## The influence of Diabetes Mellitus on the Refractive Properties of the Human Eye

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# THE INFLUENCE OF DIABETES MELLITUS ON THE REFRACTIVE PROPERTIES OF THE HUMAN EYE

The study presented in the present thesis was performed at the Department of Ophthalmology and the Institute for Research in Extramural Medicine (EMGO institute) of the VU University Medical Center, Amsterdam, the Netherlands. The EMGO Institute participates in the Netherlands School of Primary Care Research (CaRe), which was re-acknowledged in 2000 by the Royal Netherlands Academy of Arts and Science (KNAW).

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# THE INFLUENCE OF DIABETES MELLITUS ON THE REFRACTIVE PROPERTIES OF THE HUMAN EYE

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| co-promotor: | dr. M. Dubbelman |

Een heldere, scherpe blik

vergroot het inzicht

en

vervaagt

in een ogenblik

alle twijfel

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# Chapter 1

## General introduction

# Contents

# 1. Aims of the present study

The number of people with diabetes mellitus has increased rapidly, reaching epidemic proportions, and currently affecting approximately 246 million people worldwide. This number is expected to rise to approximately 380 million in 2025 (Fig 1).[1-3] The increase in the number of patients with diabetes mellitus will certainly lead to a substantial increase in morbidity and mortality, despite improvements in the screening and treatment of diabetic complications.

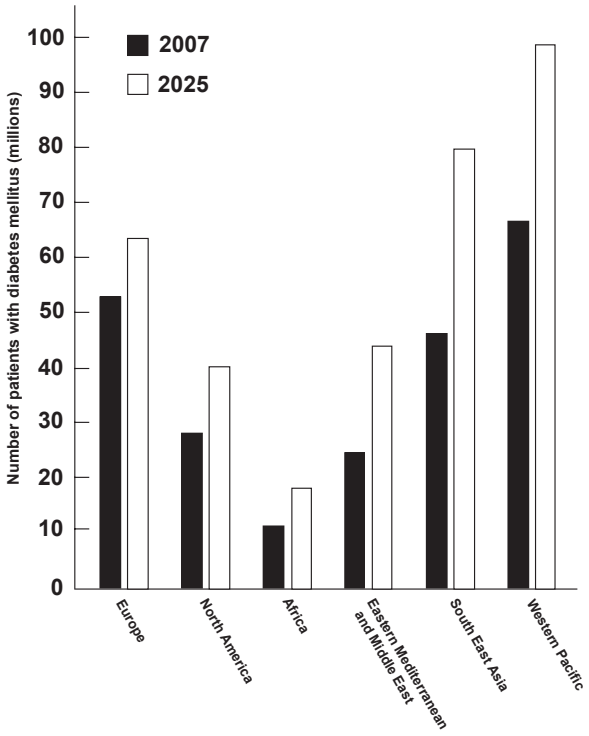



**Figure 1** *The number of people worldwide with diabetes mellitus (aged 20 – 79 years) according to region, in 2007 and 2025. (Source: Diabetes Atlas 3rd Edition, IDF 2006)*

Long-term diabetes mellitus appears to have considerable consequences for the biometry of the eye. In patients with diabetes mellitus the lens seems to become thicker and more convex, compared to that of healthy subjects.[4-6] However, in previous studies of the diabetic lens no attempt has been made to correct for distortions that are inherent to the applied measurement methods. In vivo the lens can only be observed through the cornea, and due to the refraction that occurs

at the corneal surfaces it is difficult to measure the shape of the lens accurately. Therefore, the results of these studies should be interpreted with caution. Furthermore, the exact influence of diabetes mellitus on the shape of the cornea is still unknown.

Well-known ocular complications of acute diabetes mellitus are subjective symptoms of blurred vision during hyperglycemia, but the exact cause of these symptoms is still unknown. They could be due to changes in the image formation process (i.e. the refractive system and/or the retina), or to alterations in the image-processing system (i.e. the brain). Changes in ocular refractive power during dysregulated diabetes mellitus have been frequently reported in the literature, but there is no consensus on the exact direction and cause of the refractive change. It is unclear whether the refractive error generally becomes more myopic (or near-sighted) or, on the contrary, more hyperopic (or far-sighted) in people with diabetes mellitus and hyperglycemia. Furthermore, the mechanisms underlying these refractive changes are unknown. In general, the image formation of an optical system becomes disturbed if one or more of its elements change. In the diabetic eye there could be changes in the refractive elements (i.e. the cornea and/or the lens), or the retina, that occur with an increase in the duration of the disease and with other systemic parameters, such as blood glucose levels, the use of insulin, or the presence of diabetic retinopathy. In summary, changes in the process of image formation in the eye could explain blurred vision and refractive changes in dysregulated diabetes mellitus.

