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REVIEW

# Optical quality of the diabetic eye: a review

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**Abstract**

**Diabetes mellitus is a metabolic disorder characterized by the presence of chronic hyperglycaemia. Several structural, morphological, and physiological changes in each of ocular component have been described in detail during the past decades. Due to these abnormalities, the diabetic patient undergoes a degradation of the retinal image by an increase of higher ocular aberrations and ocular scattering coming from mainly tear film, cornea, and crystalline lens. This review aims to provide an overview of current knowledge about the effects of diabetes mellitus in these optical phenomena and its consequence on the visual quality of the diabetic patient.**
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## Diabetes mellitus: an overview of the problem

### *Definition and classification*

Diabetes mellitus (DM) is a clinical syndrome characterized by a disorder in the metabolism of carbohydrates, caused by a defect in insulin secretion, insulin action, or both. This disease is determined by a chronic hyperglycaemia associated with long-term damage of different organs, particularly the eyes, kidneys, nerves, heart, and blood vessels.[1,2] In all cases, the development of the disease is attributed to a combination of predisposing genetic factors and a number of environmental factors that may act as triggers.

The most widely accepted classification divides DM in type 1, type 2, and gestational.

Type 1 DM, is also known as insulin-dependent or juvenile-onset DM (IDDM). This form of the disease includes only 5–10% of those patients with DM[2] and can be divided further into type 1A DM, due to a cellular-mediated autoimmune selective destruction of pancreatic $\beta$-cells mediated by activated T lymphocytes (known as latent autoimmune DM of adult (LADA) or type 1.5), and idiopathic DM, or type 1B, with no evidence of autoimmunity. Both subtypes are treated with insulin and have a tendency to ketoacidosis.[1–3]

The type 2 DM or noninsulin-dependent DM (NIDDM) affects about 90–95% of people with DM.[2] This type of DM may occur in genetically susceptible individuals with impaired insulin secretion or with insulin resistance and bad regulation of glucose production in the liver. Insulin resistance can be improved by weight loss and/or pharmacological treatment; although these patients do not develop ketoacidosis, they may suffer hyperglycaemic coma.[1–3]

Gestational DM is characterized by a certain degree of insulin resistance that could be due to a combination of maternal adiposity and desensitizing effects of several substances produced by the placenta. Most of the cases usually resolve with childbirth.[4]

There are other causes that can lead to the development of DM, such as genetic $\beta$-cell function defects; several forms of this type of DM are also known as maturity-onset DM of the young, characterized by the onset of hyperglycaemia before the age of 25 and autosomal-dominant inheritance, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drug-induced DM, infections, antibodies against insulin receptors, and specific diseases such as Down syndrome, Turner syndrome, Klinefelter syndrome, Wolfram syndrome, among others.[1–3]

### *Epidemiology and risk factors*

Worldwide, DM is a disease with a great health-care impact due to its increased prevalence and high mortality rate. A prospective study shows that in developed countries there will be an 11% increase in the adult population, a 27% increase in the prevalence of adult DM, and a 42% increase in the number of people with DM; while for developing countries there will be an

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82% increase in the adult population, a 48% increase in the prevalence of adult DM, and a 170% increase in the number of people with DM, between the years 1995 and 2025.[5]

According to the World Health Organization (WHO), by 2030 it may reach 366 million of people with DM in the world;[6] however, the International Diabetes Federation states that the prevalence of DM will be 9.9% and the number of people with DM will rise to 552 million people by 2030.[7]

Most people with DM are between 45 and 64 years of age in the developing countries and >64 years of age in the developed countries.[6] The prevalence of DM is similar in men and women but is slightly higher in men aged <60 years and women aged >60 years.[6]

Currently, type 1 DM cannot be prevented; although having a family member with type 1 DM, pancreas disease, exposure to some viral infections, and increased mother's age during pregnancy could contribute to its development.

Type 2 DM presents a pattern of family heritage, but the risk of developing this form of DM increases with age, ethnicity, obesity, lack of physical activity,[1,2] and polycystic ovary syndrome.[8]

### *Diagnosis of DM*

DM can be diagnosed according to the criteria described in Table 1.

