflammatory cells such as T lymphocytes, macrophages, mast cells and fibroblasts which in turn when activated secrete a variety of substances, including cytokines, their soluble receptors, enzymes and their inhibitors. This inturn alters the extracellular matrix compounds, including fibronectin; proteoglycans; and collagen types I, III, V, and VII. Increased collagen deposition in tissues is a characteristic feature of systemic sclerosis. Increased collagen production or disturbances in its degradation can cause excessive collagen deposition in tissues[15,16, 30-32]. Fibrosis can be caused by profibrotic cytokines, including transforming growth factor-beta (TGF-beta), interleukin-4 (IL-4), platelet-derived growth factor (PDGF), and connective-tissue growth factor. The vasculopathy may be linked to TGF-beta and PDGF, while the diminution of lesional cutaneous blood vessels can be attributed to anti-endothelial cell autoantibodies. The activation of the immune system is of great importance in the pathogenesis of systemic sclerosis. Antigen-activated T cells, activated infiltrate early, infiltrate the skin, and produce the profibrotic cytokine IL-4. B cells may contribute to fibrosis, as deficiency of CD19 a B-cell transduction molecule, results in decreased fibrosis in animal models[30,31].

Abnormal apoptosis has been implicated in many mechanisms linked to the pathogenesis of SS which auto-reactive lymphocytes and auto antibodies are implicated[20]. Genetics and environmental influence are also factors that are

known to stimulate this process but exact mechanism are not the clear[20,33]. General transcription factor (GTF 21) and RNA-binding motif, single-stranded-interacting protein 1 (RBMS3) have been implicated recently in women with primary Sjogren's syndrome. Viral infections such as Epstein-Barr, Human-T lymphotopic, cytomegalovirus, human herpes virus and hepatitis C virus have been implicated in causing SS[33].

Chromosomal alterations are also responsible for CTDs which can be influenced by environmental factors; for instance Marfan's syndrome has distortion of the fibrillin 1 gene on chromosome 15q21.1 leading to dysregulated matrix metalloproteinases[5,26]. The transforming growth factor beta(TGF-β) has also been implicated on that gene as well as other genes resulting in clinical features that closely similar to MfS but recently these have been considered to be other syndromes. There is no known racial genetic predilection in MfS[34]. The EDS has a defect in collagen with variable Mendelian inheritance some being autosomal dominant and other types being recessive or sporadic. Currently there are 13 subtypes and 19 casual genes that have been implicated in Ehlers–Danlos disease[35, 36]. The pathogenic defects are variable as seen in **Table 1.**

PXE is due to mutations in the gene AbCC6 on chromosome 16 q13.1 resulting in the abnormal deposition of calcium on the elastic fibres of the, blood vessels, eye and skin[26,37,38]. There has been more than 60 mutations reported with this gene and over 90% inherited in the autosomal recessive fashion and the remaining in a pseudo-dominant pattern with milder manifestations[26]. The pathophysiological mechanism of PXE has yet to be fully understood.PXE is being considered a metabolic disease in which circulating levels of an anti-mineralization factor are low. There is good evidence to suggest that the factor is inorganic pyrophosphate (PPi), and that the circulating low levels of PPi and decreased PPi/Pi ratio result from the lack of ATP release by hepatocytes harboring the mutant ABCC6 protein[38].

The pathophysiology of OI involves mutations in genes encoding for the alpha chains of type 1 collagen which is the major component of the dermis. The various mutations in the genes COL1A1 and COL1A2 are the most common cause of OI. The large size of the genes explains the several known mutations and the diverse clinical presentations. The specific genotype-phenotype correlation is yet to be recognized. Despite this limitation two different pathophysiological mechanism has been described: Loss-of-function mutations like stop mutations lead to haplo-insufficiency. Patients have a reduced amount of collagen, but this is of normal quality. In contrast, other mutations (mostly glycine substitutions) lead to qualitative alterations of the extracellular matrix, since the collagen molecules and later fibrils cannot assemble properly. This results in more severe clinical courses. Germline mosiacism can explain some of the causes of single family members being affected showing obvious non- parental involvement[26,39]. Epidermolysisbullosa is a connective tissue disease consisting of four different types-simplex, dystrophic, junctional and Kindler syndrome[28]. Mutations in genes encoding for keratin and type VII collagen have been implicated in EB. The keratin 5 and 14, plectin, α6βintegrin, plakophilin-1, desmoplakin, have been implicated in EB simplex, laminin-332(laminin 5); type XVII collagen and α 6β4 integrin been implicated in junctional EB. type VII collagen in dystrophic EB and Kindlin-1 in Kindler syndrome[28,40]. EB acquisita is an autoimmune acquired cause with presentation similar to those inherited[28,37]. Scurvy is deficiency of vitamin C (ascorbic acid), an important component for collagen synthesis which the human body cannot produce due to lack of gulonolactone oxidase which converts glucose to ascorbic acid[27].

Table 1: Types of Ehlers Danlos Syndrome[5,26,35]

Type of EDS	**Inheritance Pattern**	**Gene Defect**	**Clinical features**
Arthrochalasia	Autosomal Dominant	COL1A1 COL1 A2	Hip dislocation, hyperflexible joints, hypotonia, osteopenia, kyphosis, scolosis, rarely fragile stretchy skin
Brittle Cornea	Autosomal recessive	ZNF469, PRDM5	Arachnodactyly, bluish sclera, conductive hearing loss contractures, hip dysplasia, hypotonia, keratoconus, keratoglobus, myopia, (sensorineural hearing loss)
Cardiac-Valvular	Autosomal recessive	COL1A2	cardiac failure, easy bruising, hypertension, recurrent dislocations and fractures, scoliosis,valvulopathies,
Classical (type 1)	Autosomal dominant	Collagen Type V COL 5A1 COL 5A 2COL1A1(rarily)	Atrophic scars, easy bruising , hyper-extensible joints,
Classical-like	Autosomal recessive	TNXB (tenascin-X B)	Arthralgia, joint hyper flexibility fatigue, hypotonia,myalgia,