It is important to obtain accurate knowledge about the influence of long-term diabetes mellitus on the refractive components of the eye. Furthermore, an accurate description of the changes in the refractive properties of the eye during hyperglycemia could provide insight into the mechanisms underlying blurred vision and refractive changes in patients with diabetes mellitus and metabolic dysregulation. Therefore, the aims of the present study are:

- To accurately measure the thickness and the shape of the cornea, and the thickness, shape and internal structure of the lens in patients with diabetes mellitus type 1 and type 2 (Chapters 2, 3, and 4).

- To investigate the mechanisms underlying blurred vision and refractive changes by measuring the geometry of the cornea and the lens, the ocular refractive error, and the retinal thickness of the eye during acute hyperglycemia (Chapters 5, 6, 7 and 8).

## 2. The refractive properties of the eye and image formation

### *2.1 Ocular refraction*

The process of human vision is complex, and involves various components of the eye and the human brain. The initial steps in human vision are the refraction of incoming rays of light by the cornea and the lens, and image formation on the retina. In the ideal situations, parallel rays of light are focused sharply on the retina, a condition known as emmetropia, but if the relaxed eye is unable to bring parallel rays of light from a distant object into focus, the condition is referred to as ametropia. The three basic conditions that may produce ametropia are: myopia (near-sightedness), hyperopia (far-sightedness), and astigmatism (Fig 2). A myopic eye has excessive convergent power; the light rays focus in front of the retina and a divergent (minus) lens should be used to correct ocular refraction. On the contrary, a hyperopic eye has insufficient convergence power to focus light rays on the retina. In this condition, the rays focus behind the retina, and corrections should be made with a convergent (plus) lens. Astigmatism occurs when the cornea (and/or the lens) does not have the same radius of curvature in all meridians, and corrections should be made with a cylindrical lens. The average

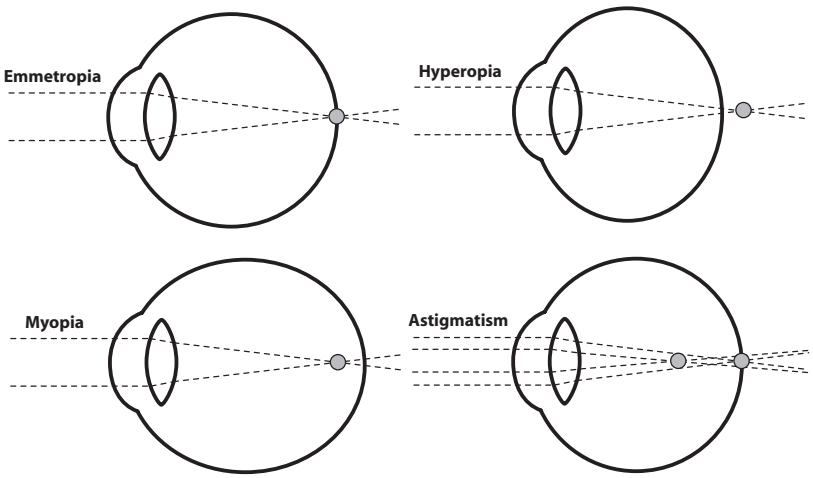


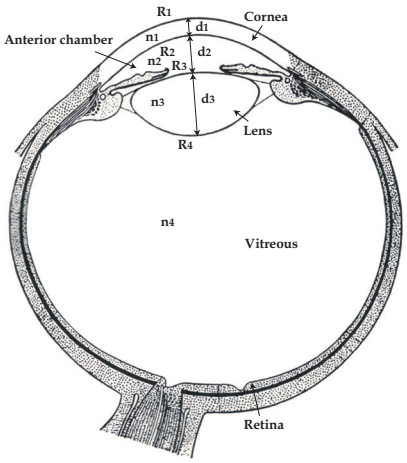

**Figure 2** *The refraction of the eye; diagrams of emmetropia, myopia, hyperopia, and astigmatism. In the emmetropic eye the rays of light are focused on the retina. Refractive errors of the eye include myopia and hyperopia, when the rays of light are focused in front of or behind the retina, respectively. In the astigmatic eye the rays of light are focused on a focal line and two focal points are formed, which can be positioned in front of, exactly on, or behind the retina.*

ocular refractive error can be expressed in the spherical equivalent, which is a combination of myopic or hyperopic astigmatism. The spherical equivalent is calculated as: power of the sphere (myopic or hyperopic correction) + 0.5 * power of the cylindrical correction.

