Review Article

Connective tissue disorders and eye: A review and recent updates

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Collagen vascular disorders (CVDs), also known as connective tissue diseases (CTDs), are a heterogeneous group of entities that affect the connective tissues and are capable of causing end-organ damage to multiple systems, primarily cardiopulmonary and musculoskeletal. However, the occurrence and severity are highly variable among patients. Ocular involvement occurs in a significant number of these disorders and may precede the onset of other extraocular features, thereby serving as an important marker in the diagnosis of these diseases. A timely and accurate diagnosis enables the management of complications. CTDs are primarily immune-mediated inflammatory diseases; however, classifications have encompassed heritable disorders affecting collagen-containing structures and disorders of vascular development. A review of literature published until 25 January 2022 and collected from various databases using the relevant keywords was conducted. All publications (original articles, review articles, as well as case reports) describing the ocular features in CTDs were studied in detail. The objective of this review is to recognize the common ophthalmic presentations of various autoimmune and heritable CTDs, distinguish them from overlapping diseases, elaborate on the prognosis and management of these varied eye presentations, and deliberate on their impact on other ophthalmic surgeries.

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Collagen vascular disorders (CVDs) or connective tissue diseases (CTDs) are primarily multisystem disorders affecting the synthesis of proteins that create the connective tissue framework of the body. Their diagnosis and management are often an interdisciplinary challenge. Ophthalmic presentations may be the primary presenting clinical feature.[1] These disorders have characteristic symptoms, signs, and autoantibodies to clinch the diagnosis. The common autoimmune CTDs are rheumatoid arthritis (RA), scleroderma, systemic lupus erythematosus (SLE), inflammatory myopathies (polymyositis [PM]/dermatomyositis [DM]), and Sjögren's syndrome.[2] Certain heritable disorders that affect the production of extracellular matrix (ECM) like collagen, elastin, fibrillin, fibulin, and mucopolysaccharides are also included under the umbrella of CVDs. They affect the bones, joints, ligaments, skin, blood vessels, and valves. The commonly included disorders are Marfan syndrome (MFS), Ehler–Danlos syndrome (EDS), osteogenesis imperfecta (OI), Alport syndrome, Stickler syndrome (SS), and a few others.[3]

This review aims to summarize the ophthalmic manifestations and management of various CTDs, their systemic associations, and recent updates.

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Autoimmune Disorders

The most frequently encountered CVDs are SLE, scleroderma, RA, inflammatory myopathies (PM and DM), and Sjögren's syndrome

Systemic lupus erythematosus

SLE is a chronic, immune-mediated, multisystem condition that might affect various parts of the eye. Of the affected individuals, 90% are usually women in the age group of 15–45 years.[4] Fever, headache, malaise, arthralgias, myalgias, and loss of appetite are some constitutional features. Renal disease is usually the primary cause of death. Skin, neurologic, vascular, and hematologic systems are a few other commonly involved systems. SLE may be triggered by stress, infection, sunlight, pregnancy, and a few drugs such as oral contraceptive pills (OCPs) and sulfonamides.

B-cell lymphocyte hyperactivity leading to the production of numerous antibodies and immune complexes causing specific tissue damage is the primary pathogenesis; however, T-cell abnormalities are seen as well. The recent diagnostic criteria by the SLE International Collaborating Clinics (SLICC)[5] have been summarized in Table 1. Laboratory findings include the presence of antinuclear antibodies (ANA) not specific to SLE. Anti-ds DNA and anti-Sm antibodies are quite specific to SLE.

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Table 1: SLICC diagnostic criteria

	Clinical criteria
1	Acute cutaneous lupus, including: Malar rash/bullous lupus/toxic epidermal necrolysis variant/maculopapular lupus rash/photosensitive lupus rash *In the absence of dermatomyositis OR subacute cutaneous lupus*
2	Chronic cutaneous lupus, including: Classic discoid rash/hypertrophic lupus/lupus panniculitis/mucosal lupus/lupus erythematosus tumidus/chilblains lupus/discoid lupus/lichen planus overlap
3	Oral, palate (buccal, tongue) OR nasal ulcers *In the absence of other causes*
4	Nonscarring alopecia *In the absence of other causes*
5	Synovitis- including >2 joints, characterized by swelling or effusion OR tenderness in >2 joints and at least 30 min morning stiffness
6	Serositis- typical pleurisy for more than 1 day OR pleural effusions OR pleural rub Typical pericardial pain OR pericardial effusion OR pericardial rub OR pericarditis by ECG
7	Renal- urine protein-to-creatinine ratio representing 500 mg protein/24 h OR red blood cell casts
8	Neurologic- seizures/psychosis/mononeuritis multiplex/myelitis/peripheral or cranial neuropathy/acute confusional state *In the absence of other causes*
9	Hemolytic anemia
10	Leukopenia (<4000/mm^3 at least once) OR lymphopenia (<1000/mm^3 at least once) *In the absence of other causes*
11	Thrombocytopenia (<100,000/mm^3 at least once)
	Immunologic criteria
1	ANA level- above the laboratory reference range
2	Anti-ds DNA antibody level- above the laboratory reference range
3	Anti-Sm- the presence of antibody to Sm nuclear antigen
4	Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticoagulant/false-positive test result for rapid plasma reagin/medium or high titer anticardiolipin antibody level/positive test result for anti-b2-glycoprotein 1
5	Low complement (C3/C4/CH50)
6	Direct Coombs test *In the absence of hemolytic anemia*

For a diagnosis of SLE, at least four criteria, including at least one clinical and one immunologic criterion, must be satisfied or the patient must have biopsy-proven lupus nephritis in the presence of antinuclear antibodies or anti–double-stranded DNA antibodies. ANA=antinuclear antibodies, SLE=systemic lupus erythematosus, SLEICC=SLE International Collaborating Clinics

Ocular manifestations

Though ocular involvement is not included in the SLICC criteria, they might present well in advance of a definitive diagnosis. Various ocular manifestations have been summarized in Table 2. Jawahar *et al*.[6] found that the prevalence of each ocular manifestation, except for retinal vaso-occlusive disease, was consistently less than 5%. The overall prevalence of dry eye disease (DED) was 16% among patients with SLE in a recent meta-analysis, where it was found that at least two positive findings were present in them among the subjective symptoms, tear function test, and vital staining test.[7] Studies show that up to 29% of patients with active SLE manifest retinal disease.[8] The exact prevalence of choroidal disease is unknown, but it is thought to be less common than retinopathy due to underdiagnosis. Optic nerve disease, represented by optic neuritis and anterior/posterior ischemic optic neuropathy, affects approximately 1% of SLE patients.[7] These ocular manifestations have been associated with neurologic flares, antiphospholipid antibodies, nephropathy, and increased mortality.