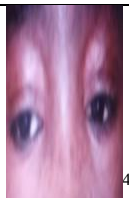
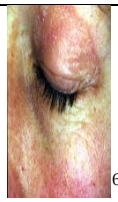
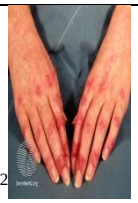
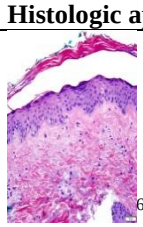
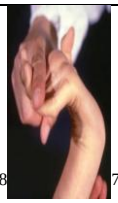
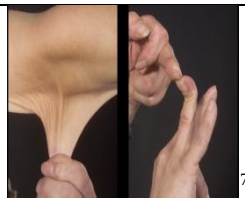
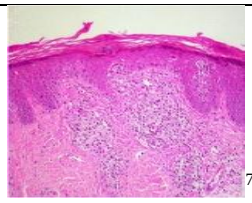
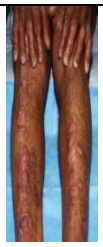
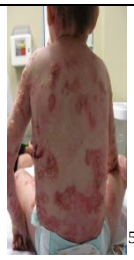
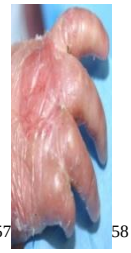
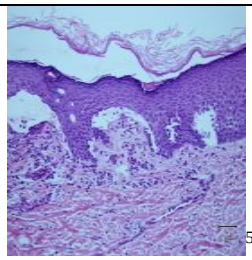
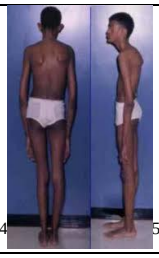
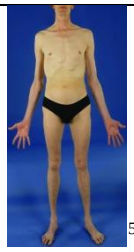
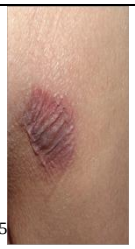
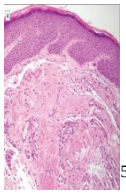
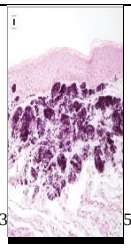
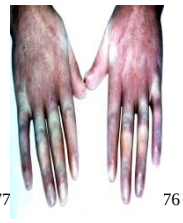
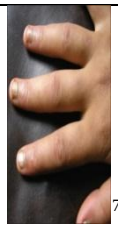
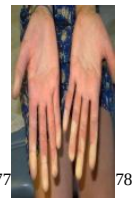
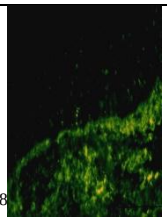
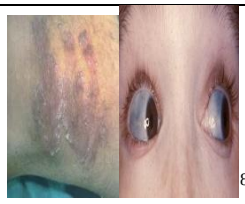
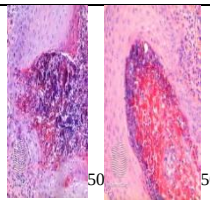
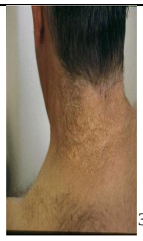
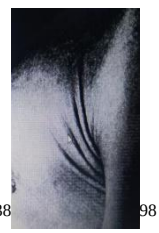
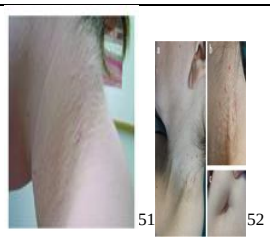
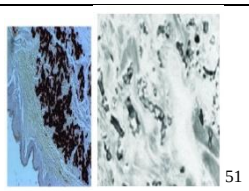
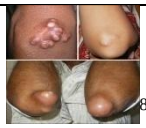
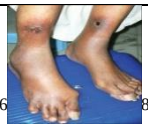
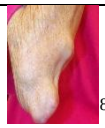
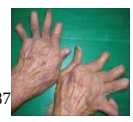
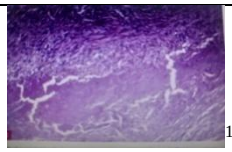
		CYP21A2(can be deleted and cause congenital adrenal hyperplasia)	hyperelastic and thin skin skeletal muscle degeneration sensory joint painCYP21A2(can be deleted and cause congenital adrenal hyperplasia
Dermatosparaxis	Autosomal recessive	ADAMTS2	Dislocations, hernias, hypermobility joints, soft, fragile doughy skin,
Hypermobile (type 3)	Autosomal dominant pattern, Sporadic	TNXB or COL3A1	Atrophic scarring, easy bruising, epitaxis, menorrhagia, gastritis, gastro-oesophageal reflux disease(GERD)
Kyphoscoliotic	Autosomal recessive	PLOD1, FKBP14	Atypical scarring of the skin, abnormal gait, delayed motor development, easy bruising, fragile arteries and skin, hyperextensible skin progressive kyphoscoliosis,
Musculocontractural Also known as adducted thumb and clubfoot syndrome	Autosomal recessive	CHST14 gene.	Adducted thumbs, Arachnodactyly, club foot, cleft palate, hypotonia, joint contractures, wrinkled palms
Myopathic	Autosomal dominant manner, autosomal recessive	COL12A1	Childhood contractures, hypermobility, myopathy
Periodontal (type 8)	Autosomal dominant	Genetically diverse. Chromosome 12 implicated	atrophic scars, dental deformities,gum overgrowthhyperextensible skin, hyperflexible joints, periodontitis, short stature
Spondylodysplastic	Autosomal recessive	B4GALT7, B3GALT6, or SLC39A13 genes	Bone deformities, bowing of legs, delayed cognitive development,
Vascular	Autosomal dominant, sporadic	COL3A1,	Aneurysms, Blood vessel dissections, Fragile arteries, hyperextensible skin, hypermobile joints

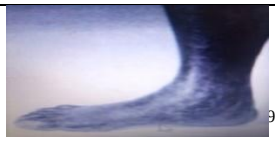
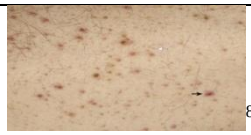
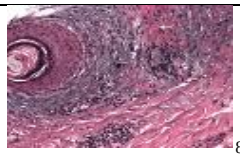
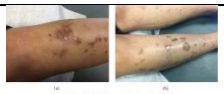
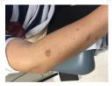
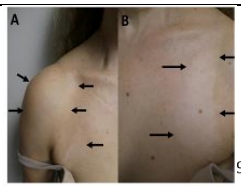
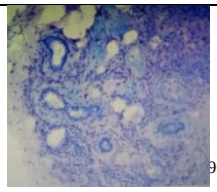
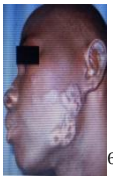
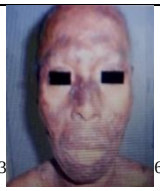
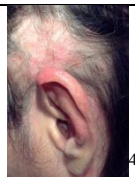
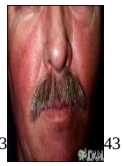
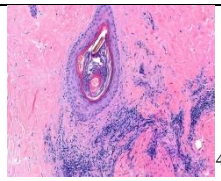
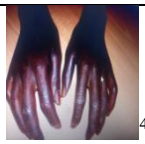
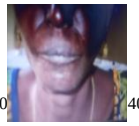
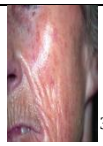
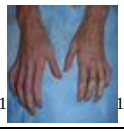
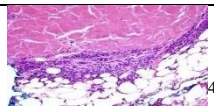
Pathology

The overlapping histopathologic feature of the skin regarding CTDs is one of the areas that can pose a challenge in distinguishing one disorder from another. The main contribution of histopathology in the diagnosis of CTDs is to confirm, rule out, or signal clinicians to the possibility of CTD as a disease category, rather than producing definitive diagnoses of specific entities; hence exact classification of CTDs requires clinical, immunologic, and serologic correlation in addition to make substantial diagnosis without any reasonable doubt[41]. Most CTDS are characterized by vasculitis such as SLE, RA (leucocytoclastic), DM and SS[5, 10,15,17,19]. The unique features of SLE are immune complex deposition and vasculopathy. Deposition of IgG and mononuclear cell infiltration are seen at the derma-epidermal junction(DEJ) with injury to the basal keratinocytes with inflammation dominated by T lymphocytes in the DEJ, blood vessels(perivascular) and appendages(peri-appendagal)[19, 42, 43]. Hyperkeratosis, dermal oedema and mucin deposition also contributes to the dermal thickening[19, 43]. The different clinical and serologic forms of lupus erythematosus (LE) cannot reliably be distinguished histologically, which supports the premise that LE is a disease with a wide spectrum of clinical manifestations but with a common underlying pathogenesis. Discoid LE is characterized by epidermal atrophy or hypertrophy, attenuation (flattening) of rete ridges, hyperkeratosis and follicular keratotic plugging[43]. DM is characterized by epidermal atrophy, necrosis or cell-poor interface dermatitis and increased mucin which is difficult to distinguish from SLE which has similar histologic features[17,18,44]. Fibrosis affecting multiple organs is a distinguishing feature of SSc[15]. Skin biopsy in diagnosing SSc is not routinely done however tissue samples gotten from skin biopsiesin patients with SSc have been genetically tested and it has been noted that both clinically affected and that not yet affected have similar genetic expressions. It is also done when there is a need to distinguish the cause of sclerosis if it is due to an iatrogenic cause. Localized scleroderma and systemic sclerosis have mostly indistinct histologic features[45]. The histopathological features consists of early skin lesions characterized by presence of thickened collagen bundles within the reticular dermis that run parallel to the skin surface, and inflammatory cell infiltrates composed mainly of activated T cells[15,45]. Panniculitis may also be part of the early feature where by subcutaneous fat is replaced by fibrous tissue[15]. The late features consist of excessive accumulation of extracellular matrix components leading to increased skin thickness. There is paucity of inflammatory cells[45]. At this stage also the pilosebeceous unit and eccrine glands shrink off and disappear with occasional effacement of the rete ridges[15]. RA shows vascular neutrophilic infiltration, fibrinoid necrosis and haemorrhage. Palisaded granulomatous reactions are seen