The refractive power (P) of a surface, which is expressed in diopters (D), depends on its radius of curvature (R) and the refractive indices ($n_1$ and $n_2$) of both sides of the surface, and has been defined as:[7]

$$P = \frac{n_2 - n_1}{R}$$

Parameters $n_1$ and $n_2$ are the refractive indices on the incident and the refracted side of the surface, respectively. An overview of the various parameters (radius of curvature, thickness, and refractive index) of the cornea and the lens, as described by Gullstrand[8] in 1909, is presented in Figure 3. The total refractive power of the human eye is approximately 60 D. The anterior surface of the cornea accounts for the largest contribution to the refractive power of the eye, providing approximately 70% (or ~ 42 D) of the total ocular refraction. The posterior corneal surface and the anterior and posterior surface of the lens account for the remaining refractive power of the eye.




**Gullstrand eye model**

**R1 (anterior radius cornea) = 7.7 mm**
**R2 (posterior radius cornea) = 6.8 mm**
**R3 (anterior radius lens) = 10 mm**
**R4 (posterior radius lens) = -6 mm**

**d1 (thickness cornea) = 0.5 mm**
**d2 (anterior chamber depth) = 3.1 mm**
**d3 (thickness lens) = 3.6 mm**

**n1 (refractive index cornea) = 1.376**
**n2 (refractive index anterior chamber) = 1.336**
**n3 (refractive index lens) = 1.427**
**n4 (refractive index vitreous) = 1.336**

**Figure 3** *Parameters of the Gullstrand eye model: R1 = anterior radius cornea, R2 = posterior radius cornea, R3 = anterior radius lens, R4 = posterior radius lens, d1 = thickness cornea, d2 = anterior chamber depth, d3 = thickness lens, n1 = refractive index cornea, n2 = refractive index aqueous, n3 = refractive index lens, n4 = refractive index vitreous.*

*2.2 The cornea*

The cornea is the transparent front part of the eye and the absence of blood vessels contributes to this remarkable corneal transparency. The cornea receives its nutrients predominantly from the aqueous humour and oxygen is obtained via diffusion from the air via the tear fluid at the anterior surface and from the aqueous humour at the posterior surface. The cornea is innervated by unmyelinated nerve fibres which are sensitive to touch, temperature and chemicals; touching the cornea causes an involuntary reflex to close the eyelid. The human cornea consists of five different layers: epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium.[9] The corneal epithelium is a thin multicellular layer of fast-growing and easily-regenerating cells. Irregularity or edema of the corneal epithelium disrupts the smoothness of the tear film, which is a significant component of the total refractive power of the cornea. Bowman's membrane (anterior limiting membrane) is a tough layer of irregularly-arranged collagen fibers that protects the corneal stroma. The corneal stroma (substantia propria) is a thick, transparent layer of regularly-arranged collagen fibers, sparsely populated with keratocytes. Descemet's membrane (the posterior limiting membrane) is the basement membrane of the corneal endothelium. The corneal endothelium is a low-cuboidal monolayer of mitochondria-rich cells responsible for regulating fluid and solute transport from the aqueous to the posterior layers of the corneal stroma.

Although the overall shape of the cornea remains stable with age,[10,11] it has been shown that with age the asphericity of both the anterior and the posterior corneal surface can change, resulting in a slight peripheral thinning of the ageing cornea.[12]

*2.3 The lens*

The lens is a transparent, biconvex structure located immediately behind the iris. The lens is connected with the surrounding circular ciliary muscle by a complex system of zonular fibres. During accommodation the shape of the lens is altered by relaxation and contraction of the ciliary muscle, leading to changes in the tension of the zonular fibres and consequently to changes in the shape of the lens body. This enables the eye to focus on objects at varying distances. The ability of the lens to accommodate from distant to near focus gradually declines with age; a condition called presbyopia. Clouding or opacification of the lens, referred to as cataract, may also occur with age. Cataracts that interfere with vision can be corrected by surgery, during which the clouded lens is removed and preferably replaced by an artificial intraocular lens. The lens consists of a lens capsule, a layer of epithelial cells and the lens fibres. Figure 4 presents a