Dry eye symptoms and abnormal Schirmer's test were found in 26% and 24% of patients with SLE, respectively, and 12% of patients also met the criteria of secondary Sjögren's syndrome.[6] Retinal vasculitis, uveitis, and isolated cotton wool spots were associated with more active SLE disease. Retinopathy in SLE is suggestive of high disease activity, and it is a marker of poor visual outcome and prognosis for survival.[9]

Ocular investigations

Corneal confocal microscopy identifies distal corneal nerve fiber loss and increased immune cell density in patients with SLE, and corneal nerve loss is associated with disease activity.[10] Patients suspected of SLE should receive optical coherence tomography angiography (OCTA) examination in a comprehensive eye examination to detect changes in ocular microcirculation at an early stage.[11] Liu *et al*.[12] demonstrated decreased inner retinal thickness and superior vascular in OCTA.

Management

Adequate systemic treatment is required for disease control using various drugs as follows: immunosuppressants (hydroxychloroquine, azathioprine, mycophenolate,

cyclophosphamide, and glucocorticoids) and biologicals (rituximab, belimumab, epratuzumab). Anticoagulants are required in patients with antiphospholipid syndrome. Ophthalmic manifestations may be an indicator that the underlying SLE is not adequately managed. They are managed symptomatically; for instance, DED may be managed based on Dry Eye WorkShop (DEWS) recommendations. Few reports have highlighted the role of intravenous corticosteroid (methylprednisolone pulse therapy) along with a tapering regimen of oral prednisolone despite treatment with systemic azathioprine in vision-threatening conditions.[13] Rituximab, in particular, has been found beneficial in SLE retinal vasculitis and orbital pseudotumor that is refractory to steroids and cyclophosphamide.[14]

Table 2: Ocular manifestations of SLE

Ocular Structure	Common Ocular Manifestations
Eyelids	Discoid lupus of the eyelids
Cornea and conjunctiva	Commonly- KCS, conjunctivitis Others include superficial punctate and interstitial keratitis, PUK
Sclera	Episcleritis/scleritis
Uvea	Uveitis, ischemic choroidopathy, choroidal vasculitis
Retina	Commonly- vascular occlusions (venous and arterial) Others include cotton wool spots, hemorrhages, vasculitis, proliferative retinopathy, pseudo-RP–like retinopathy, serous detachments
Neuro-ophthalmic	VI nerve palsy, optic neuritis, ischemic optic neuropathy, INO, pupil and oculomotor abnormalities, hemianopia and amaurosis, visual hallucinations, geniculocalcarine blindness
Orbit	Myositis, pseudotumor, trochlearitis, vasculitis, paniculitis

INO=internuclear ophthalmoplegia, KCS=keratoconjunctivitis sicca, PUK=peripheral ulcerative keratitis, RP=retinitis pigmentosa, SLE=systemic lupus erythematosus

Table 3: Ocular manifestations of scleroderma

Ocular Structure	Common Ocular Manifestations
Eyelids	Periorbital edema and fibrosis leading to blepharophimosis, lid telangiectasia, lid induration, cicatricial ectropion, MGD
Cornea and conjunctiva	KCS, subepithelial fibrosis, and progressive forniceal shortening are most common. Congestion and telangiectasia, exposure keratopathy (secondary to lid changes), decreased corneal sensation, keratoconus
Sclera	Scleral ischemia, scleral pit
Uvea	Iritis, iris sector atrophy and heterochromia, iris sphincter dysfunction, choroidal hypoperfusion, and ischemic choroidopathy
Retina	Cotton wool spots, retinal hemorrhages, hard exudates, retinal vascular occlusions, macular ischemia, parafoveal telangiectasia
Neuro-ophthalmic	Optic disk neovascularization, perineuritis
Orbit	Acquired Brown syndrome, painful retrobulbar fibrosis, ocular myopathy (superior rectus commonly)

KCS=keratoconjunctivitis sicca, MGD=meibomian gland dysfunction

Scleroderma

Scleroderma is s chronic, acquired CTD that results in progressive thickening of the connective tissues.[15] It could be classified into two major forms – localized scleroderma (involving only skin) and systemic sclerosis (SSc; multisystem involvement). Localized scleroderma is subdivided into limited morphea, generalized morphea, and linear scleroderma. SSc is subdivided into limited and diffuse based on the extent of skin involvement.[16]

The primary site of pathogenesis is the small vessels such as arterioles and capillaries. Microvascular endothelial cell damage leads to initial increase in permeability and interstitial edema, followed by fibroblast and myofibroblast stimulation that results in fibrosis and ischemic injury. Trophic factors such as Platelet Derived Growth Factor (PDGF) play a critical role in the regulation of collagen synthesis. Helper T cells play a vital role in pathogenesis as a treatment against them helps in skin tightness in these patients.[17,18] The diagnostic criteria were laid by the American College of Rheumatology/European League Against Rheumatism, which included skin thickening proximal to metacarpophalangeal joints, fingertip lesions like ulcers or pitting scars, telangiectasia, abnormal nailfold capillaries, Raynaud phenomenon, pulmonary artery hypertension with/without interstitial lung disease, and SSc-related antibodies (anticentromere, anti-topoisomerase I [anti–Scl-70], anti-RNA polymerase III); however, no ocular features were included in the diagnostic criteria.[19]

Raynaud's phenomenon is the most common finding in scleroderma patients (90%). Skin and gastrointestinal tract are the commonly involved organs in SSc.[20] Cardiac (myocardial fibrosis, dysrhythmias, myocardial ischemia, and heart failure) and pulmonary (interstitial fibrosis, pulmonary hypertension, pleuritis) involvement must be looked for in these patients. Renal failure is the leading cause of death in patients with SSc.[21]

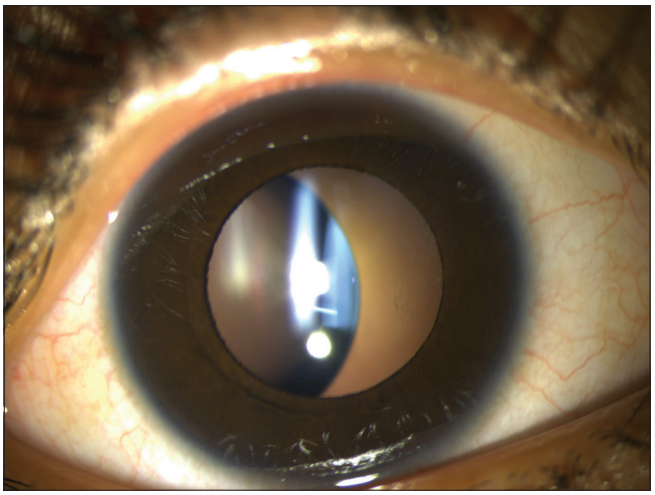

Figure 1: Temporal subluxation of crystalline lens in a patient of Marfan syndrome