only in rheumatic nodules[10,46]. SS also shows glandular atrophy however the various cutaneous manifestations of SS have varying histological features[20,47]. The leuco cytoclastic vasculitis features such as vascular neutrophilic infiltration and fibrinoid necrosis seen in RA and other autoimmune diseases is also seen in some cases of cutaneous vasculitis. There could also be vascular mononuclear inflammatory cells invasion[20]. Annular erythema can occur in SS resembling those that occur in SLE but the histopathologic features vary because great amounts of much in depositions seen[47]. The commonest manifestation of Marfan's syndrome is striae which are also considered as a scar. The histopathological features of striae associated with MFS and other conditions are similar: the epidermis is thin and flattened, and the upper dermis is decreased in thickness and characterized by straight thin collagen bundles arranged parallel to the skin along with elastic fibers that are arranged similarly. The elastic fibers are present in greater quantity than in the surrounding skin, possibly as dense bundles of parallel fibers. Beneath this zone, a localized absence of elastic fibers may be seen, and in the borders between the striae and normal skin, curled, broken, and reticular elastic fibers are occasionally observed[48]. The key cutaneous manifestation of EDS is skin frailty. Skin biopsies done and examined under the electron micrograph show abnormal collagen fibrils irregular in outline and vary widely in diameter[26,37,40,41]. Skin biopsy is not needed to make a diagnosis of OI but skin biopsy is done to obtain dermal fibroblasts which are subjected to collagen analysis and it shows decreased or abnormal procollagen type 1 molecules[26]. Elastosis perforans serpiginosa (EPS) is not common in OI. It can also occur in EDS, MfS, and PXE[49]. Histologic features include a column of keratotic debris forming a focal invagination through a hyperplastic epidermis on low power magnification with haematoxylin and eosin stain while with Elastic-Van Gieson (EVG) staining there is highlight of elastic fibre portraying them as black fibres transgressing through the focus of transepidermal(transepithelial) elimination. Brightly eosinophilic fibres are seen within the extruded material, mixed with keratinous debris and a mixed inflammatory cell infiltrate as well[49,50]. Histopathologic features of other dermatologic skin manifestations such as scars, keloids can also be seen with a reduction of type[49]. PXE can have similar histologic features as in OI although there is normal laxity in OI. The localized acquired and periumblical perforating PXE both show fragmented, thickened and mineralized elastic fibres in the mid and deep reticular dermis. In addition the periumblical perforating PXE has elimination of basophils and elastic debris through channels as a distinguishing histologic feature characteristic of EPS. This is also seen in other tissues as well with calcification. Calcification and ossification can also be seen in the skin[51]. This progressive mineralization and fragmentation of mid-dermal elastic fibers as already described in the various forms of PXE is termed elastorrhexis, is the primary histological feature of cutaneous PXE and it is essential for the definitive diagnosis of PXE[52]. The most common skin findings in MFS are striae, especially at unusual sites and histologic findings support the view that striaedistensae are scars. Cutaneous histology is not commonly done but histology of the skin in a patient, show abnormal fragmented elastic fibres[26,41,48,53]. The abnormal elastic fibres is described as having a moth eaten[26] or cobweb like appearance[53] with collapsed distorted adipocytes[26]. The histopathologic appearance of the skin in epidermolysis bullosa(EB) is variable depending on the type, however the characteristic findings consists of sub-epidermal blister with variable inflammation and a superficial dermis which is fibrotic[56]. EB simplex lesion demonstrates intact stratum corneum and upper epidermis, with vesicle formation in the lower epidermis at the basal layer caused by degeneration of individual epidermal cells[57]. The histopathology of the skin manifestations of scurvy shows decreased collagen, capillary ectasia, and hemorrhage from capillary rupture which are indicative of impaired collagen formation[58]. The histologic feature of mixed connective tissue disease(MCTD) shares similar histologic features with the major components of the disease. Reported cases of MTCD's histology showeda cell- poor and/or lichenoid interface dermatitis with suprabasilar exocytosis around necrotic keratinocytes in the absence of deep periadnexal or perivascular extension or conspicuous follicular plugging, a pattern similar to that of sub-acute cutaneous lupus erythematosus(SCLE), but the lesions differed from SCLE by virtue of vasculopathic alterations comprising vascular ectasia, hypovascularity, and/or luminal thrombosis confined to the superficial vascular plexus and a sclerodermoid tissue reaction[59,60]. Other histologic possibilities include pustular leuko cytoclastic vasculitis (LCV) and pauci-inflammatory subepithelial blister formation with hyalinization of dermal papillae capillaries which resembles that of porphyria cutaneous tarda(PCT). These two histological appearances can also co-exist in patients with MTCD. Nuclear keratinocyte decoration with Ig Gand C5b-9 was common in all cases studied[59]. Anti-RNP is a protein complex to U1 RNA which is not specific for SLE; high titers associated with syndromes that have overlap features of several rheumatic syndromes including SLE; more common in blacks than whites[19].

Table 2: Cutaneous and histologic features of common connective tissue disorders

Cutaneous features	Skin of colour	Caucasian skin	Histologic appearance
Dermatomyosistis-DM	 40  40	 62 	 64
Ehlers Danlos	 68  71	 70	 72
Epidermolysis Bullosa	 58  58	 57  58	 57
Marfan's syndrome	 54  54	 55 	 53  53
Mixed Connective Tissue Disease	 77  76	 77  78	 78
Osteogenesis Imperfecta	 80	 83	 50 50
Pseudoxanthoma Elasticum	 38  98	 51 52	 51
Rheumatoid Arthritis	 86  86	 87 	 10

Scurvy	 90	 87	 88
Sjogren's Syndrome	  94	 93	 96
Systemic Lupus Erythromatosis	 63  63	 43  43	 43
Systemic Sclerosis	 40  40	 31  15	 45

Cutaneous Features of CTDS

Heritable disorders of connective tissue matrix are often characterized by easy bruising such as petechiae, ecchymosis and purpura due to vasculitis. Cutaneous manifestations of EDS include thinness, translucency, hyper extensibility (rubber person syndrome), easy bruisability, impaired elasticity, predisposition to scarring(cigarette-paper scars) and elastosis perforans serpiginosa. Blue sclera and cutis laxa are seen in OI and MfS. EB has mainly blisters[26]. Race and ethnicity have been noted to affect the expression of rheumatologic cutaneous CTDs such as DM, primary SjS, SLE and SSc[61]. Black Americans when compared to White Americans may be more affected by DM[62], however the low frequencies of cutaneous manifestations could probably be explained by underestimated cases of CTDs due to diagnostic difficulties related to the skin color[63], The specific skin manifestations of DM are the heliotrope rash which consists of a violaceous discolouration with periorbitaloedema, a v- shaped patterned pokiloderma on the anterior chest and on the back and shoulder(shawl sign) which areknown to be photosensitive and pruritic[17,18,32,37,61-64]. Other aspects of the body can be involved such as the central face mimicking seborrhoeic dermatitis, the lateral aspects of the hips and thighs called the Holster sign[17]. Others in DM include malar rash, scaly scalp or diffuse hair loss, periungual and cuticular changes. Nail changes include ragged cuticles and red nail folds while hair changes seen include itchy scaly scalp with inflammation and diffuse, non-scarring thinning of the hair, and sometimes poikiloderma[18,62]. Rarely, there is presence of vesicobullous erosive lesions (exfoliative erythroderma) which may be likely linked to cancer[17]. There may be presence of other skin manifestation of other diseases such as poikiloderma atrophicans (T cell cutaneous lymphoma) and calcinosis cutis (scleroderma). Overlap features of both scleroderma and dermatomyositis can be seen together in some persons.In classification of DM by Bohan and Peter in 1975, the fifth criterion which is 'compatible cutaneous disease' was the only one related to the integumentary system. It gave rise to a subset known as dermatomyositis sine myositis or amyopathic or hypomyopathic dermatomyositis. These have no myopathic features clinically but may have some abnormal finding on imaging studies[17]. It is known that cutaneous lesions in DM may precede by several months or years muscular manifestations hence their importance[17,18,62,63]. On Caucasian skins, these cutaneous lesions are typical and easily recognized by the physician because of the erythema associated with periorbitaledema which is a very characteristic sign of the disease[17,18,62]. In a study done in patients of darker skin heliotrope rash was reported in less 30% of cases. Heliotrope rash which is quite a visible sign on Caucasian skin seems to be hidden by the dark coloration of the skin[62,63]. Peri-orbital oedema characterized aselastic and painless was seen in all cases[63].