diagram of the human crystalline lens. For the sake of transparency it does not contain blood vessels or nerves. The lens capsule is a thick, elastic basal lamina, which is generated by the epithelial cells. The zonular fibers are inserted into the lens capsule. The epithelial cells only cover the anterior part of the lens, and are mitotically active in the pre-equatorial region. After division, the post-mitotic cells gradually move towards the equator of the lens where they start to differentiate into lens fibres. Lens fibers are unusually elongated (up to 12 mm) hexagonal cells. In the absence of blood supply the lens fibers obtain nutrients from the surrounding fluid, i.e. the aqueous humour that bathes the front of the lens. Lens fibers are located immediately underneath the epithelium anteriorly, and the lens capsule posteriorly, and form the various parts of the lens body (the lens cortex and lens nucleus). They are closely packed and the intercellular space is extremely small (<4%). The hexagonal lens fibers are strongly interlocked

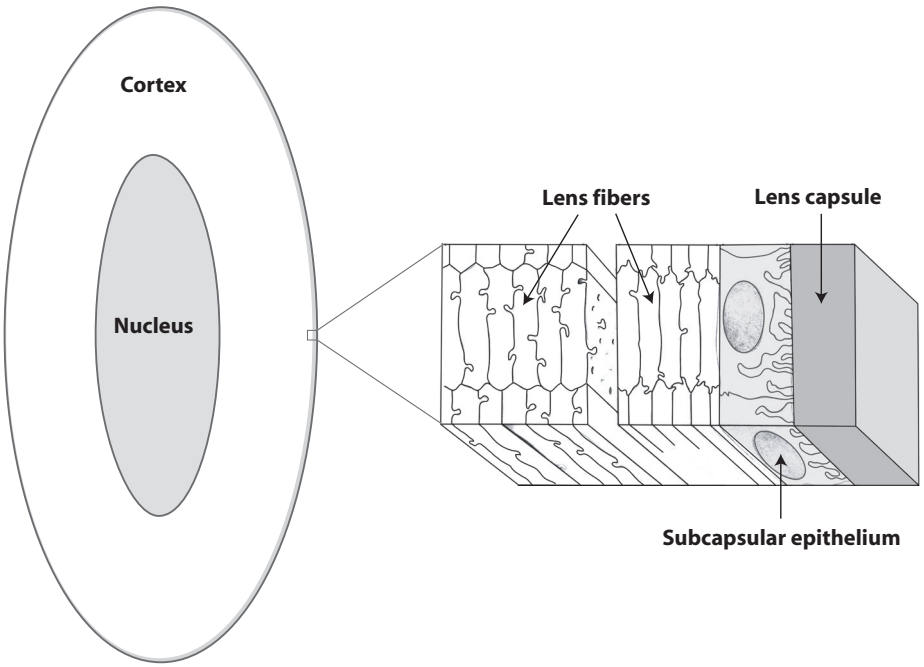



**Figure 4** *Diagram of the lens and the multiple layers of the lens cells: (A) lens capsule, which is a thickened, smooth basement membrane and completely envelops the lens. (B) Epithelial cells, which show mitotic activity in the equatorial region of the lens in particular. (C) Lens fibers, elongated cells with a hexagonal shape in cross-section. Lens fibers fit in close packing order with other lens fibers, the adjacent long sides of the lens fibers interlock with grooves and ridges, and ball-and-socket junctions, as indicated.*

by edge protrusions, ball-and-socket junctions, and in the deeper aspects of the cortex by grooves-and-ridges. On account of light scattering properties (zones of discontinuity) the cortex of the lens is sub-divided into several zones, which have been given different names and numbers in different studies.[13-16]

In contrast to the cornea, the size and shape of the lens is highly age-dependent. The annual increase in thickness of a healthy human lens is 0.024 mm.[17] Furthermore, the lens becomes more convex, with a yearly decrease in the anterior and posterior radius of curvature of 0.057 and 0.012 mm, respectively.[18] Generally, with a more convex shape of the refractive surface, the refractive power increases. Assuming that the other refractive components of the eye remain constant, the more convex shape of the aging lens would increase the refractive power of the eye, and a myopic shift in ocular refractive error should occur. However, it has been reported that with age (between 30 and 60 years of age) ocular refraction actually becomes more hyperopic (Fig 5).[19,20] The paradoxical feature of the increase in convexity of the lens, with no myopic shift in ocular