In cases of gestational DM, the criteria is fasting plasma glucose ≥92 mg/dl after an oral glucose load of 75 g after 1 h ≥180 mg/dl and after 2 h ≥155 mg/dl[2].

### *Ocular complications of DM*

DM is associated with the development of several complications within the eye, such as cataract[9–11] (2–4 times more than healthy people), glaucoma,[12] keratopathy,[13] refractive changes, oculomotor nerve paralysis, chronic inflammation of the eyelids, or diabetic retinopathy (DR).[14,15]

### *Impact of DM in the refractive power of the eye*

From an optical perspective, the structures directly involved in the overall refractive power of the eye that might deteriorate its optical quality are the tear film, the cornea, the crystalline lens, and the vitreous. All of them are susceptible to change as a consequence of DM.

### *Tear film*

Due to the great impact of DM in the ocular surface and the fact that maintaining a normal ocular surface is essential for retinal image quality, changes in tear film with DM have been studied in detail over the recent decades.[16–26]

Some ocular manifestations of DM are associated with lachrymal gland dysfunction and have been related to dry eye. Several clinical studies have demonstrated that people with DM are more vulnerable to dry eye than healthy subjects.[16–19]

In people with DM, the most frequent and measurable alterations of the tear film function are reduced tear secretion,[16–22] tear film instability (tear film break-up time (TBUT)),[17,18,20,21] higher degree of conjunctival squamous metaplasia,[16–18,21] lower globet cell density,[17,21] and reduced corneal sensitivity.[17,19,21,22]

Although the mechanisms of these changes in the ocular surface with DM are still unclear, some studies suggest that diabetic neuropathy affects the innervation of the lachrymal gland and that the fluctuation in the glycaemic control could affect the ocular surface and lachrymal gland secretory function, causing a decrease in basal tear secretion and TBUT.[17,20,21] However, other studies showed that basal tear secretion and TBUT values do not change, but total and reflex tear secretions are significantly reduced in subjects with DM, suggesting that the decreased reflex tearing is due to a diminished sensitivity in cornea and conjunctiva.[16,22]

Usually the aforementioned findings are accompanied by globet cell loss and conjunctival squamous metaplasia. Goebbels[16] suggested that a decrease in tear secretion together with a disturbed trophic function of the tear film, such as vitamin A and epithelial growth factors, might cause chronic conjunctival damage leading to conjunctival metaplasia. Dogru *et al*[17] showed, however, that the conjunctival metaplasia was due to a loss of neurotrophic effects as a result of corneal hypoesthesia, glucose level fluctuation, and metabolic control insufficiency.

**Table 1** Diagnosis of hyperglycaemia states according to WHO criteria[96]

| | |
|---|---|
| Diabetes mellitus | Fasting plasma glucose (FPG) ≥126 mg/dl |
| | Plasma glucose level ≥200 mg/dl after 2 h of oral glucose test tolerance (OGTT) |
| | Symptoms of hyperglycaemia and glucose level ≥200 mg/dl |
| Impaired glucose tolerance | OGTT values after 2 h ≥140 and <200 mg/dl |
| Impaired fasting glucose | FPG≥110 and <126 mg/dl |

DM is often associated with increased oxidative stress and free radical production,[23,24] which may damage epithelial tissues such as the conjunctiva and the lachrymal glands. As the tear film is rich in several antioxidants such as ascorbic acid (vitamin C), found in high concentrations in the eye, Peponis *et al*[24] demonstrated that orally administered antioxidant supplements for a period of 10 days improved the tear film stability and secretion, and the antioxidant properties of vitamins C and E could protect the ocular surface from the attack of free radicals and preserve the integrity of the epithelium.