EDS is characterized by several distinct entities of which majority have a genetic bases however the hyper mobile type which is known to have mainly dermatologic manifestations such as, atrophic cutaneous scars, hematomas, hyper extensive stretch ability, piezogenic papules and soft skin is yet to have an identified genetic linkage. Other skin manifestations such as elastosis perforans serpiginosa and livedo reticularis which are seen in other CTDs can be seen as well, making diagnosis to be challenging[65]. Additional skin manifestations of EDS that has been reported depending on the type of EDS include cigarette paper-like, fish mouth, fisherman and shoe shape atrophic scars, easybruisinghaemoosiderotic scars, hernias, hypertrophic scars, keratosis pilaris-like lesions, molluscoid pseudotumours,

skin laxity, striae, subcutaneous spheroids and varicose veins[26,66].The differences between the manifestations in the skin of colour have not being noted to be different from that of the white skin but contrary to the opinion that there is no racial predilection some studies showed a higher prevalence of EDS in black African women and thus may have more symptoms[67]. Skin hyper extensibility and laxity remains two cardinal features that are reoccurring in cases reported regardless of race[26,36,66-72]. EBS is characterized by blisters form shortly after birth due to pressure, rubbing or trauma[40,56,73,74]. The children with EBS are often termed "butterfly children" because their skin is as delicate as a butterfly's wings[74]. The blisters cause scarring or milia on dorsum of hands, elbows and knees and oromucosal lesions. These blisters are recurrent and result from the slightest trauma to the skin. The blisters occur similarly in all racial groups but erythematous or pinkish hue that is marked in the Caucasian skin might not be seen in the skin of colour[40,56]. The continuous blistering, and scarring of the hand and feet can lead to fusion of the digits resulting in contractures causes the appearance described as mitten deformity or pseudosyndactyly likened to the piece of wear called mitten which is a type of glove[40].

Skin manifestations of Marfan's syndrome include striaeatrophicus, papyraceous scars and skin hyper extensibility[26,34,54,55,75]. Skin hyper extensibility has been well co-related with other manifestations of Marfan's syndrome such as joint hyper mobility in different age groups[75]. There are no clear cut differences in the cutaneous manifestations of Marfan's syndrome among the various racial groups[34, 75]. MTCD is the disease condition in which features of more than one CTD as SLE, DM/polymyositis, SSc and occasionally SS co -exist. It is seen as an intermediate stage and will progress to one disease eventually[26]. Raynaud's phenomenon is usually the initial cutaneous feature that MTCD presents with before manifesting as SLE or SSc. The hands are usually characterized by having sausage-shaped fingers, and swelling of the dorsa of the hands without sclerodactyly(puffy hands) are the most typical features[76-78]. Other features seen are mechanic hands which are described as thickened, hyperkeratotic, bilaterally symmetric eruptions along the fingers, palpable purpura, small vessel vasculitis that can be complicated by gangrene and leg ulcers can be found[76-78]. In a study done amongst Indian patients showed that there were significant clinical differences distinguishing MTCD from overlap syndrome particularly the presence of synovitis. Swollen hands, acrosclerosis, and myositis were manifestations seen in both groups with no significant difference[77]. Overlap syndromes do occur amongst autoimmune CTDs. It is when there is manifestation of the clinical features of more than one autoimmune CTD. Undifferentiated CTD is when there is evidence of autoimmunity but not enough to make diagnosis of any individual CTD[26]. Cutaneous manifestations of OI include thinness, translucency, easy bruisability, impaired elasticity and elastosis perforans serpiginosa (EPS).The wide differential for the dermatologic features of OI includes chronologic aging, photoaging, steroid-induced atrophy and other connective tissue diseases[79]. Acrocyanosis and bluish sclera are cutaneous manifestations seen in black patients at birth and even in later life[80-83].

The first clinical sign of PXE is almost always small yellow papules on the nape and sides of the neck and in flexural areas which may have a peaud' orange appearance in some patients[26,38, 51,52]. This may not be fully appreciated in the skin of colour particularly those of darker shades such as the Fitzpatrick type V and VI. PXE is rare in the general population and even rarer when compared to populations whose founding members where predominantly Caucasian and genetic predisposition may result from the founder effect[84]. This rarity might affect the appearance and recognition of the skin manifestations seen in those with darker pigments. In rare cases, patients with genetically confirmed PXE may have histologically normal skin[38]. The oral, vaginal and rectal mucosae may also be affected with these yellowish papules. The papules are initially isolated or found in patches but coalesce into reticulated plaques as the disease progresses, giving a cobblestone aspect to the skin. The skin subsequently becomes loose and wrinkled, although not to the extent seen in cutis laxa. It has been suggested that the presence of horizontal and oblique chin creases before the age of 30 years is specific for PXE[38]. These lesions begin to grow in childhood and adolescence period grow unpredictably into adulthood[52]. Less common skin manifestations of PXE include acneiform eruptions, EPS, reticulate pigmentation and granulotomatous nodules[26].

The cutaneous manifestations of rheumatoid arthritis vary however the commonest skin manifestation in RA is rheumatoid nodule seen in about 25% of the patients[5, 30,37, 85]. Several other varieties of cutaneous manifestations have been reported in RA including granuloma, dermatitis, vasculitis, pyoderma gangerosum and By water lesions(digital pulp papules), atrophy of the skin, easy bruising, petechiae, purpura, digital infarcts, gangrene, livedo reticularis, and in severe cases large, corn and callosities, palmar erythema, neutrophilic dermatosis , Raynaud's phenomenon, panniculitis and painful lower extremity ulcerations[5,30,37,85-87]. Nail changes that have been noted include brittle nails, clubbing, nail ridging, onycholysis, splitting, and ventral pterygium[87]. There has been no noted differences in the distribution of these skin lesions among the different ethnic groups with varying shades of skin tone[5,30,37,85]. The vasculitic ulcers seen may be difficult to distinguish from those caused by venous insufficiency but is treated successfully with immunosuppressive agents as well as skin grafting[85,86]. Rheumatoid vasculitis is commonly seen in males but there are no racial differences noted in presentation, however it is likely that the reddish (erythematous) and purplish (violaceous) lesions seen with rheumatoid skin manifestations might not be fully appreciated in darker skin types such as Fitzpatrick V and VI even of those within the same ethnicity.

