Cystic fibrosis (CF) is the most common lethal autosomal disorder in Caucasian populations. It is characterised by a variable degree of pulmonary infections, pancreatic enzyme insufficiency and premature death. Ocular complications in CF range from abnormal tear volume to impaired dark adaptation. With improvements in CF life expectancy, ocular complications are of greater relevance to the optometrist. This article provides an overview of the ocular complications associated with CF.

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**Learning objectives**

To obtain relevant history and symptoms for patients presenting with CF (Group 1.1.1)

To recognise the manifestations of ocular disease in CF (Group 6.1.13)

**Learning objectives**

Understand the implications of the manifestations of ocular disease in CF (Group 8.1.5)

**About the authors**

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Cystic fibrosis (CF) is the most common lethal autosomal recessive disorder (see Figure 1) in Caucasian populations, currently affecting over 9,000 people in the UK alone. It results from the defective functioning of an epithelial membrane protein known as Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). CFTR acts as a chloride ion channel and is found in the epithelial cells of many organs, including the pancreas, lung, gastrointestinal tract, kidneys and the eyes. Chloride transport is the driving force for maintaining the correct balance of electrolytes and fluids within many different organs. Without proper chloride transport via CFTR, organs such as the lungs and the pancreas can become damaged with thick, viscous secretions. There is a wide spectrum of genetic mutations in CF; some are very mild, causing only a slight decrease in normal chloride transport, while other mutations, which result in complete absence of CFTR from the epithelium, cause a particularly severe form of the disease.

As CFTR is found in multiple organs throughout the body, the effects of CF are far-reaching, leading to multi-organ and system dysfunction. The lungs are most critically affected in CF, with progressive lung disease and secondary pulmonary complications accounting for over 90% of all deaths in CF. Vitamin deficiencies (A, D, E and K) and CF-related diabetes (CFRD) are common secondary complications of CF. Vitamin deficiency in CF is the result of fat maldigestion due to damaged pancreatic cells which are not releasing the necessary pancreatic enzymes. Along with poor growth and increased mortality, clinical consequences of vitamin A deficiency (VAD) also include impaired dark adaptation, in addition to conjunctival and corneal xerosis. CFRD affects 45-50% of CF patients over the age of 30. While it has features common to both Type 1 and Type 2 diabetes which optometrists are more familiar with, it is classified as a distinctly different disease. Although the pathogenesis of CFRD is not completely understood, increasing evidence suggests that insulin-deficiency, exacerbated by peripheral and liver insulin resistance, is the primary cause. Insulin-deficiency results from β-cell apoptosis in the pancreas in conjunction with defective insulin secretion by the remaining β-cells. CFRD is often particularly difficult to control as insulin resistance is aggravated by respiratory infection and corticosteroid treatment, and therefore fluctuates over time.

Due to the wide-reaching health complications associated with CF, many different forms of treatment are required to adequately manage the disease. Treatment regimes include physiotherapy, nutritional supplementation, pancreatic enzyme replacement and pharmaceutical treatment to control chronic respiratory infection and inflammation. Gradual progress is being made in emerging protein repair and gene therapy, both of which aim to develop therapeutic strategies which target specific CFTR mutations, in order to improve or restore CFTR function. Although further development is needed before these emerging therapies become a viable option, it is hoped that they may continue to change the outlook for CF patients in the future. Until then, lung transplantation remains the only definitive treatment option for patients with progressive respiratory failure.

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Figure 1 Autosomal recessive inheritance of CF

To date, CFTR has been found in human corneal and conjunctival epithelium, corneal endothelium and retinal pigment epithelium, where it has been shown to play an active part in chloride ion secretion across cell membranes. Active transport of chloride ions is known to provide the driving force for subsequent osmotically-driven fluid secretion. Within the eye, chloride ion transport is involved in: basal tear production, the preservation of corneal transparency via the endothelial pump, and subretinal space volume regulation. The absence of CFTR from the eye leads to the following complications:
The Tear Film

Ocular complications in CF

The Tear Film

Classically, the tear film is reported to consist of three layers: an outer lipid layer, a middle aqueous layer and an inner mucous layer. The production and turnover of the pre-ocular tear film is essential in providing tissues with nourishment and lubrication, and for maintaining ocular health. The aqueous layer, which is composed of proteins, electrolytes, enzymes, metabolites and water, is principally produced by the lacrimal gland and accessory lacrimal glands, although recent evidence suggests a small proportion of electrolytes and water are secreted by the cornea and conjunctiva, via ion channels, including CFTR (see Figure 2).