**Figure 5** *Change in cycloplegic refraction of the human eye with age (after Slataper).*[20]

refractive error with age, has been called the "lens paradox".[21] The lens paradox can be explained by a decrease in the equivalent refractive index of the lens with age, which compensates for the more convex shape of the aging lens and therefore prevents the eye from becoming more myopic.[18,22-25]

*2.4 The retina*

With a normal refraction of light by the cornea and the lens, a sharp image is focused on the retina, and this is often compared to the film in a photo camera. The retina is a thin layer of neural cells that lines the back of the eyeball, and it is the only part of the central nervous system that can be observed directly. The retina contains photoreceptor cells (rods and cones) that respond to light; the resulting neural signals then undergo complex processing by other neurons of the retina. This retinal output takes the form of action potentials in retinal ganglion cells whose axons form the optic nerve. From the optic nerve the action potentials travel to the brain to be further processed.

## 3. Diabetes mellitus and the refractive properties of the eye

*3.1 Diabetes mellitus*

In general, patients with diabetes mellitus have a relative or absolute shortage of insulin, and consequently high blood glucose levels.[26] Insulin, which is produced by the beta-cells of the islets of Langerhans in the pancreas, regulates blood glucose concentration by enabling glucose to enter body cells and by storing an overload of glucose or glycogen elsewhere (e.g. in the liver, the muscle fibers, or fat tissue). On the other hand, glucagon enhances blood glucose concentration by stimulating mainly the formation of glucose from glycogen in the liver. This mechanism normally establishes narrow blood glucose levels (between 4.0 and 7.8 mmol/l) in healthy people. Although the pancreatic beta-cell and its secretory product insulin are central in the pathophysiology of diabetes mellitus, the mechanisms which cause hyperglycemia differ widely. There are several different forms of diabetes, which are caused by a complex interaction of genetic, environmental, and life-style factors, but there are two major forms of diabetes mellitus: type 1 and type 2. Diabetes type 1 is characterized by an absolute insulin deficiency due to a genetic defect leading to defective insulin secretion. It accounts for 5 - 10% of all patients with diabetes mellitus.[27] The onset of diabetes type 1 is sudden, and it usually affects people at a relative young age. Patients with diabetes type 1 have to use insulin to prevent the development of ketoacidosis and

diabetic coma. Diabetes mellitus type 2 has a genetic predominance that causes insulin resistance, and/or the induction of a relative insulin shortage because of the inability of the pancreas to produce sufficient insulin to encounter the induced insulin resistance as the underlying etiology.[28] It is the most common type, representing approximately 90% of the diabetes population globally.[29] The onset of diabetes type 2 is gradual, and it usually starts at an older age in people with various risk factors, such as for example obesity. Patients with diabetes type 2 are not dependent on exogenous insulin, but may require it to control their blood glucose levels if this is not achieved with dietary restrictions alone or with oral hypoglycemic agents.

The characteristic initial symptoms of diabetes mellitus are excessive urine production (polyuria), excessive thirst and increased fluid intake (polydipsia), and subjective symptoms of blurred vision, but these symptoms are likely to be absent if the blood glucose level is only mildly elevated. Considering the fact that diabetes mellitus is a common disease, and that it is often under-diagnosed, ophthalmologists and optometrists should always take it into consideration in patients with blurred vision.[30] Other symptoms include fatigue, and increased susceptibility to infections, particularly of the skin and genitalia.[31] Chronic elevation of the blood glucose level results in damaged blood vessels. The resulting problems are grouped in microvascular complications (due to damage of the small blood vessels) and macrovascular complications (due to damage of the large arteries). Macrovascular illness leads to cardiovascular disease and mortality, to which accelerated atherosclerosis is a contributor. Microvascular complications include diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy.[32]

*3.2 Sustained refractive changes and diabetes mellitus*

Sustained or chronic refractive errors that are reported in patients with diabetes mellitus not only include myopia, but also a tendency towards hyperopia, or no change in ocular refraction at all. Epidemiological studies (Barbados Eye Study, Los Angeles Latino Eye Study) revealed that diabetes mellitus was an independent risk factor for the development of moderate myopia (> -3 D)[33] and low-grade myopia (< -1 D)[34]. Furthermore, in the Danish adult population, a predominance of myopia was reported in patients with diabetes, compared to non-diabetics.[35-37] Poor metabolic control of diabetes mellitus has also been suggested as a risk factor for myopia.[38] In contrast, in other population studies (Beaver Dam Eye Study, a rural South Indian population) the presence of diabetes mellitus was related to an increased shift towards hyperopia,[39,40] and no associations were found between refractive error and glycemic control or duration of diabetes.[41] Furthermore,