According to the tear composition in subjects with DM, some studies have shown significant differences compared with healthy subjects, as the number of peaks in diabetic tear protein is significantly higher compared with tear protein patterns of non-diabetic.[25,26] This could be the result of glycosylation of tear proteins that often leads to changes in the protein structure that may influence protein function.[25] Moreover, Grus *et al*[26] observed differences in protein patterns in the molecular weight range of 30–50 kDa, although they could not identify one single peak that was present in all diabetic patients. These proteins were not observed in healthy subjects and could be decisive therefore in the pathogenesis of DM and/or the development of eye-related complications of diabetic disease.[26]

### *Cornea*

DM has important effects on every corneal structure and shows significant and characteristic signs, such as epithelial defects, recurrent epithelial erosions, delayed reepithelization, slower wound repair, increased epithelial fragility, reduced sensitivity, increased autofluorescence, altered epithelial and endothelial barrier functions, ulcers, oedema, and increased susceptibility to injury,[27,28] all of these affecting morphological, metabolic, physiological, and clinical aspects of the cornea. All these signs are included within the term 'diabetic keratopathy' and are present in $>70\%$ of the people with DM.[29]

The corneal epithelium acts as a diffusion barrier that avoids the penetration of polarized substances such as water or ions and participates in maintaining the dehydrated state of the corneal stroma.[30] Some studies with fluorophotometry show that this barrier function is weakened in DM leading to an increase in permeability to fluorescein.[30,31]

The corneal epithelium in patients with DM exhibits alterations in both cellular components and basal membrane, which could impair the physiology of the corneal epithelial barrier function[32] and cause the cornea to be more vulnerable to foreign pathogens, such as bacteria and fungi.

The abnormalities observed in corneal epithelial cells include a decrease in the number of cells, bullae, polymorphism, polymegathism, changes in the cellular coefficient of variation,[27] an accumulation of glycogen granules, and areas of epithelial cell degeneration.[32] Although the cause of theses abnormalities is not clear, some studies suggested that these disorders may be due to altered basal membrane structure and/or epithelial integrin expression,[28,31] increased glycosylation of type IV collagen[32] and fibronectin, abnormal regulation of the synthesis of extracellular matrix, increased IV collagen, and decreased laminin[31] and heparin sulfate.[27]

As far as epithelial basal membrane alteration is concerned, people with DM show an accumulation of fibrillar and granular material between the epithelial cells and Bowman's membrane, thickening and multilayering of the basal membrane,[32,33] and accumulation of glycation end products (AGEs).[34] Despite this, Quadrado *et al*[29] found that basal membrane in DM was lower in density compared with healthy subjects, and they suggested that this could be result of a combination of different mechanisms, such as decreased innervation at the subbasal nerve plexus, basal membrane alterations, and higher turnover rate in basal epithelial cells.

These disorders are associated with alterations in the basal membrane anchoring complex (anchoring fibrils, anchoring plaques, basal lamina, and hemidesmosomes)[27,28,33] resulting in a critical adherence of the basal membrane to the corneal stroma, causing delayed epithelial healing rates and epithelial instability.[27,28,31]

With regards to corneal stroma, Rehany *et al*[32] observed that stromal keratocytes contain vacuoles of lipids and prominent endoplasmic reticulum, and in DM both stroma and Descemet's membrane are loaded with randomly distributed aggregates of normally spaced collagen fibrils. Also, wrinkles in Descemet's membrane may occur and may be considered as a sign of increased corneal hydration.[35]

The maintenance of a relative degree of dehydration of the strongly hydrophilic stroma is mainly due to the action of fluid barrier and pumping mechanisms in the corneal epithelium and endothelium.[27] Although this dehydration state is essential for corneal transparency and thickness, in the corneal endothelium of subjects with DM, hyperglycaemia can inhibit $Na^+$, $K^+$ ATPase activity, and therefore corneal hydration[36] and corneal thickness will increase and therefore affect corneal transparency.

Some researchers indicate that corneas of patients with DM have a tendency to present greater central corneal thickness (CCT). Roszkowska *et al*[37] reported

significantly increased CCT values in people with type 2 DM compared with non-diabetic subjects. Inoue *et al*, however, reported that people with type 2 DM have damaged corneal endothelial structure but found similar CCT values compared with non-diabetic subjects.[38–40] In people with type 1 DM, Schultz *et al*[40] observed similar CCT values to those of healthy subjects, while Roszkowska *et al*[37] found a significant increase in type 1 DM patients.