Several clinical studies have reported an increase in signs of dry eye in CF patients compared to controls. Abnormally low tear secretion, as assessed by Schirmer’s test, has been observed in 29-81% of CF patients in a number of separate studies. Findings of decreased tear break-up time in CF subjects compared to healthy controls indicates poor tear quality in CF. Additionally, reports of corneal fluorescein staining in 60-82% of CF patients, along with increased expression of inflammatory markers adds further evidence to the link between dry eye and CF.

With the localisation of CFTR to the corneal and conjunctival epithelium, and its known contribution to basal tear secretion, it is thought that dry eye could be a primary manifestation of CF. However, as increased vitamin A deficiency (VAD) has been correlated with reduced TBUT in CF, it is possible that this secondary complication also adds to the clinical observation of dry eye in CF. In light of these findings, practitioners should be aware of the increased likelihood of CF patients suffering from signs and symptoms of dry eye. It may, therefore, be appropriate to ask CF patients tailored questions relating to dry eye when taking their history and symptoms.

Xerophthalmia

As discussed, vitamin A deficiency (VAD), is a common secondary complication of CF. Xerophthalmia refers to the entire clinical spectrum of ocular manifestations caused by VAD. It is the leading cause of childhood blindness worldwide, but is uncommon in developed countries. The primary manifestation of xerophthalmia is extreme dryness of the conjunctiva and cornea due to a failure of the secretory activity of the mucin-secreting goblet cells of the conjunctiva. Xerophthalmia also encompasses night blindness, conjunctival and corneal xerosis, Bitot spots and corneal ulceration. Early descriptions of CF found a high prevalence of xerophthalmia. However, with recent improvements in supplementation for CF patients, reports of xerophthalmia have almost been eliminated.

Although cases of xerophthalmia in patients with CF are rare, it highlights the importance of considering VAD in those patients who present with ocular complications. It also demonstrates the importance of regular eye examinations, with any patients showing signs of xerophthalmia being referred appropriately for further examination by their CF consultant to confirm clinical vitamin A deficiency before treatment is commenced.

Corneal morphology and integrity

CFTR expression has previously been localised to the apical membrane of the corneal endothelium, where it is known to facilitate fluid efflux in order to maintain corneal transparency. It is, therefore, reasonable to predict that loss of CFTR function in CF could cause an increase in corneal thickness and a decrease in transparency, unless other Cl- channels provide a certain level of compensation.

Only two studies have investigated corneal thickness in CF, with equivocal outcomes. The most recent study, which used the Oculus...
Pentacam, found no significant difference in either central or peripheral corneal thickness in CF subjects compared to healthy controls. Conversely, a preceding study found corneal thickness to be increased in CF, as determined using contact video specular microscopy. Reduced endothelial cell area, elevated endothelial cell density and permeability, as well as increased relative endothelial pump rate were also observed. These morphological differences suggest that the corneal endothelium actively compensates for impaired Cl− transport via CFTR.

Cataracts
Steroid use, a known risk factor for the development of posterior subcapsular cataracts, is commonplace in CF for managing pulmonary inflammation. It is, therefore, unsurprising that posterior subcapsular cataracts have been observed in CF patients receiving steroid treatment. Antioxidants, including vitamins A, C and E are associated with reduced cataract formation. Digestive insufficiency, secondary to pancreatic insufficiency in CF, causes vitamin deficiency and lowers antioxidant availability. Therefore, a higher incidence of cataract may be expected. Crystalline lens transparency can be significantly reduced in CF patients, with the greatest reduction in transparency seen in those with more severe digestive insufficiency.

The role of oxidative stress in the aetiology of cataract formation has been clearly established, and persistent pulmonary infection in CF is known to increase levels of oxidative stress. This, combined with decreased levels of antioxidants, which usually protect the crystalline lens, could contribute to the development of decreased lens transparency in CF. While diabetes is also strongly associated with the development of cataracts, the effect of CFRD on the lens in CF is yet to be determined.

The retina and diabetic retinopathy
Due to the increased mortality of CF patients with CFRD, life expectancy was previously considered to be too short for the development of diabetic complications, including diabetic retinopathy (DR). However, greater longevity of CF patients has been accompanied by increasing reports of microvascular complications. DR is predominantly seen in patients with duration of CFRD of at least 10 years (see Figure 3). Interestingly, the prevalence of DR in CFRD has been found to be significantly lower compared to age and disease duration matched Type 1 diabetic subjects.