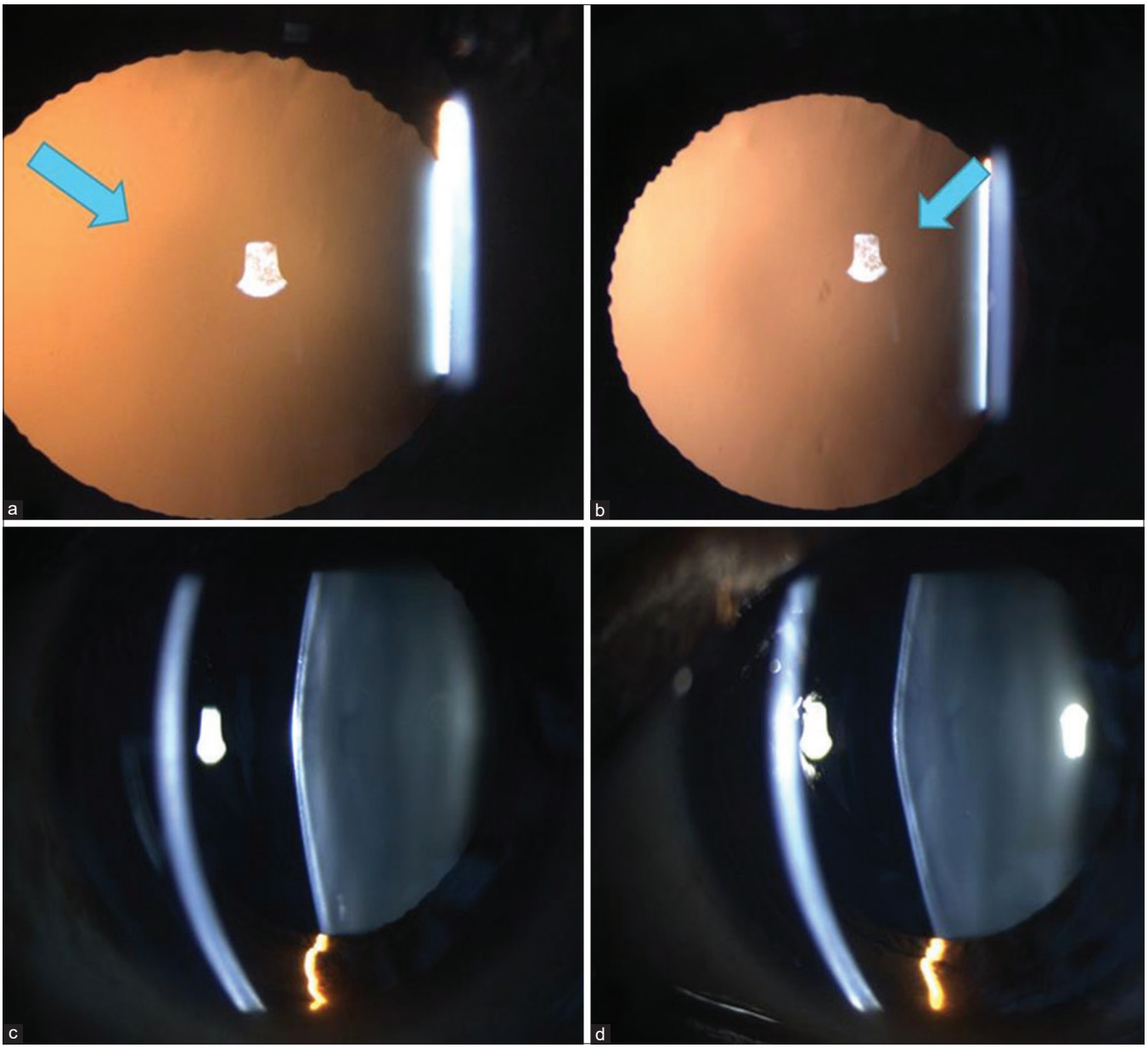

Figure 2: (a, b) Retroillumination images of bilateral anterior lenticonus in a patient with Alport syndrome. (c, d) Slit images of anterior lenticonus in the same patient

ANA can be detected in >90% of the patients. Other major antibodies present are anticentromere antibodies (almost exclusively in limited cutaneous SSc), anti-topoisomerase, anti-RNA polymerase, and antihistone antibodies (in diffuse cutaneous SSc).

Ocular manifestations

A systematic review revealed limited proven associations and association with eye, mainly in terms of DED and choroidal thickness.[22] Vision-threatening occlusive retinal vasculitis may develop in selected patients with SSc.[23] The presence of elevated anti-phospholipid antibody titers may confer increased risk for this vision-threatening complication.[23] SSc itself may affect retinal and choroidal microvasculature, independent of hypertension.[24] Various ocular manifestations are compiled in Table 3.

Ocular investigations

In vivo confocal microscopy of the cornea in patients with SSc demonstrated lower keratocyte cell densities in the anterior stroma and significantly lower sub-basal nerve fiber parameters.[25] Multimodal evaluation in SSc demonstrated reduced anterior chamber depth (ACD), corneal elasticity, and endothelial density before there are any detectable changes in corneal thickness or intraocular pressure (IOP).[26] Nagy *et al*.[27] demonstrated that all pachymetric values, corneal volume, and ACD were significantly lower among SSc patients. Corneas were found to be steeper in these patients.[28]

Decrease in radial peripapillary capillary network and macular microvascular vessel densities and changes in Optic nerve Head (ONH) parameters were found in OCTA.[29,30] However, this difference was not found with

Table 4: Rheumatoid arthritis classification criteria: American College of Rheumatology/European League Against Rheumatism[36]

Ocular Structure	Common Ocular Manifestations
Joint involvement	
One large joint	0
2–10 large joints	1
One to three small joints, ±large joint	3
>10 joints (at least one small joint)	5
Serology (need at least one)	
Negative RF, negative anti-CCP	0
Low positive RF or low positive anti-CCP	2
High positive RF or high positive anti-CCP	3
Acute phase reactants (need at least one)	
Normal CRP, normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
<6 weeks	0
>6 weeks	1

>6/10- definitive RA. CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, RA=rheumatoid arthritis, RF=rheumatoid factor

Table 5: Ocular manifestations of rheumatoid arthritis

Ocular Structure	Common Ocular Manifestations
Cornea and conjunctiva	KCS (most common), filamentary keratitis, peripheral ulcerative keratitis (contact lens cornea), sterile central ulceration/keratolysis, sclerosing keratitis, secondary microbial keratitis
Sclera	Episcleritis, scleritis (diffuse/nodular/scleromalacia perforans/necrotizing with inflammation)
Others	Subcutaneous rheumatoid nodules on eyelid (especially at the outer canthus of upper lids), venous stasis retinopathy, orbital apex syndrome (due to orbital nodules), cranial nerve palsies, geniculocortical blindness, vertebrobasilar insufficiency, Brown syndrome (inflammation of trochlea)