Mucocutaneous manifestations of scurvy are phrynoderma (earliest sign) ecchymosis,easy bruising, perifollicular haemorrhages, cork screw hair, swan neck, hairs petechiae, haemoarthrosis, bleeding gums, spontaneous breakdown of old wounds and vasculitis. Follicular hyperkeratosis and perifollicular hemorrhages are pathognomonic examination findings on histology of the skin[27,58,88]. The legs are the most common sites of affection. Two key lesions found on the lower extremities are the palpable perifollicular purpura and woody oedema. The woody oedema is characterized by pain and ecchymosis[27]. Another manifestations of scurvy is keratosis pilaris(chicken skin) which appears 3-5 months of inadequate intake of vitamin C deficiency and risk factors such as alcoholism, smoking and those on prolonged dialysis. In dark skinned. Africans with severe scurvy the overlying skin was darkly stained or oedematous and woody to touch; the lesion felt hot and dry and formed a hard tender mass. The purplish or pinkish hues were not appreciable. Xerosis, spoon shaped fingernails with splinter haemorrhages are also some of the manifestations that could be seen in scurvy[89]. The scarring and hyper pigmented area of the sock area could persist for as long as six months. Hyperkeratotic hair follicles were noted at the site of perifollicular haemorrhages[90]. Cutaneous lesions are the commonest extra glandular manifestations of SS [20, 91-92]. Sjogren's syndrome have vascular and non- vascular cutaneous manifestation, however xerosis of the skin and mucous membrane are the principal symptoms. Other major ones are urticarial and necrotizing vasculitides, erythema multiforme, erythema perstans, erythema nodosum and Raynaud's phenomenon which is also seen in other CTDs like SLE, SSc[20]. Purpura has been shown to be the commonest cutaneous lesion seen in more than half of the patients with primary SS. This was independently associated with decreased C4 and cryoglobulinemia[91]. Lichen planus and erythema nodosum is also seen in some patients [92]. Annular erythema with scales, localized especially on the face and neck, is recognized as a cutaneous manifestation of Sjögren's syndrome. The patches are recurrent and resolve without hyperpigmentation; no photosensitivity is observed. Annular erythema is a common cutaneous manifestation in Japanese and other Asian patients; however, it is rarely seen in white patents. Those lesions bear some clinical similarities to the annular lesions of sub-acute cutaneous lupus erythematosus, but their histopathologic features are distinct from those of sub-acute cutaneous lupus erythematosus. In Japanese patients with Sjögren's syndrome, annular erythema is divided into the following 3 types:Sweet disease–like annular erythema with an elevated border, sub-acute cutaneous lupus erythematosus–like, marginally scaled erythema and papular erythema[20]. It has been noted that alopecia and vitiligo can also occur in those with primary SS[20,93]. Urticaria and hypergammaglobulinemic purpura were the most frequent cutaneous manifestations seen in some report of cases[94,95]. The histologic findings of these cutaneous lesions were more in keeping with cutaneous vasculitis[95]. Skin dryness(xerosis) is potentially being considered as a key manifestation in primary SS and has been attributed to dysfunctional sweating and sebaceous gland infiltration. The exact mechanisms are not clearly understood[96].Eye dermatitis and angular chelitisare also being seen often as manifestations. The pathological changes in cutaneous tissue of those with primary SS include epidermis infiltrated with mononuclear cells when stained with toluidine blue. Immunofluorescence analysis of the same skin specimen can also show CD20-positive B lymphocytes and CD3-positive T lymphocytes. Skin biopsy is currently being advocated to be a key test in management of SS as a result of the emergence of anti-B lymphocyte monoclonal antibodies as a new form of treatment[96].

Coins (discoid) and butterflies (malar) rashes are poetic descriptions of skin manifestation in SLE[97]. Photosensitivity, oral ulcers, purpura, scarring and non-scarring alopecia and mouth ulcers are also present[19,25,29,40-43]. Skin manifestation of SLE is what makes most persons present to the dermatology clinic. In the diagnosis of SLE, skin signs make more than 1/3rd (four out of the eleven) diagnostic criteria set by the American College of Rheumatology[19,63].In studies done in blacks, it shows that lupus erythematosus is the most common CTD and can manifest solely as cutaneous lesions or with systemic involvement[25,63]. Studies done amongst dark skinned patients of African descent showed that the acute and sub-acute forms are rare however this can be attributed the fact that the dermatological features may be difficult to see to the presence of higher amount of melanin pigmentation[63]. Discoid plaque which was characterized by a greyish hyperkeratotic edge(raised margins) with a central atrophied area seen in dark skin takes an achromic picture. This contrasts what is seen in the lighter skinned individuals of European descent that typically have erythema, central atrophy and hyperkeratosis. This finding was seen in both the dark skinned Africans with chronic lupus erythematosus in studies done in Togo and Cote d'Ivoire[63,98]. Scarring alopecia was the second commonest finding with very few cases of acute cutaneous lupus erythematosus [63].The systemic form of lupus that is SLE had discoid lesions, alopecia, oral sores, erythematous malar rash, extensive cutaneous necrosis and photosensitivity as common skin findings which are also seen in those of lighter skin shades of non-African origin[25,63,98].

Three rhythmic descriptions of scleroderma are fibrosis, sclerosis and xerosis[97]. **CREST** syndrome (**C**alcinosis cutis, **R**aynaud's phenomenon, **E**sophageal dysfunction, **S**clerodactyl and **T**elangiectasia) is commonly found in the limited form in those with sclerosis. Pulmonary fibrosis, cardiac involvement and scleroderma renal crisis are commonly seen in the diffuse form. Puckering of the mouth (fish mouth) and mat like telangiectasia on the face are common features[15,16,24,31-32]. Just like in PXE were limited manifestations such as redundant skin were reported as the only manifestations in some of the dark skinned patients[99]; cutaneous manifestations have also been reported as the sole clinical manifestations seen in most of the dark skinned Africans with SSc. Scleroderma was the second and third

commonest CTD seen in studies done in Nigeria, Cote d'Ivoire and Togo[25,63,100].Diffuse sclerosis was seen in all the cases in the study done in Cote d' Ivoire; followed by sclerdactyl and vitiligo[63]. Raynaud's phenomenon shows variable incidence in skin of colour, with studies such as the one done in Cote d'Ivoire[63], was very low while that in Togo had 40 % of cases with Raynaud's phenomenon. The diagnostic ability to visualize the white , blue and red colours in the dark skin is a most likely limitation, hence a detailed history such as it hand stiffness on exposure to cold is likely to be more useful in determining the presence of Raynaud 's phenomenon[63,100].

Some common CTDs such as benign hypermobility syndrome which has a high prevalence in Africans and is being considered to be within the spectrum of type III EDS (hypermobility) disease barely has skin manifestations[101]. The Spondyloarthritides are known to be associated with arthritis and HLA B27 but may hardly present with skin changes except for psoriatic arthritis[102]. The primary vasculitis syndromes don't commonly manifest with cutaneous signs except for the small/ medium vessel disease that may have features like ecchymosis, petechiae and livedoreticularis [5,26,40].

Management

Management would include taking an adequate history, physical examination, investigations and treatment[1-5, 26-30]. With regards to investigations auto antibodies are the hallmarks of systemic autoimmune diseases[25], Management of cutaneous symptoms of OI involves gentle skin care, sun protection which is general for all dermatological conditions[25-30,35,40-41,79]; off-label use of topical retinoids and targeted treatments for EPS and hyperhidrosis[79]. Future studies are required to determine the efficacy of dermatologic interventions in OI-associated skin conditions[79]. Auto antibodies such as antinuclear antibodies and rheumatoid factor are non- specific but varying in frequencies. Specific onesassociated with different autoimmune conditions include anti double stranded DNA (SLE), anti-histone (drug induced SLE),anti Ro/La(SS), anti-Mi-2(DM), anti-centromere (limited SSc), anti-Scl70(diffuse SSc), anti-cyclic citrullinatedpeptide (RA) and anti-RNP(MTCD)[26,40]. Other investigations would include skin biopsy, muscle biopsy, electromyography, and genetic and chromosomal analysis, complete blood count, erythrocyte sedimentation rate, imaging studies e.g. chest x-ray, abdominal scan, CT. MRI etc.[5,7-10,40]. Treatment includes immunosuppressive such as corticosteroids, cytotoxic drugs, biologics and management of co-morbidities[26,35,40-41, 79]. Prevention strategies would include pre conceptual counseling, patient education, nutritional support, adequate skin care, avoidance of deteriorating factors; treatment of opportunistic infections, regular follow up visits, appropriate referral to specialists and support groups[1-5,7-10,26-30, 40-41]. The prognosis depends on the individual's genetics, extent of skin and systemic involvement[1,40].