Aldose reductase in the corneal endothelium and the osmotic stress that occurs secondary to sorbitol accumulation could recur periodically over the life of people with DM and lead to altered endothelial morphology and cell loss. In diabetic corneas, endothelial cells show morphological abnormalities such as high coefficient of variation of cell area and a decrease in the percentage of hexagonal cells.[27,28,37–40] Although there are many reports about corneal endothelium in people with DM, the results remain controversial. Inoue *et al*[38] found a decrease of 4.1% in endothelial cell density in patients with type 2 DM and a higher coefficient of variation of cell area but did not observe a decrease in the percentage of hexagonal cells. Despite these results, there are also some studies reporting that the endothelial cell density in patients with type 2 DM is similar to that found in healthy subjects.[29,40]

Regarding endothelial cell hexagonality loss (pleomorphism), some authors reported a decrease in the percentage of hexagonal cells.[37,40]

A number of studies have shown that people with DM have decreased corneal sensitivity,[17,19,21,22,27,28,33] make them more vulnerable to corneal trauma. Thickening and thinning of Schwann cell basal lamina, irregular distribution in the nerve beading pattern, and occasional axonal degeneration of the nonmyelinated corneal nerves have been found in people with DM.[27] Dogru *et al*[17] suggested that keratopathy and corneal neuropathy might be manifestations of distal peripheral neuropathy of DM and proposed that changes of intraneural concentration of myoinositols and increased sorbitol levels within the Schwann cell basal lamina could be responsible for either mechanical compression or toxic axonal damage. McNamara *et al*[36] showed reduced corneal sensitivity during episodes of hyperglycaemia as a consequence of changes in corneal hydration control.

*Corneal autofluorescence* As previously mentioned, people with DM show an increased corneal autofluorescence compared with healthy subjects.[27,28,41–44] Up until now, there are two mechanisms that have been suggested as responsible for an increase in corneal autofluorescence.

On the one hand, several studies have demonstrated that corneal autofluorescence originates from the same fluorophores in people with DM and healthy subjects, flavoproteins in oxidized state, and pyridine nucleotides in reduced state,[42–44] located in the corneal epithelium and endothelium. During hyperglycaemia, damage of mitochondrial electron transport is produced, causing an increase in the percentages of flavoproteins within the respiratory chain that predispose to oxidation,[45] thus resulting in an increase of corneal autofluorescence.

Second, Van Schaik *et al*[41] reported that both in diabetic subjects and controls fluorescence was distributed throughout the cornea and decreased from endothelium to epithelium. Because of high glucose levels in aqueous after the breakdown of the blood–aqueous barrier, the diffusion of glucose from the aqueous along the cornea might induce a glucose gradient in the cornea, resulting in the increase the non-enzymatic glycation of corneal proteins and collagen (via Maillard), increasing therefore the fluorescence of the cornea.[41]

Some researches consider that corneal autofloure-scence would be a useful diagnostic method for screening retinopathy in the diabetic population[43] due to a reported correlation between increased corneal autofluorescence and proliferative diabetic retinopathy (PDR).[41–43,46] This relation suggests a common pathogenesis, but the explanations remain uncertain. A first possible explanation could be that the vascular component of DM might be responsible for specific microangiopathy, and consequently progressive retinopathy may be related to the metabolic disorder (elevation of blood glucose level associated with alterations in lipid and protein metabolism). This metabolic disorder can also affect the cornea, resulting in a progressive metabolic impairment associated with an increase in corneal autofluorescence.[43] A second explanation reported could involve neovascularization-mediating substances produced in a retina with DR that induce neovascularization of the iris (rubeosis iridis), which may reach the cornea as well and consequently induce changes in corneal metabolism, resulting in increased values of autofluorescence.[43,46]

Other studies have shown a significant relationship between corneal autofluorescence and glucose levels in patients with PDR and that corneal autofluorescence levels in these patients vary greatly throughout a day.[44] Corneal autofluorescence was found, however, to be independent of age in healthy controls, NIDDM, and IDDM.[47]

### *Crystalline lens*

People with DM often complain of discomfort in certain activities, such as reading or driving, and blurred vision with their own glasses. In patients with DM, a rapid reduction in blood glucose could cause an aggravation of

both retinopathy status and refractive changes, so that visual acuity often decreases. Refractive changes occur frequently in people with DM and can be either acute or long term.