KCS=keratoconjunctivitis sicca

limited scleroderma.[31] OCTA can disclose early ocular vascular abnormalities, which could have a potential role in diagnosis, monitoring, and prognosis stratification in SSc.[32]

Management

Scleroderma is difficult to treat, and the management is directed toward specific organ involvement. D-Penicillamine is useful to reduce interstitial fibrosis. Immunosuppressive drugs are necessary when there is life-threatening renal and pulmonary involvement. Antiplatelet drugs and calcium channel blockers are required to tackle Raynaud's phenomenon. Ocular management involves copious lubricants to treat keratoconjunctivitis sicca (KCS). Periocular skin involvement benefits from systemic colchicine and D-penicillamine.[33] Severe vision-threatening cases of retinopathy and choroidopathy benefit from systemic steroids, chlorambucil, azathioprine, and cyclophosphamide.

Rheumatoid arthritis

RA is a chronic, debilitating, autoimmune CTD affecting primarily the joints with multisystem involvement. Initial inflammation of the microvasculature (postcapillary venules) facilitates recruitment of various inflammatory cells (T and B cells, macrophages) and an array of cytokines (tumor necrosis factor [TNF] and interleukin [IL]-1, IL-6, gamma-interferon [γ-IFN], and matrix metalloproteinases), resulting in chronic synovial inflammation and destruction of the connective tissue. IL-17 has especially been found to play a crucial role in pathogenesis, which gives an opening for new targeted treatment strategies.[34] Similarly, collagen and proteoglycans present in the cornea and sclera get involved.

Patients predominantly present with symmetric involvement of the proximal interphalangeal, metacarpophalangeal, and wrist joints. They usually complain of pain, joint swelling, and morning stiffness (lasting >1 h) along with deformities in chronic cases.[35] Various extra-articular manifestations include subcutaneous nodules (periarticular and pressure areas), pulmonary manifestations (interstitial fibrosis, pleuritis, pneumonitis), cardiac involvement (pericarditis, myocarditis, endocardial and valvular nodules), rheumatoid vasculitis, and hematological and neurological manifestations.

Rheumatoid factor (RF) is usually present in 30% of the RA patients; however, this is nonspecific. Anticitrullated peptide antibodies have enhanced the diagnostic specificity and are also especially useful as a prognostic marker. Recent RA classification criteria given by American College of Rheumatology/European League Against Rheumatism have been compiled in Table 4.[36]

Ocular manifestations

In a large study, DED was found to be the most common ocular manifestation in RA (28%).[37] Other manifestations include episcleritis (3%), scleritis (2%), peripheral ulcerative keratitis (PUK) (1%), and sclerosing keratitis (1%). There is a strong association between the presence of Anti-cyclic citrullinated peptide (anti-CCP) antibodies and ocular manifestations of RA. RA is a major cause of secondary Sjögren's syndrome; hence, DED has to be considered regardless of RA disease activity/severity.

DED can result from meibomian gland dysfunction (MGD) or lacrimal gland or goblet cell dysfunction. Abd-Allah *et al*.[38] found the severity of DED is not correlated with the activity of RA, but with its duration. The cornea in these patients is found to be thinner and steeper compared to healthy individuals.[39] PUK is a serious, vision-threatening complication presenting with peripheral thinning, neovascularization, and epithelial defect. PUK could be a sign of impending systemic vasculitis similar to scleritis.[40,41] Various ocular manifestations in RA are summarized in Table 5.

Ocular investigations

Detailed DED evaluation including Schirmer's test, tear film break-up time, tear osmolarity, and staining with rose bengal, fluorescein, or lissamine green should be done.[40] Noninvasive break-up time using interferometry, topography, confocal microscopy, and aberrometry should also be considered.[42]

Ultrasonography (USG) reveals T-sign or any associated exudative retinal detachment in cases with posterior scleritis. Meibography or LipiView can be used to analyze the meibomian glands and conjunctival impression cytology to analyze the goblet cells.[43]

Table 6: Ocular manifestations of dermatomyositis

Ocular Structure	Common Ocular Manifestations
Eyelids	Heliotrope rash (periorbital edema along with violaceous discoloration of the eyelids)-characteristic, telangiectatic vessels at the eyelid margin,[15] urticarial patches with fine scaling on eyelids,[15] calcified subcutaneous nodules (calcinosis) with secondary ulceration and cellulitis, poikiloderma, plaque-like atrophic patches, vitiligo or hyperpigmentation[50]
Cornea and conjunctiva	Dry eye[51] Conjunctival and episcleral vessel tortuosity[52]
Uvea and retina	Chorioretinopathy with paracentral acute middle maculopathy,[53,54] CRVO,[55,56] Purtscher-like retinopathy,[57] frosted branch angiitis,[58] retinal venous stasis[59]
Neuro-ophthalmic	Diplopia[60] Papillitis[59]
Orbit	Myositis, orbital inflammatory pseudotumor[61]

CRVO=central retinal vein occlusion

Management

Early initiation of the conventional synthetic disease-modifying antirheumatic drug (csDMARD) helps in reducing further disability. Commonly used csDMARDs include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. A short course of systemic glucocorticoid therapy should be considered during initiation or changing treatment. Biologicals such as infliximab, adalimumab, and rituximab should also be considered. TNF inhibitors improve tear production and promptly recover the goblet cells, which could also be used as a biomarker to look for the response to treatment.[44]

Ocular management for dry eye includes lubricating drops, topical cyclosporine, and oral pilocarpine (secretagogues). Autologous serum eye drops can also be considered. Varenicline solution (0.03 mg) was the first approved nasal spray for the treatment of DED.[45] Lifitegrast, a novel T-cell inhibitor (leukocyte function-associated antigen [LFA-1] and intracellular adhesion molecule-1 [ICAM-1]), could also be considered.[46] Punctal occlusion, amniotic membrane transplantation, and tarsorrhaphy can be performed in severe cases, along with medical management.