CONCLUSION

Cutaneous manifestations of CTDs are of public health importance because they affect the quality of life of sufferers. They cause morbidity and predispose them to increased mortality by reducing their mental, emotional and physical capacity. CTDs are commonly characterized by clinical cutaneous features. These clinical features can be obscure in the skin of colour because most studies carried out have been done in those with lighter skin who are resident in more developed countries where there is more advancement in medical knowledge and awareness of CTDs. Knowledge of the varying ways in which CTDs present in skin of colour enhances early diagnosis, treatment and secondary prevention.

REFERENCES

1. Cleveland Clinic(2022). *Connective tissue Disease*. Available at https://my.clevelandclinic.org/health/diseases/14803-connective-tissue-diseases.Accessed (24-08-2022)
2. Shiel, WC(2022). *Connective Tissue Disease*. Available at https://www.medicinenet.com/connective tissue disease/aticle.html. Accessed (24-08-2022)
3. Rodnan, GP(2022). *Connective tissue disease.* Available at: https://www.britannica.com/science/connective-tissue-disease, Accessed (24-08-2022)
4. Healthline(2022). *Collagen Vascular Diseases*. Available at https://www.healthline.com/health/collagen-vascular-disease, Accessed (24-08-2022)
5. Prockop, J, Bateman J. *'Heritable Disorders of Connective Tissue Disorders'* In: Longo D et al ed. Harrison's Principles of Medicine, 19th edition, United States of America, The McGraw-Hill companies pp. 2504
6. Taylor, SC,Kyei, A –Definition of Skin of Colourhttps://accessmedicine.mhmedical.com/content.aspx?bookid=2585&sectionid=211763356, Accessed (15-09-2022)
7. Gaubitz, M. (2006). Epidemiology of connective tissue disorders. Rheumatology, 45(suppl_3), iii3-iii4.
8. Bone and Joint Initiative.*'Connective Tissue Diseases,'* Available at https://www.boneandjointburden.org/fourth-edition/iiib23/connective-tissue-disorders, Accessed (26-08-2022)
9. Spagnolo, P., Cordier, J. F., & Cottin, V. (2016). Connective tissue diseases, multimorbidity and the ageing lung. European Respiratory Journal, 47(5), 1535-1558.

10. Haverstock C., Jorrizo J(2008). Rheumatoid Arthritis, Rheumatic Fever and Gout; Fitzpatrick's Dermatology in General Medicine, 7th ed. In Wolff K et al ed. New York McGraw- Hill, pp. 1569-1573
11. MacGregor AJ, Riste LK, Hazes JM, Silman AJ(1994). Low prevalence of rheumatoid arthritis in black-Caribbeans compared with whites in inner city Manchester. Ann Rheum Dis;53(5):293-297. doi:10.1136/ard.53.5.293
12. Dowman B, Campbell RM, Zgaga L, Adeloye D, Chan KY(2012). Estimating the burden of rheumatoid arthritis in Africa: A systematic analysis. J Glob Health ;2(2):020406. doi: 10.7189/jogh.02.020406. PMID: 23289081; PMCID: PMC3529310.
13. Malaviya, A. N., Kapoor, S. K., Singh, R. R., Kumar, A., & Pande, I. (1993). Prevalence of rheumatoid arthritis in the adult Indian population. Rheumatology international, 13(4), 131-134.
14. Zeng, X. F., Zhu, S. L., Tian, A. C., & Xie, X. P. (2013). Systematic review of research on disease burden and quality of life in rheumatoid arthritis in China. Chin. J. Evid. Based Med, 13, 300-307.
15. Wolff K et al ed, (2008). Denton C, Black C, *Sclerodema(Systemic Sclerosis)* Fitzpatrick's Dermatology in General Medicine, 7th ed. New York, McGraw- Hill pp.1553-1562
16. Amit, A(2022).*Review of Global Incidence and Prevalence of Systemic Sclerosis*, Available at https://www.rheumatologyadvisor.com/home/topics/scleroderma/global-incidence-prevalence-burden-of-systemic-sclerosis-scleroderma/,Accessed (15-09-2022)
17. Sontheimer R, Costner M, *Dermatomyositis*Fitzpatrick's Dermatology in General Medicine, 7thed. In Wolff K et al ed. New York, McGraw- Hillpp 1536-1553
18. Femia A(2022).*Dermatomyositis*; Available at https://emedicine,medscape.com.article/3327683-overview, Accessed (19-09-2022)
19. Costner M, Sontheimer R, '*Lupus Erythromatosus'* Fitzpatrick's Dermatology in General Medicine, 7th ed. In Wolff K et al ed. New York, McGraw- Hill pp. 1515-1535
20. Danielides, S., Illei, G(2008). *Sjogren Syndrome*Fitzpatrick Dermatology in General Medicine7th ed. New York, McGraw- Hill, pp 1577-1583
21. Patel, R., Shahane, A(2014). The epidemiology of Sjögren's syndrome. Clinical epidemiology, p247–255.
22. Larkin, M(2022).'Location & Ethnicity Affect Manifestations of Primary Sjogren's Syndrome, Available at https://www.the-rheumatologist.org/article/location-ethnicity-affect-manifestations-primary-sjogrens-syndrome/,' Accessed (20-09-2022)
23. Gelber AC, Manno RL, Shah AA, et al(2013). 'Race and association with disease manifestations and mortality in scleroderma: a 20-year experience at the Johns Hopkins Scleroderma Center and review of the literature. Medicine (Baltimore). p191-205.'
24. Erzer, J. N., Jaeger, V. K., Tikly, M., & Walker, U. A. (2020). Systemic sclerosis in sub-Saharan Africa: a systematic review. The Pan African Medical Journal, 37.
25. Mercy, E., Otike-Odibi, B., & Altraide, D. (2015). Profile of autoimmune connective tissue disorders in the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria. Nigerian Health Journal, 15(2), 39-47.
26. Lacouture M, Paller, A(2008).Heritable Disorders of Connective Tissue with Skin Changes Fitzpatrick's Dermatology in General Medicine, 7th ed. pp. 1297-1311
27. Jen M, Shah K, Yan A(1993)*'Cutaneous changes in Nutritional Disorders'* Fitzpatrick's Dermatology in General Medicine, 7th ed. In Wolff K et al ed. New York, McGraw- Hill, pp. 1212-1213
28. Cleveland Clinic(2022).*'EpidermolysisBullosa'* Available at https://my.clevelandclinic.org/health/diseases/17792-epidermolysis-bullosa#(Accessed (04-05-2022)
29. Distler, O., Müller-Ladner, U.(2006).*'Novel aspects in the epidemiology, pathophysiology and treatment of connective tissue diseases,'* Rheumatology, Pages iii1–iii2, https://doi.org/10.1093/rheumatology/kel279
30. Kumar P, Clark M(2012), *'Rheumatology and Bone Disease'*, Kumar and Clark's Clinical Medicine; Kumar P, Clark M., 8th edition, United Kingdom, Saunders Elsiviers, p 493-566
31. Schwartz, RA(2022). *'Systemic Sclerosis'* Available at https://emedicine.medscape.com/article/1066280-overview, Accessed (30-03-2022)
32. *Systemic Sclerosis(Scleroderma)*In: Longo D et al ed. Harrison's Principles of Medicine, 18th edition, United States of America, The McGraw-Hill companies, chap.323
33. Yao, T., Hongyi, Y., Na, L., Yan, L., and Jie, C.(2021). *Advances in Pathogenesis of Sjögren's Syndrome, Journal of immunology Research*, Available at https://www.hindawi.com/journals/jir/2021/5928232/, (Accessed 13-04-2022)
34. NORD(2022). 'Marfan Syndrome' Available at https://rarediseases.org/rare-diseases/marfan-syndrome/, Accessed(18-04-2022)
35. Ritelli M, Colombi M(2020). *Molecular Genetics and Pathogenesis of Ehlers-Danlos Syndrome and Related Connective Tissue Disorders. Genes (Basel).* 2020 May 13;11(5):547. doi: 10.3390/genes11050547. PMID: 32414079; PMCID: PMC7288446.
36. Ehlers- Danlos News(2022).*"Types of Ehlers-Danlos"* Available at https://ehlersdanlosnews.com/types-of-ehlers-danlos-syndrome/, Accessed (18-04-2022)