Regarding long-term changes, Duke-Elder[48] in 1925 described that hyperglycaemia led to the development of myopia, while relative hypoglycaemia with respect to initial hyperglycaemia state led to hyperopic changes. Gwinup and Villareal[49] supported his theory 50 years later, both in acute and chronic changes, and demonstrated that the hyperopic changes are mainly due to the lens.

As for the acute changes, a reduction of plasma glucose levels leads to hyperopic refractive changes, and hyperglycaemia causes variations in the refractive index of the lens in people with DM[50,51] that may lead to transient cataract development. However, it has been also reported that hyperopic changes occur with plasma glucose level, regardless of whether it was an increase or decrease.[52] The underlying mechanism of the relation between plasma glucose concentration and refractive change in subjects with DM remains therefore to be established.

A possible hypothesis to explain what happens in the crystalline lens during transient hyperopic changes in people with DM could be that when the body rapidly changes from a hyperglycaemic to a hypoglycaemic state, an excess of glucose accumulated in the lens flows out into the aqueous humour and freely enters the intracellular space, but sorbitol (less permeable) remains in the lens for a longer time.[53] This process causes a difference in osmotic pressure leading to an influx of water from the aqueous humour into the crystalline lens, and therefore the lens becomes thicker with hyperopic refractive changes.

Some researchers support this hypothesis, like Saito *et al*[50] who found that the lens thickness increased and the anterior chamber depth decreased significantly during transient hyperopia in 10 eyes of 5 patients with DM. Other researchers, however, observed that the lens thickness did not increase significantly and the anterior chamber depth did not decrease significantly during hyperopic changes, explaining why this hypothesis cannot be confirmed without knowing the effects of each of these contributing factors in the power of the lens (thickness, curvature of anterior and posterior surfaces, refractive index of the aqueous humour lens, and vitreous body), as an increase in lens thickness resulted in myopic changes by reducing the radius of curvature.[51]

The human lens continues to grow throughout life due to the addition of new fibres, becoming thicker and more convex; in addition, the refractive index of crystalline lens undergoes changes due to ageing and cataract development. In patients with DM, the lens has been found thicker and more convex compared with healthy subjects.[54–56] Wiemer *et al*[57] observed an increase in the average lens thickness of 0.2 mm and a significant decrease in equivalent refractive index with age in both diabetic patients and control subjects, the greater decrease corresponded, however, to patients with type 1 DM. The fact that crystalline lens is thicker in people with DM might be due to not only an abnormality in the growth of the lens, greater cortical thickness, or osmotic swelling but also as a result of an increase in cell membrane permeability or deficiency in the ions pump.[58]

Sparrow *et al*[59] found that in people with type 1 DM the duration of the condition had a determining power on the biometry of the lens, a finding corroborated by Wiemer *et al*,[57] who also found that type 2 DM had no effect on the lens thickness, shape, or equivalent refractive index.

### *Vitreous*

The vitreous is a hydrated gel matrix composed of a complex network of cross-linked collagen (types II, V, IX, and XI), fibrils, and the hydrophilic glycosaminoglycan, hyaluran. With aging or disease development, vitreous gel may undergo liquefaction due to biochemical and physiological changes that cause dissociation of collagen and hyaluran. Many of these disorders manifest as opacities in an optical structure that is normally transparent.

Patients with DM experience vitreous degeneration earlier than those without DM,[60] such as asteroid hyalosis (AH), a degenerative process resulting in small, white vitreous opacities consisting calcium phosphate and complex, layered lipid deposits. The prevalence of this condition in the general population is 1.92%,[60] affecting all races with a male to female ratio of 2 : 1[61] and associated with age.[62] AH is unilateral in 75% cases.[61] Although its aetiology is still not clear, a significant association between AH and DM has been reported,[61] although Moss *et al*[62] found no evidence to suggest a relationship between HA and DM, remaining therefore controversial.

Hyperglycaemia may have a direct role in vitreous pathology by altering the structure and function of the collagen network through increased glycation (non-enzymatic glycosylation) and abnormal cross-linking of the collagen fibrils, resulting in vitreous destabilization.[60,63] Lundquist and Osterlin[63] showed that whereas the glucose level in the vitreous is generally lower than in the blood, in people with DM it will reach levels that might increase the glycation rate, which might in turn lead to the formation of cross-links in the vitreous collagen.