Systemic steroids with or without immunologic agents are the mainstay treatment for PUK. Additionally, topical medroxyprogesterone and acetylcysteine (collagenase inhibitors) and oral tetracycline (Matrix metalloproteinase Inhibitors (MMP) inhibitors) should be considered. Surgical interventions for tectonic support, such as tissue adhesives, Amniotic Membrane Graft (AMG), and keratoplasty (lamellar/full-thickness patch grafts), should be considered in cases of severe thinning.[47]

Episcleritis is usually self-limiting, and a short course of low potent topical steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) can be considered for symptomatic relief. Scleritis, however, is a painful, vision-threatening condition. Topical therapies are generally ineffective in scleritis, and systemic therapy with NSAIDs or corticosteroids is mandatory. In refractory cases, infliximab and adalimumab are currently recommended.[41] Various other agents such as subconjunctival sirolimus, gevokizumab, rituximab, and tofacitinib are under trial. Tectonic patch graft might be necessary in cases of necrotizing scleritis with severe thinning.

DM and PM

These are idiopathic inflammatory CTDs, characterized by progressive proximal muscle weakness predominantly, due to autoantibodies against the striated muscles. DM is also associated with cutaneous involvement.[48] Pathognomonic cutaneous manifestations include Gottron papules (violaceous papules over dorsal interphalangeal and metacarpophalangeal joints) and heliotrope rash. Other cutaneous findings include Gottron sign (erythematous papules or macules over elbows/knees), facial erythema, poikiloderma, shawl, and V-sign (erythema over the posterior and anterior aspects of the neck, respectively). Various other systems such as cardiac, respiratory, and esophageal are involved.[49] Approximately one-third of patients with DM may be associated with malignancy (paraneoplastic). Ocular involvement other than eyelids is quite rare, and various individual case reports have been described, which are compiled in Table 6.

Similar to other CTDs, DM patients have thinner corneas, and decreased corneal parameters are significantly associated with the occurrence of some extramuscular manifestations.[51]

Investigations

Blood investigations include muscle enzymes such as creatine kinase, lactate dehydrogenase, aspartate and alanine aminotransferases, and aldolase. Autoantibodies such as ANA, antisynthetase antibody (most commonly, myositis-specific antibody), and anti-Jo should be looked for. Muscle biopsy of the weak (involved) muscle is the most accurate way of diagnosis. Electromyography of the affected muscle is a noninvasive method for diagnosis.

It is important to rule out any underlying malignancy; colonoscopy, fecal occult blood, urine analysis, mammography, pap smears, and computed tomography (CT) chest, abdomen, and pelvis should be considered.[48]

Management

The first line of treatment is systemic corticosteroids. They are initially started at high doses till the muscle enzyme levels decline and the strength is regained and later tapered over 9–12 months. Immunosuppressants alleviate the long-term side effects of steroids; hence, they should be initiated along with corticosteroids to decrease the need for it. Azathioprine and methotrexate are the usually preferred agents. In resistant cases, mycophenolate mofetil, calcineurin inhibitors, or intravenous immunoglobulin should be administered. Calcinosis could be managed with calcium channel blockers (diltiazem). Physiotherapy and general sun-protective measures should be advised.[48]

Heritable Connective Tissue Disorders

Heritable disorders of the connective tissue (HDCTs) are syndromes that disrupt connective tissue integrity. They include MFS, EDS, Alport syndrome, SS, OI, and a few other disorders. Many patients with HDCTs have refractive errors, commonly myopia, and often seek refractive surgery.

Marfan syndrome

MFS, first described by Antoine Bernard-Jean Marfan, is an autosomal inherited multisystem CTD caused by a mutation in the *FBN-1* gene on chromosome 15 encoding for fibrillin-1.

Table 7a: Revised Ghent criteria for diagnosing Marfan syndrome and related conditions

Criteria	Diagnosis
Family history of Marfan syndrome absent	
AO (*Z*-score >2) and ectopia lentis[a]	Marfan syndrome
AO (*Z*-score >2) and *FBN1* gene mutation	Marfan syndrome
AO (*Z*-score >2) and systemic score[b] >7[a]	Marfan syndrome
Ectopia lentis and *FBN1* gene mutation with known AO[c]	Marfan syndrome
Ectopia lentis with or without systemic score >7[b] and *FBN1* gene mutation Unknown with AO[d] or no *FBN1* gene mutation	Ectopia lentis syndrome
AO (*Z*-score <2) and systemic score[b] >5, with at least one skeletal feature, without ectopia lentis	MASS
Mitral valve prolapse, AO (*Z*-score <2), and systemic score[b] <5, without ectopia lentis	Mitral valve prolapse syndrome
Family history of Marfan syndrome present	
Ectopia lentis	Marfan syndrome
Systemic score>7[a]	Marfan syndrome
AO (*Z*-score >2) in patients aged >20 years, (*Z*-score >3) in patients aged <20 years[a]	Marfan syndrome

[a]Without discriminating features of Shprintzen–Goldberg syndrome, Loeys–Dietz syndrome, or vascular form of Ehlers–Danlos syndrome and after collagen biochemistry and *TGFBR1* and 2 and *COL3A1* gene testing, if indicated. [b]As described in Table 7b. [c]*FBN1* gene mutation that has been identified in a patient with aortic aneurysm. [d]*FBN1* gene mutation that has not been associated with aortic root aneurysm/dissection. AO=aortic diameter at the sinuses of Valsalva with indicated *Z*-score or aortic root dissection; *FBN1*=fibrillin-1 gene; MASS=mitral valve prolapse, aorta root diameter at the upper limit of normal, striae, and skeletal features similar to Marfan syndrome

Table 7b: Systemic scoring system for the diagnosis of Marfan syndrome

Feature (points)	Maximum possible score
Chest deformity Pectus carinatum deformity (2) Pectus excavatum (1) Chest asymmetry (1)	2
Dural ectasia (2)	2
Facial features[a] (1)	1
Foot deformity Hindfoot deformity (2) Plain pes planus (1)	2
Mitral valve prolapse, all types (1)	1
Myopia >3 D (1)	1
Pneumothorax (2)	2
Protrusio acetabuli (2)	2
Reduced elbow extension (1)	1
Reduced US/LS ratio, [b]increased arm/height, and no severe scoliosis (1)	1
Skin striae (1)	1
Spine deformity Scoliosis (1) Thoracolumbar kyphosis (1)	1
Wrist and thumb deformities Wrist sign (1) Thumb sign (1) Wrist and thumb signs (3)	3

Maximum total score 20. [a]Presence of three of the following features: dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia. [b]US length is the total arm span from each finger. LS is measured from the top of the symphysis pubis to the floor. LS=lower segment, US=upper segment

This protein is involved in the formation of connective tissue in the cardiovascular, musculoskeletal, ophthalmologic, and pulmonary systems.[62]

The Ghent nosology criteria for diagnosis of MFS stressed the importance of a positive genetic finding to differentiate it from other syndromes which may clinically overlap with MFS.[63] Ectopia lentis (EL) was a major criterion based on this nosology, and other ocular features such as abnormally flat cornea, increased axial length, and hypoplastic iris or ciliary body are included as minor criteria.