Several factors may account for the lower prevalence of DR in CFRD compared to other forms of diabetes:
- Maintenance of a variable degree of insulin secretion, which may have a protective effect on cell survival
- Dislipoproteinemia appears to play a role in the pathogenesis of diabetic retinopathy, but cholesterol levels are low in CF due to digestive insufficiency
- Hypertension, a known risk factor in the development of DR, is generally mild in CF
- Tendency towards more stringent diabetic control in CF due to regular outpatient appointments

Retinal vascular abnormalities have previously been reported in CF patients, with retinal haemorrhages, retinal vein tortuosity and engorgement, noted only in those patients with moderate to severe pulmonary disease, and often showing resolution with improvement of respiratory function. Similar retinal vascular findings have been reported in patients with chronic pulmonary insufficiency and carbon dioxide retention from other causes.

The macula
Although supplementation of the major
vitamins is common practice in patients with CF, this does not typically include carotenoids, resulting in low carotenoid concentrations.76,77 Carotenoids, including lutein and zeaxanthin, are antioxidant micronutrients,78 and are particularly important in CF patients who, due to persistent pulmonary infection, are susceptible to higher levels of oxidative stress.82

Lutein and zeaxanthin accumulate at the macula and are believed to play a major part in protecting the retina from free-radicals, by absorbing the phototoxic effects of short-wavelength light and through their action as free radical scavenging antioxidants.79,80 Low plasma concentration of lutein and zeaxanthin is associated with an increased incidence of macular degeneration.81 Lutein and zeaxanthin are responsible for macular pigment and account for the yellow colouration of the macula due to their absorption of short wavelength light.82 Patients with macular degeneration have been reported to have significantly lower concentrations of macular pigment, compared to those with normal vision.83

As CF patients are known to have low concentrations of carotenoids, combined with increased levels of oxidative stress, it could be predicted that their macular carotenoid levels would be reduced, making CF patients more susceptible to premature age-related macular changes. Indeed, the literature demonstrates that CF patients have significantly lower serum concentrations of lutein and zeaxanthin compared to controls, correlated with lower retinal macular pigment density concentrations;84 these findings may explain the observation of premature drusen in young CF patients (aged 20 to 25 years) in a recent study,85 and highlight the importance of a thorough macular examination in all CF patients seen in practice.

**Visual function**
To date, a large-scale assessment of visual acuity, ametropia and binocular status in CF patients has not been undertaken. However, one small-scale study reported that VA, binocular status and refractive error in CF adults was comparable to matched controls,82 suggesting normal emmetropisation83 and orthophorisation occur in CF.86 However, low birth weight and prematurity are associated with CF,87 which are both linked with a greater incidence of ametropia, strabismus and amblyopia,88 highlighting the importance of regular eye examinations in children with CF.

Contrast sensitivity, colour vision and dark adaptation have all been found to be impaired in CF patients.7,25,89-92 CFTR has been localised to the RPE where it is believed to contribute to Cl− transport.93 Unless other Cl− channels compensate for this fundamental CFTR dysfunction, normal photoreceptor function may be affected by altered inter-photoreceptor matrix composition. With the RPE’s involvement in several functions, vital for the maintenance of normal visual function, including transport of nutrients to photoreceptors and retinal regeneration,94 it seems clear that RPE impairment could result in photoreceptor degradation and reduced visual function.

It is well established that vitamin A is essential for normal photoreceptor function,95 therefore it is unsurprising that VAD in CF has been identified as the cause of this defect.104,105 It is reasonable to predict that visual function would be similarly affected by CFRD, and may account for some of the reductions in visual function seen in previous studies.

**Conclusion**
It is apparent that numerous ocular complications exist in CF (see Figure 4). It is, therefore, important that CF patients are advised to have regular eye examinations, and those with CFRD to attend annual retinal screening. Eye care practitioners must be aware of the breadth of ocular complications associated with CF in order to provide tailored and appropriate care to CF patients. Further improvements in life expectancy in CF are likely to be coupled with increases in the frequency of DR, cataract and potentially, AMD. Given the risk of significant visual loss associated with DR and AMD, CF patients should be educated to take appropriate action, in the event of any visual problems.