Increased AGEs in serum and tissues is a characteristic of DM and may have an important role in the destabilization, premature liquefaction, and complicated posterior vitreous detachment.[60] The vitreous in people with DM manifests changes in angiogenic and metabolic factors concordant with abnormalities in the retinal microvasculature occurring in the pathogenesis of DR. Retinal neovascularization occurs towards the vitreous cavity, with microproliferation and migration of cells onto the posterior vitreous cortex.[64] As disease progresses, angiogenic factors that induce the growth of new retinal blood vessels (neovascularization) are secreted.[65] Yokoi *et al*[66] found that the vitreous levels of AGEs and vascular endothelial growth factor (VEGF) correlate with each other, both of which are inversely associated with vitreous total antioxidant capacity in patients with DR. Kinnunen *et al*[67] showed differences in growth factor expression between people with type 1 and type 2 DM with retinopathy, while VEGF-A was most abundantly present in type 1 DM, and VEGF-D was more copious in the neovascular tissues of patients with type 2 DM. They suggested the possibility that an inflammatory mechanism accelerates proliferative retinopathy in type 2, by VEGF-D-dependent pathways, and type 1 DM hypoxia is more important in the development of proliferative retinopathy than inflammation. This difference in growth factor expression might contribute to the pathogenesis of both form of the disease.[67]

These abnormalities of diabetic vitreous would produce traction upon the structures attached to the vitreous cortex, such as the new vessels present in PDR, and contribute to the progression of retinopathy by either traction on the new vessels or induction of new vessels rupture, thus causing a vitreous haemorrhage.[68]

## Optical quality in people with diabetes

Nowadays, the objective assessment of the optical quality of the eye is of great interest in clinical practice. The optical system of the eye has some limitations due to its shape and the composition of its media. Ocular diffraction, aberrations, and scattering influence intraocular retinal image quality, therefore affecting the visual performance of the subject. In human eyes, it is possible to improve image quality by minimizing aberrations and ocular scattering; but it is impossible to exceed the limits of image quality due to diffraction. Both aberrations and ocular scattering, and therefore optical quality of the retinal image, are affected by DM.

### *Aberrations*

As previously mentioned, people with DM have a series of morphological, structural, metabolic, and physiological changes in different ocular structures. Although there are few studies that related these changes with the impact on visual quality,[69,70] people with DM undergo variations in blood glucose levels and cause changes in spherical and cylindrical components of refraction, both acute and long term; these changes also known as lower-order aberrations account for approximately 90% of the total ocular aberrations. Although higher-order aberrations (HOAs) make a small contribution ($\leq$10%) to the overall wave aberration in the eye,[71] some authors have shown a large effect of degradation in the quality of the retinal image and affect visual acuity.[72] There are factors that may contribute to the change in aberrations, such as ageing,[73–77] accommodation,[78] photoreceptors,[73] pupil size,[71,79–82] refractive surgery,[76,83–85] and tear film.[86,87] Even though there are no studies evaluating the impact that these factors could have on HOAs in people with DM, these do have a thicker and more convex lens,[54–56] can develop premature cataracts,[9–11] and suffer a series of changes associated with lachrymal gland dysfunction and dry eye syndrome.[16–26] Patients with DM who undergo laser-assisted *in situ* keratomileusis are also at a significantly higher risk of developing postoperative epithelial complications, and refractive results tend to be worse compared with healthy people.[88]

Few authors have investigated HOAs in people with DM. Shahidi *et al*[69] found that HOAs were increased in their 22 chronic patients with DM and suggested that the presence of increased ocular aberrations were caused by disease-related changes in the optics (cornea and crystalline), although they did not provide information about the relative contribution of these optical components to the total amount of aberrations measured.