These criteria were further revised to give more importance to the characteristic clinical features of MFS, aortic root aneurysm, and EL.[64] The revised Ghent's criteria emphasized that in the absence of positive family history, the presence of these two cardinal features is enough to establish a diagnosis of MFS. If either of them is absent, the presence of *FBN-1* mutation or a combination of systemic associations is required [Table 7a]. The revised criteria offered the advantage of making genetic testing not mandatory; however, at the same time, they gave adequate importance to genetic testing. The only ocular feature included besides EL is myopia >3 D. The revised classification also included a systemic scoring, thereby elaborating on the various phenotypic features [Table 7b].

The most devastating feature of MFS is aortic root dissection. However, with the advent of aortic root surgery, the life expectancy of MFS patients has increased.

Ocular manifestations

Ocular features may be the initial presentation even before the cardiovascular manifestations. The most prominent features are superotemporal subluxation of the crystalline lens, myopia, glaucoma, cataract, keratoconus, and retinal detachment.[65]

EL can be present in 50% of eyes and may develop both in childhood as well as in adults. (Fig 1) Studies in different age groups have reported varied frequencies in children; however, there might be a progression of EL after childhood, and most dislocations develop before 18 years of age.[66,67]

Since increased axial length (altered fibrillin allows for increased stretching of sclera) induces myopia and flattened

Table 8: Ocular manifestations of Ehler–Danlos syndrome

Ocular Structure	Common Ocular Manifestations
Eyelid and conjunctival abnormalities[78]	Epicanthal folds, telecanthus, floppy eyelids, conjunctivochalasis[79]
Strabismus	
Cornea[80]	Thin cornea, keratoconus, keratoglobus, damage on minor trauma, brittle cornea,[81] microcornea
Globe perforation[82]	Blue sclera, abnormal scleral fragility
Xerophthalmia[77]	Higher OSDI scores, lower Schirmer's and TBUT values
Pathologic myopia[77]	
Lens opacities[77]	Minor lens opacities
Retinal detachment[83]	

OSDI=ocular surface disease index, TBUT=tear break-up time

cornea decreases this effect, the refractive error depends on their net effect. However, myopia >3 D tends to be stable over time in adult patients.[68,69]

Cataracts develop at an earlier age than in the general population.[63] The risk of retinal detachment due to increased axial length is between 4% and 15%.[67] Due to the changes in elastic fibers, there is also a higher risk of keratoconus reported in a few studies.[69]

Management

Correction of refractive error with spectacles may suffice in mild cases. If the subluxated lens bisects the pupil, aphakic correction may provide better vision by overcoming lenticular astigmatism. In a few patients, contact lenses provide an acceptable alternative.[70]

Lens extraction is indicated in patients unable to achieve good corrected vision and in those with impending or complete dislocation, secondary glaucoma, or cataract. All efforts should be made to preserve the capsular bag.[71] In cases where the zonular weakness is not extensive, the capsular bag can be preserved and low-flow phacoemulsification is feasible. In some cases, surgery can be performed with the aid of retractors, enabling intralenticular lens aspiration and "in-the-bag fixation of IOL" with appropriate capsular fixation devices. If the lens subluxation is severe, the capsular bag may have to be sacrificed by performing lensectomy and vitrectomy. The IOL can then be fixated to the iris or scleral fixated (sutured and nonsutured).[72] The creation of a well-sized and centered capsulorrhexis is critical and can be achieved manually or with the aid of femtosecond laser-assisted cataract surgery (FLACS).[73] Postoperative complications include IOL decentration, cystoid macular edema, and the risk of retinal detachment.

Management of other complications

Corneal refractive surgery is not recommended for most patients with MFS as the cornea is flat in these cases. Retinal detachment surgery in MFS is challenging because of a thin sclera and the possibility of multiple breaks. Preoperative retinal screening before lens surgery is critical. Retinal screening in the fellow eye should also be done. Patients should be advised to seek consultation in case of flashes, floaters, or loss of visual acuity.[74]

Ehler–Danlos syndrome

The hallmark of EDS is defective connective tissue synthesis, manifesting principally as skin hyperelasticity, joint hypermobility, easy bruising, and tissue fragility. The genetic mutations affect type I, III, and V collagen and are commonly inherited in an autosomal dominant manner. The overall prevalence varies between 1 in 2500 and 1 in 5000.[75] There are at least 13 subtypes identified based on their varying clinical presentations: classical, classical-like, cardiac-valvular, vascular, hypermobile, arthrochalasia, dermatosparaxis, kyphoscoliotic, spondylodysplastic, musculocontractural, myopathic, periodontal, and brittle cornea syndrome (BCS).[76] Classical, kyphoscoliotic, and BCS subtypes are associated with significant ophthalmologic findings (i.e., globe rupture). The other subtypes present with minor ocular presentations.

Ocular manifestations

Ophthalmic features are commonly minor, though not infrequent in EDS. A prospective, cross-sectional study of 44 eyes reported that the most consistent association in EDS included xerophthalmia, steeper corneas, pathologic myopia, vitreous abnormalities, and minor lens opacities.[77] Various ocular manifestations are summarized in Table 8.

Importance in ophthalmic surgery

A large case series of EDS reported that 24% of patients required some form of ophthalmic surgery, of which 45.5% had at least one complication, which is an unusually high rate compared to the general population.[84] The complications included regression, dry eye, and corneal ectasia following refractive surgery. After cataract surgery, the reported complications included wound leak, dry eye, retinal detachment, and pigment dispersion. Most patients had undergone primary surgery before their diagnosis of EDS. This highlighted the importance of preoperative screening to look for EDS before surgery, especially refractive surgery.[85]

Refractive errors prompt patients with EDS to seek refractive surgery; however, it is considered as a contraindication to refractive surgery, given the collagen abnormality and reported ectasias after surgery. For kyphoscoliotic EDS and BCS, refractive surgery is not advocated due to corneal thinning and ocular fragility. Corneal perforation has also been reported following crosslinking in these eyes. Those with normal corneal tomography, central corneal thickness (CCT) >500 μm, and no dry eye may receive refractive surgery with appropriate counseling regarding the postoperative complications.[86]

Alport syndrome

Alport syndrome is a heterogeneous disorder that results from mutations in collagen IV genes, thereby involving the glomerular, cochlear, and ocular basement membranes.[87] It was described initially in 1927 as a syndrome of hereditary nephritis and deafness.[88] Ocular features were subsequently described in 1956.[89] It affects one in 5000 newborns, and males are more likely to be affected than females.