37. Bolognta J. Braverman I., *'Skin manifestations of Internal Diseases'* In: Longo D et al ed. Harrison's Principles of Medicine, 19th edition, United States of America, The McGraw-Hill companies pp. 364-365
38. Germain, D.P(2017). '*Pseudoxanthomaelasticum*.'Orphanet J Rare Dis, 12, 85 (2017).
39. Etich J, Leßmeier L, Rehberg M, et al(2020). *Osteogenesisimperfecta-pathophysiology and therapeutic options*. Mol Cell Pediatr;7(1):9.
40. Yusuf, S. 'African Dermatology,' Abuja Ibadan University Press, 1-430
41. Laga AC, Larson A, Granter SR(2017). *Histopathologic Spectrum of Connective Tissue Diseases Commonly Affecting the Skin*. p477-503
42. Systemic Lupus Erythromatosus In: Longo D et al ed. Harrison's Principles of Medicine, 18th edition, United States of America, The McGraw-Hill companies, chap.319
43. Aghighi,M., Motaparthi, K(2022). *'Lichenoid and interface reaction patterns: Chronic cutaneous lupus,'*Available at https://www.pathologyoutlines.com/topic/skinnontumorlupussle.htmlAccessed (26-11-2022)
44. Qudsiya Z, Waseem M(2022). *'Dermatomyositis.'* In: StatPearls [Internet]. Treasure Island (FL): StatPearls Available from: https://www.ncbi.nlm.nih.gov/books/NBK558917/, Accessed (18-04-2022)
45. Duran, J(2022). PlazaDermal collagen and elastic tissue alterations, and cutaneous deposits: Morphea and systemic sclerosis, Available at https://www.pathologyoutlines.com/topic/skinnontumorscleroderma.html, Accessed (26-11-2022)
46. Chimenti MS et al(2018). '*Histopathology of the skin in rheumatic diseases*.' Reumatismo. p187-198.
47. Ranatunga, SK(2022). *Sjogren Syndrome Clinical Presentation*, Available at https://emedicine.medscape.com/article/332125-clinical#b3, Accessed (16-05-2022)
48. Bergman R, Nevet MJ, Gescheidt-Shoshany H, Pimienta AL, Reinstein E(2014). *'Atrophic Skin Patches With Abnormal Elastic Fibers as a Presenting Sign of the MASS Phenotype Associated With Mutation in the Fibrillin 1 Gene.'*p885–889
49. Shapiro, JR(2022).*'OsteogeneticImperfacta,'* Dermatology Advisor, Available at https://www.dermatologyadvisor.com/home/decision-support-in-medicine/dermatology/osteogenesis-imperfecta-2/, Accessed (16-05-2022)
50. Tallon, B(2022). 'Elastosisperforansserpiginosa pathology' Available at https://dermnetnz.org/topics/elastosis-perforans-serpiginosa-pathology'Accessed (16-05-2022)
51. Hosen, MJ, Lamoen, A, De Paepe, A. and Vanakker, OM(2012).*'Histopathology of PseudoxanthomaElasticum and Related Disorders: Histological Hallmarks and Diagnostic Clues,'*Available at https://www.hindawi.com/journals/scientifica/2012/598262/. Accessed (16-05-2022)
52. Marconi, B. et al(2015).*'Pseudoxanthomaelasticum and skin: Clinical manifestations, histopathology, pathomechanism, perspectives of treatment.'* Intractable Rare Dis Res. p113-22
53. Bergman, R., Nevet, M. J., Gescheidt-Shoshany, H., Pimienta, A. L., & Reinstein, E. (2014). Atrophic skin patches with abnormal elastic fibers as a presenting sign of the MASS phenotype associated with mutation in the fibrillin 1 gene. JAMA dermatology, 150(8), 885-889.
54. Inna, P., Thomson, J.(2022).*'Marfan Syndrome'*Available at https://emedicine.medscape.com/article/1258926-clinical, Accessed(08-06-2022)
55. Pessler, F.(2022).*'Marfan's Syndrome'*Available at https://emedicine.medscape.com/article/1258926-treatment, Accessed(08-06-2022)
56. Hamodat M(2022). *'Epidermolysisbullosa.'* PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/skinnontumorepidermolysisbullosa.html. Accessed(10-06-2022)
57. Alikhan, A., Farshidi, D., & Shwayder, T. (2009). Case of mistaken identity: bullous congenital ichthyosiform erythroderma mistaken as epidermolysis bullosa simplex. Dermatology Online Journal, 15(9).
58. Yan, A(2022). *Scurvy (Vitamin C deficiency, Ascorbic acid deficiency)*. Available at https://www.dermatologyadvisor.com/home/decision-support-in-medicine/dermatology/scurvy-vitamin-c-deficiency-ascorbic-acid-deficiency, Accessed (03-07-2022)
59. Magro, C. M., Crowson, A. N., & Regauer, S. (1997). Mixed connective tissue disease: a clinical, histologic, and immunofluorescence study of eight cases. The American journal of dermatopathology, 19(3), 206-213.
60. Singsen, B. H., Swanson, V. L., Bernstein, B. H., Heuser, E. T., Hanson, V., & Landing, B. H. (1980). A histologic evaluation of mixed connective tissue disease in childhood. The American Journal of Medicine, 68(5), 710-717.
61. Piram, M., Maldini, C., & Mahr, A. (2012). Effect of race/ethnicity on risk, presentation and course of connective tissue diseases and primary systemic vasculitides. Current opinion in rheumatology, 24(2), 193-200.
62. Ngan, V., Sapsford, S(2022). *'Adult-onset dermatomyositis,'* Available at https://dermnetnz.org/topics/adult-onset-dermatomyositis, Accessed (08-06-2022)
63. Abdoulaye, S., Joseph, EE, Hamdan KS, Mamadou, K., Patric, GI, et al(2015). *'Dermatological Manifestations of Connective Tissue Diseases in Black People.'* J ClinExpDermatol Res, doi:10.4172/2155-9554.1000264
64. Hamodat, M(2022). *'Lichenoid and interface reaction patterns: Dermatomyositis,'* Available at https://www.pathologyoutlines.com/topic/skinnontumordermatomyositis.html, Accessed (06-06-2022)