Wiemer *et al*[70] measured HOAs, as well as the shape of the cornea and the lens in 25 patients with DM (15 type 1 DM, 10 type 2 DM) during the presence and absence of hyperglycaemia and blurred vision. They observed that only four patients presented a significant increase in HOAs (mean increase in root mean square error: 0.07 $\mu$m). Although this increase in HOAs might reduce visual acuity,[72] they did not detect changes in visual performance. They suggested that symptoms of blurred vision due to hyperglycaemia should be attributed to other factors such as the cerebral cortex or the retina, which might cause subjective symptoms of blurred vision, or that more serious and long-lasting hyperglycaemia would be needed to induce changes in ocular structures large enough to increase aberrations to a level that produces blurred vision.[69]

Calvo-Maroto *et al* measured total, corneal, and internal HOAs in 18 patients with well-controlled DM (7 type 1 DM, 11 type 2 DM) and reported that people with DM showed high values of total and internal

vertical coma ($Z_3^{-1}$). They observed that the greatest contributor of total ocular HOAs was internal vertical coma ($Z_3^{-1}$) for both groups and suggested that certain changes in posterior cornea or crystalline produced by DM are responsible for increased HOAs in people with DM (Calvo-Maroto *et al*, submitted).

### *Ocular scattering*

In a normal healthy eye, each optical component may cause some scattering of the light that goes towards the retina; this includes both refractive elements of eye (cornea and lens), the media in which they are immersed (vitreous and aqueous humour), and the supporting structures (sclera and iris). The intraocular scattering increases with age,[73,74] pigmentation, associated diseases, or ocular surgery.[89]

As previously discussed, the cornea undergoes changes associated with DM, such as corneal oedema,[36] increased corneal thickness,[37,38] and abnormalities of basement membrane.[31,32] These changes could lead to an increase of light scattering as it passes through it, due to local fluctuations in refractive indices of the oedematous cornea, increased hydration, or disruption of the orientation of the collagen fibres. Morishige *et al*[90] measured the scattering of the corneal epithelial basement membrane in 65 patients with type 2 DM with DR and 18 healthy subjects and found that the light scattering index (LSI) was significantly higher in people with DM with PDR compared with healthy subjects. They also observed that the LSI correlated with the severity of DR but not with the duration of DM, blood glucose levels in a fasting state, or with glycated haemoglobin A1c (HbA1c) levels and suggested that the LSI increases with the stage of DR.[90] Takahashi *et al*[91] described the development of a light scattering detection system (LSDS) for measuring light scattering of corneal epithelial basement membrane and measured 20 diabetic patients with vascular hyperpermeability, 20 patients with diabetic vascular occlusion, and 30 healthy subjects. They could not specify if this light scattering was generated by the basement membrane or Bowman's layer but observed that LSDS index was significantly higher in people with DM.[91]

In contrast, Holden *et al*[92] did not detect any difference in central corneal light scatter in a group of patients with IDDM compared with a normal control group.

Another cause of light scattering in a normal eye is that produced by the lens.[89] With age, the lens loses its transparency due to nuclear sclerosis, becomes yellow, and ends with possible development of premature cataracts in people with DM.[10,11] Weiss *et al*,[93] in their study with 38 patients with DM and 19 control subjects, observed higher light scatter in people with DM patients and demonstrated that young people with DM seem to have scatter values similar to those older subjects without DM.

Normally, the vitreous does not contribute to the total light scattering, but certain abnormalities such as AH that have been reported in people with DM might increase total light scattering values.[94] During the course of DM, a partial breakdown of the blood–retinal barrier occurs, causing abnormalities in the tertiary and quaternary structure of the vitreous molecules as well as their diffusivity. Such changes can be detected by dynamic light scattering (DLS) when there no visible corneal alterations and no onset of DR. Therefore, some authors have suggested that DLS in the vitreous should be more effective for an early detection of DR.[95]

## Summary

Ocular structures responsible for maintaining a good visual quality (tear film, cornea, crystalline lens, vitreous, and retina) undergo numerous morphological, structural, and physiological changes during the course of DM. These changes may alter visual quality of people with DM by means of increased HOAs and ocular scattering, as reported in some studies. Up until now, there are no standardized values in people with DM, but new optical technologies provide a fast, objective, and non-invasive method for assessing the contribution of HOAs and ocular scattering to the optical quality of the retinal image and establishing the baseline values for normal subjects compared with people with DM. Due to the high prevalence of DM, determination of optical quality in diabetic eyes could be a useful complementary test for screening and monitoring of the condition.

## Conflict of interest

The authors declare no conflict of interest.

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