Diagnosis is based on genetic testing, the presence of typical clinical features (renal failure, hearing loss, lenticonus), or renal biopsy. The individuals may present with hematuria, proteinuria, and eventually progress to renal failure. Early diagnosis is important as it facilitates close observation of

Table 9: Ocular manifestations and their management in Alport syndrome

	Abnormality	Description	Symptoms	Treatment
Common presenting features	Anterior lenticonus	Central portion of the lens protrudes forward into the anterior chamber Mostly bilateral	Difficulty in focusing	Corrective spectacles/contact lenses/IOL surgery
	Dot fleck retinopathy	Whitish or yellowish flecks in the central retina sparing the fovea OR Peripheral coalescent flecks	Do not affect vision	No treatment
	Retinal thinning[94]	Thinning temporal macular "staircase pattern" on OCT	-do- Associated with early-onset renal failure	-do-
Other reported abnormalities	Posterior lenticonus	Cone shaped protrusion/bowing on posterior lens surface	Astigmatism	Refractive correction/ lens surgery
	Subcapsular cataracts			Surgery
	Posterior polymorphous dystrophy[95]	Visible on slit-lamp/specular microscopy- thickened DM, endothelial vesicles in isolation or band like clusters. typically, bilateral	Commonly asymptomatic. rarely corneal edema	May require posterior lamellar keratoplasty
	Recurrent corneal erosions[95]	Commonly bilateral	Episodes of pain, photophobia, watering	Lubricants, patching, avoidance of triggers
	Keratoconus[96]			Refractive correction, crosslinking for progressive disease
	Giant macular hole		Reduced vision	Surgery
	Bull's eye maculopathy[94]	Choroidal thinning		
	Macular retinoschisis[94]	Impairment of basement membrane of RPE- Bruch's membrane causes passage of fluid into the retina		
	Loss of choriocapillaris[121]	Evident on swept-source OCT angiography		

DM=Descemet's membrane; IOL=intraocular lens; OCT=optical coherence tomography; RPE=retinal pigment epithelium

the affected individuals and relatives, thereby enabling early initiation of appropriate treatment.

Collagen IV is found in various basement membranes of the eye, including cornea, lens capsule, and retina. The genes mentioned above code for collagen IV α5, α4, and α3 chains. Mutations occur in the *COL4A3*, *COL4A4*, and *COL4A5* variants of the gene. The *COL4A5* gene is located on the X chromosome, while the other two variants are located on chromosome 2.[90] Hence, the disease can be inherited by the following mechanisms: X-linked, autosomal recessive, and autosomal dominant, resulting in the variants mentioned below:

1. X-linked form of Alport syndrome (XLAS)- 80%
2. Autosomal recessive Alport syndrome (ARAS)- 15%
3. Autosomal dominant Alport syndrome (ADAS)- rare

Ocular manifestations

Identifying the cardinal ocular features in Alport syndrome can help in diagnosis, to detect treatable complications such as a macular hole, and to identify the risk of early-onset renal failure. Lenticonus is pathognomonic of Alport syndrome, occurring in one-fourth of these patients. It may result in progressive lenticular myopia and significant astigmatism. It is evident clinically as an "oil droplet" on direct ophthalmoscopy. Anterior lenticonus is absent at birth, but usually develops by the second or third decade of life.[91] Examination on slit lamp reveals a bulge in the anterior lens surface. The lenticonus may be easily missed on an undilated examination. (Fig 2a and b) Small ruptures in the lens capsule can lead to cataract formation.

A recent cross-sectional study described the importance of temporal retinal thinning in this disorder and indicated that the presence of thinning as evidenced on optical coherence tomography (OCT) distinguished Alport syndrome from the more benign thin membrane nephropathy. It is also indicative of a clinically worse disease.[92]

The macular holes in Alport syndrome differ from idiopathic macular holes as they have an earlier age of onset and are larger.[93] Other ocular manifestations are summarized in Table 9.

Ocular investigations

The investigative modalities for ocular features include slit-lamp biomicroscopy, corneal topography, endothelial microscope analysis, OCT, and fundus photography.

Management

Management of refractive errors due to the abnormal lens curvature includes corrective glasses. The threats to visual acuity include anterior lenticonus and retinal holes and require surgical intervention.

The challenges of performing phacoemulsification surgery in anterior lenticonus include accurate IOL power calculation in patients with irregular astigmatism and a fragile anterior capsule, leading to a difficult capsulorrhexis. The use of trypan blue dye has been advocated to increase capsular stiffness. Moreover, FLACS, intraoperative aberrometry, and toric IOLs have been described as useful in these eyes.[97]

Table 10: Ocular manifestations of Stickler syndrome

Ocular Structure	Common Ocular Manifestations
Refractive	Congenital nonprogressive high myopia[100]
Retina[101]	Retinal detachment Foveal hypoplasia Multiple retinal tears Giant retinal tear
Vitreous	Vitreous anomalies Pigment dispersion
Glaucoma	Infantile/secondary[102]
Cataract[103]	Nuclear sclerotic Lamellar Quadrantic Cortical

Table 11: Ocular manifestations of osteogenesis imperfecta

Ocular Structure	Common Ocular Manifestations
Cornea	Reduced thickness Keratoconus[110] Corneal rupture due to minor trauma[111] Microcornea Bowman membrane agenesis
Sclera	Low ocular rigidity Blue sclera[111]
Glaucoma	Congenital glaucoma Primary open-angle glaucoma[107]
Lens	Ectopia lentis
Vitreous/retina	Subhyaloid hemorrhage Retinal detachment[112] (fragile sclera) Optic atrophy
Refractive errors	Myopia due to altered corneal and scleral biomechanics[107]

Ocular manifestations of Alport syndrome can help in the right diagnosis of this multisystemic disease. A nephrologist consultation is mandatory to monitor renal abnormalities. The patient's close relatives should also be examined, and genetic counseling should be offered.

Stickler syndrome

SS is a heritable CTD caused by mutations in the *COL2A1* and *COL11A1* genes. It was initially described by Stickler *et al*.[98] in 1965 as a hereditary progressive arthro-ophthalmopathy. The estimated incidence is between 1 in 7000 and 9000. Though four subtypes have been described, STL1 and STL2 are the most common and are autosomal dominant. The mutations affect collagen I and II. Clinical features include ocular, auditory (hearing loss), craniofacial (micrognathia, cleft palate), and articular (early-onset arthritis and joint mobility) manifestations.

Ocular manifestations

The overall prevalence of childhood myopia among SS is reported to be 86%, with the mean refractive error ranging between −8.70 and −14.50 D. The risk of developing a retinal detachment varies between 14% and 65%, and it usually has an earlier onset (first two decades of life) and bilateral involvement. Presenile cataract (30%) and glaucoma (11%) are seen less frequently.[99] Various ocular manifestations of SS have been summarized in Table 10.