65. Edimo, C. O., Wajsberg, J. R., Wong, S., Nahmias, Z. P., & Riley, B. A. (2021). The dermatological aspects of hEDS in women. International Journal of Women's Dermatology, 7(3), 285-289.
66. Burrow, N(2022).*'Skin Changesin EDS: What are they and How to manage them.'*, A webinar,Oct, 2018 Available at https://www.youtube.com/watch?v=5ZJzXrgN0gE, (Accessed 11-07-2022)
67. Syx, D., Symoens, S., Steyaert, W., De Paepe, A., Coucke, P. J., & Malfait, F. (2015). Ehlers-Danlos syndrome, hypermobility type, is linked to chromosome 8p22-8p21. 1 in an extended Belgian family. Disease markers, 2015.
68. Olaosebikan, A. & Wolf, B. (1993). Ehlers-Danlos syndrome in a Zimbabwean child. Central African Journal of Medicine, 39(1), 20-22.
69. Ehlers, C. M. (2012). Danlos syndrome, hypermobility type: an underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. ISRN Dermatol, 2012, 751768.
70. Burkhart, NW , Perkins, C(2022). *Recognizing the clinical signs of Ehlers-Danlos syndrome,* Available at https://www.rdhmag.com/pathology/article/14189665/recognizing-the-clinical-signs-of-ehlersdanlos-syndrome, Accessed 17-07-2022
71. Defendi, G(2022).*'Genetics of Ehlers-Danlos Syndrome',* Available at, https://emedicine.medscape.com/article/943567-overview, Accessed 17-07-2022
72. Mainetti, C., Terziroli Beretta-Piccoli, B., & Selmi, C. (2017). Cutaneous manifestations of dermatomyositis: a comprehensive review. Clinical reviews in allergy & immunology, 53(3), 337-356.
73. Fine, J. D. (Ed.). (1999). Epidermolysis bullosa: clinical, epidemiologic, and laboratory advances, and the findings of the National Epidermolysis Bullosa Registry. Johns Hopkins University Press.
74. Zimlich, R(2022). *All About EpidermolysisBullosa, Also Called Butterfly Skin Disease,* Available at https://www.healthline.com/health/butterfly-skin, Accessed 03-08-2022
75. Grahame, R., & Pyerttz, R. E. (1995). The Marfan syndrome: joint and skin manifestations are prevalent and correlated. Rheumatology, 34(2), 126-131.
76. Schwartz, R(2022). '*Dermatologic Manifestations of Mixed Connective Tissue Disease Clinical Presentation'*Available at https://emedicine.medscape.com/article/1066445-clinical, Accessed (08-08-2022)
77. Sen, S., Sinhamahapatra, P., Choudhury, S., Gangopadhyay, A., Bala, S., Sircar, G., ... & Ghosh, A. (2014). Cutaneous manifestations of mixed connective tissue disease: study from a tertiary care hospital in eastern India. Indian Journal of Dermatology, 59(1), 35.
78. Greidinger, EL(2022). '*Mixed Connective-Tissue Disease (MCTD),*' Available at https://emedicine.medscape.com/article/335815-overview, Accessed (03-09-2022)
79. Chien AL, Mu, EW, Kang, S.,*Skin in osteogenesisImperfecta; OsteogenesisImperfecta: A traditional approach to brittle bone disease,* New York, Elsevier Inc.pp283-288
80. Edelu, B. O., Ndu, I. K., Asinobi, I. N., Obu, H. A., & Adimora, G. N. (2014). Osteogenesis imperfecta: a case report and review of literature. Annals of Medical and Health Sciences Research, 4(1), 1-5.
81. Chamunyonga, F., Masendeke, K. L., & Mateveke, B. (2019). Osteogenesis imperfecta and pregnancy: a case report. Journal of Medical Case Reports, 13(1), 1-4.
82. Mwangi, G. C., & Macharia, J. T. (2016). Pattern of distribution of patients presenting with osteogenesis imperfecta at AIC cure Children's International Hospital, Kijabe. East African Orthopaedic Journal, 10(1), 21-26.
83. Liu, L(2022).*'OsteogenesisImperfecta / Brittle Bone Disease'* Available at https://step1.medbullets.com/msk/112036/osteogenesis-imperfecta--brittle-bone-disease, Access (08-08-2022)
84. Moitra, K. et al(2017). "*ABCC6 and PseudoxanthomaElasticum: The Face of a Rare Disease from Genetics to Advocacy".*Int J Mol Sci. Jul 11;18(7):1488.
85. Haverstock, CI, Jorizzo, JL(2008). *'Rheumatoid Arthritis, Rheumatic Fever and Gout'*, Fitzpatrick's Dermatology in General Medicine, 7th ed. pp. 1569-1576
86. Ghosh SK, Bandyopadhyay D, Biswas SK, Darung I(2017). *'Mucocutaneous Manifestations in Patients with Rheumatoid Arthritis: A Cross-sectional Study from Eastern India.'*Indian J Dermatol. Jul-Aug;62(4):411-417.
87. Ngan, V(2022). *'Rheumatoid arthritis and the skin',* Available at https://dermnetnz.org/topics/rheumatoid-arthritis-and-the-skin, Accessed (17-09-2022)
88. Fossitt, DD, Kowalski, TJ(2014). '*Classic Skin Findings of Scurvy'* Mayo clinical Proceedings, 89(7) E61
89. Julsen, E(2022).*15 Signs of vitamin C deficiency*, Available at https://www.healthline.com/nutrition/vitamin-c-deficiency-symptoms, Accessed (26-10-2022)
90. Grusin, H., & Kincaid-Smith, P. S. (1954). Scurvy in adult Africans. A clinical, haematological, and pathological study. American Journal of Clinical Nutrition, 2, 323-335.
91. Durigan, V., Secco, A., Duarte, V., Troitiño, C., Pellet, A. C., Mamani, M., ... & Santiago, L. (2018). Extraglandular cutaneous manifestations in patients with primary Sjögren's Syndrome. Revista Colombiana de Reumatología (English Edition), 25(2), 79-84.
92. Ueki, H., Inagaki, Y., Hamasaki, Y., & Ono, M. (1991). Dermatological manifestations of Sjögren's syndrome. Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und Verwandte Gebiete, 42(12), 741-747.
93. Gutierrez, N., & Cohen, P. R. (2020). Vitiligo as the Presenting Manifestation of Sjogren's Syndrome: Case Report and Review of Vitiligo and Its Associated Autoimmune Conditions. Cureus, 12(10).

94. Alexander, E. L., & Provost, T. T. (1983). Cutaneous manifestations of primary Sjögren's syndrome: a reflection of vasculitis and association with anti-Ro (SSA) antibodies. Journal of Investigative Dermatology, 80(5), 386-391.
95. Boddu P, Mohammed AS, Khandelwal S(2016). *Skin Findings in a Patient with Sjogren'sSyndrome.* Case Rep Rheumatol.
96. Tobón, GJ,Rougedas, A., Misery, L., Youlou, P. Pers, J(2022). *'Skin biopsy as a routine diagnostic tool for primary Sjögren's syndrome'*,Available athttps://www.openaccessjournals.com/articles/skin-biopsy-as-a-routine-diagnostic-tool-for-primary-sjgrens-syndrome.pdf, Accessed (24-11-2022)
97. Amadi, E (2017); *Psalms of Infirmity*, Abuja, Best Choice Global Network Limited, pp. 351, 359
98. Kombate, K., Saka, B., Sodonougbo, K. P., Mouhari-Toure, A., Pitche, P., & Tchangai-Walla, K. (2007, January). CA25-Lupus érythémateux systémique à Lomé: profil sémiologique et évolutif de 16 cas. In Annales de Dermatologie et de Vénéréologie (Vol. 134, No. 1, pp. 75-76). Elsevier Masson.
99. Jacyk, W. K., Lodder, J. V., & Dreyer, L. (1988). Pseudoxanthoma elasticum in South African black patients. A report on 7 cases. South African Medical Journal= Suid-afrikaanse Tydskrif vir Geneeskunde, 74(4), 184-186.
100. Pitche, P., Amanga, Y., Koumouvi, K., Oniankitan, O., Mijiyawa, M., & Tchangaï-Walla, K. (1998). Scleroderma in a hospital setting in Togo. Médecine Tropicale: Revue du Corps de Santé Colonial, 58(1), 65-68.
101. Birrell, F. N., Adebajo, A. O., Hazleman, B. L., & Silman, A. J. (1994). High prevalence of joint laxity in West Africans. Rheumatology, 33(1), 56-59.
102. Stolwijk C, BoonenA, van Tubergen A, Reveille JD(2012). *Epidemiology of spondyloarthritis.* Rheum Dis Clin North Am,p441-76.