Retinal detachment can be potentially devastating to the visual acuity. Prophylactic treatment using laser or cryotherapy reduces the risk of developing a detachment.[104] A recent case series concluded that cryopexy combined with scleral buckling significantly reduced the risk of fellow eye Retinal Detachment (RD) in SS patients who had already lost one eye to RD.[105]

Osteogenesis imperfecta

OI is a heritable CTD caused by mutations in the *COL1A1* and *COL1A2* genes affecting the production of type I collagen, which is found in cornea and lens.[106] It is commonly inherited as an autosomal dominant disorder with an incidence of around 1 in 15,000 births. It is divided into subtypes from Type I to Type VII based on clinical and radiographic findings. Common manifestations include blue sclera, hearing loss, bone deformities and fractures, short stature, dental anomalies, and cardiovascular disorders.[107]

Ocular manifestations

The literature on ocular features in OI is mostly limited to case reports. However, few case series have documented the common ocular manifestations.[106,108,109] The ocular features in OI have been summarized in Table 11.

A recent systematic review suggested that the most significant association is globe rupture following minor trauma and complications of routine ophthalmic surgeries.[107]

Reduced CCT, corneal hysteresis (CH), and Corneal resistance factor (CRF) lead to underestimation of IOP.[108] This, coupled with the altered structure of the trabecular meshwork, contributes to the development of glaucoma.

Blue sclera is a common finding that occurs due to reduced scleral thickness and increased visibility of underlying choroid. In patients with corneal or scleral rupture following minor trauma, EDS, OI, and BCS should be excluded.[111] Performing a patch graft in these eyes could be challenging due to thinned-out host tissue. It has been recommended that patients with OI should wear protective eyeglasses to shield them from accidental trauma.

Ophthalmic surgeries that might result in complications such as scleral perforation include strabismus surgery, trabeculectomy, and scleral buckling. Hence, any ophthalmic surgery in a patient with OI should be approached cautiously.[107]

Loeys–Dietz Syndrome

Loeys–Dietz syndrome (LDS) is an autosomal dominant CTD caused by mutations in the genes coding for components of the transforming growth factor-beta (TGF-β) signal pathway. The estimated prevalence is <1 in 100,000.[113] There is an overlap of clinical features with MFS. The overlapping features are vascular aneurysms, scoliosis, pes planus, anterior chest deformity, spontaneous pneumothorax, and craniofacial anomalies. However, the distinguishing features of LDS include hypertelorism, bifid uvula, cleft palate, and aortic and arterial tortuosity. The cardiovascular malformations are more severe, with an increased propensity of aneurysm dissection.[114]

Ocular manifestations include myopia blue sclera, RD, cataracts, retinal tortuosity, and strabismus. Characteristically, there is no association with EL, the myopia is less severe, and the association with blue sclera is present. Given the more aggressive aortic root dissections, these patients need careful monitoring and distinction from MFS.

Epidermolysis bullosa

Epidermolysis bullosa (EB) can be inherited in an Autosomal dominant (AD) or Autosomal Recessive (AR) manner with mutations involving keratin, laminin, or collagen. It is characterized by fragile epithelium that results in blisters and erosions with minor trauma. There are four main types: EB simplex, dystrophic EB, junctional EB, and Kindler syndrome.[115]

Ocular features include corneal erosions, conjunctival injection, bullous keratopathy, DED and its sequelae like pannus, scarring, symblepharon, and ectropion.[116]

Wagner syndrome

Wagner syndrome is a vitreoretinopathy caused by an autosomally dominant inherited mutation of the *VCAN* gene on chromosome 5q that codes for an ECM responsible for the integrity of the vitreous. It is a rare disorder with an estimated prevalence of 1 in 1,000,000.[117] Ophthalmic features include an optically empty vitreous with avascular strands, membranes, or veils. The other features are myopia, chorioretinal atrophy causing night blindness, retinal detachment due to peripheral vitreoretinal adhesions, and a presenile cataract. Detachment can be rhegmatogenous or tractional and has an earlier onset. However, there are no associated systemic features, which distinguish it from SS.[118]

These patients require periodic screening by a retina specialist. It is also important to screen family members to recognize asymptomatic RD or those at risk for RD.

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum (PXE) is caused by an autosomal recessive inherited mutation in the *ABCC6* gene on chromosome 6 that affects cell membrane transport and buildup of abnormal calcification in the elastic tissues of the skin, eyes, and blood vessels. The prevalence is between 1 in 25,000 and 100,000.[119] Clinical features include yellow skin plaques on the neck and flexural areas, wrinkled loose skin, atherosclerotic cardiovascular disease, angioid streaks, and gastrointestinal bleed in a few patients.

The most common ocular feature is angioid streaks (85%), followed by optic disk drusen, chorioretinal atrophy, and macular degeneration with choroidal neovascular membrane (CNVM). Angioid streaks appear as jagged lines radiating from the optic disk and are crack-like dehiscences in the Bruch's membrane. They are mostly asymptomatic. Macular CNVM can lead to irreversible visual loss. Periodic follow-up is recommended to look for and treat CNVM.[120]

Refractive Surgery in Connective Tissue Disorders

A recent review by Moshirfar *et al*.[86] suggested that since myopia is more prevalent in patients with CTD and the presentation between patients is quite diverse, it is not appropriate to consider them as a blanket contraindication to refractive surgery. Certain subtypes of CTD may be amenable to surgery.[86] Chen *et al*. suggested that among the autoimmune disorders, except for primary Sjögren's syndrome, other patients who are well controlled with no recent flare-up of the disease process and not on multidrug regimens may undergo refractive surgery with appropriate counseling regarding postoperative recovery and complications.[122]

A review of literature was conducted by searching the following databases: PubMed (United States National Library of Medicine), Embase (Reed Elsevier Properties SA), Web of Science (Thomson Reuters), and Scopus (Elsevier BV). Only peer-reviewed scientific reports were included. Articles in languages other than English were included if the abstract was available in English or if the translated version of the article was available. The last electronic search was conducted on 25 Jan 2022. The literature search used various combinations of the following keywords: ONE from connective tissue disorders (CTDs), collagen vascular disorders (CVDs), rheumatoid arthritis, systemic lupus, Marfan, Ehler Danlos, heritable, autoimmune and ONE from ocular features, ophthalmic manifestations. Prospective studies, randomized controlled trials (RCTs), relevant retrospective studies, and case reports were included. Full text and reference lists of all studies were screened to ensure that any relevant study was not excluded.

Conclusion

To conclude, CVDs (both autoimmune and heritable) frequently present with various ophthalmic manifestations, with specific disorders having different common presentations. A comprehensive ocular evaluation by the ophthalmologist enables early detection of disease, appropriate referral to other subspecialities, initiation of immunomodulatory therapy, limitation of end-organ damage involving other systems, arresting the progression of disease, and management of the sight-threatening ocular complications.

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Conflicts of interest

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