diabetes mellitus was not associated with a shift in ocular refraction in other epidemiological studies (Andhra Pradesh Eye Disease Study, Blue Mountains Eye Study).[42,43] In summary, the relationship between diabetes mellitus and chronic refractive changes is controversial and needs to be confirmed in further studies. As in healthy individuals, large myopic shifts in ocular refraction have not been consistently observed in patients with long-term diabetes mellitus, despite the significant increase in thickness and convexity of the diabetic lens.

*3.3 Changes in the cornea with diabetes mellitus*

Diabetes mellitus can lead to structural changes in the epithelial[44-49] and endothelial cells of the cornea,[50-54] which may result in diabetic keratopathy. Diabetic keratopathy becomes manifest as recurrent corneal erosions, superficial punctuate keratopathy, persistent epithelial defects, decreased corneal sensitivity,[55,56] endothelial dysfunction, and delayed wound healing. Because of this increased risk of corneal complications, refractive surgery may be contra-indicated in patients with diabetes mellitus.[57,58] It is unclear from the literature whether diabetes mellitus causes a change in the thickness of the cornea. Some studies have reported that the cornea is thicker in diabetic than in healthy subjects,[59-61] but other studies reported no difference between the corneal thickness of subjects with diabetes and that of healthy subjects.[62-63]

*3.4 Changes in the lens with diabetes mellitus*

In patients with diabetes mellitus the lens is thicker than in healthy subjects,[4,5,64-69] and this is mainly due to thickening of the cortex of the lens.[70,71] Other biometric changes in the lens include a steepening of the anterior and posterior surfaces of the lens and a decrease in the depth of the anterior chamber.[4,5] These changes appear to be more pronounced in diabetes mellitus type 1 than in diabetes mellitus type 2. The duration of the disease, as well as the level of retinopathy, have been reported as important determinants of lens biometry. With each year of diabetes the thickness of the lens increases with an additional 70% of the annual age-related increase.[4,5] Until now, however, the profound increase in lens dimensions with diabetes mellitus is not fully understood. It could be due to an accelerated growth of the lens, but it could also be caused by osmotic swelling of the lens, either as a result of an increase in cell membrane permeability or deficient ion-pumping. More knowledge about changes in the histology and ultrastructure of the lens with diabetes mellitus could provide insight into the cause of the increase in the size of the diabetic lens. For more details see section 4.2: The lens and the sorbitol pathway.

Another lens complication that is related to diabetes mellitus is the early

development of cataract.[72-75] Cataract can be induced by hypoglycemia,[76] and it can already be present as juvenile cataract (snowflake cataract, affecting the anterior and posterior cortical layer of the lens in young individuals with diabetes),[77] or as age-related cataract (nuclear, cortical, and posterior sub-capsular cataract).[78] Juvenile cataract is characterized by rapid swelling of the lens, inducing a myopic shift of refraction.[79] However, hyperopic refractive power changes with acute diabetic cataract have also been reported.[80,81] Furthermore, studies of young subjects with diabetes mellitus type 1, with no detectable cataract after slit-lamp examination, suggest that there is an increased scatter of light in diabetic subjects that appears to correlate with the level of the glycated hemoglobin (HbA1c) and the severity of diabetic retinopathy.[82-86]

### *3.5 Changes in the retina with diabetes mellitus*

Diabetic retinopathy is the most common ocular disease in patients with diabetes mellitus, and it is the most frequent cause of blindness among adults aged 20-79 years.[87-90] The duration of diabetes has been shown to be an important determinant in the onset and progression of diabetic retinopathy: respectively 97% and 80% of the patients with diabetes type 1 and type 2 will have retinopathy after 15 years.[91,92] An interesting observation is that diabetic retinopathy is less likely to develop in patients with diabetes mellitus and myopia of -5 D or more.[93,94]

Diabetic macular edema is a microvascular complication that is associated with diabetic retinopathy, and it is the major cause of visual impairment in patients with diabetes mellitus.[95,96] Diabetic macular edema appears to occur more frequently as the severity of diabetic retinopathy increases, but it can develop during all stages of diabetic retinopathy.[97,98] Risk factors that contribute to the progression of diabetic macular edema include elevated blood glucose levels, increased duration of the diabetes, and the severity of diabetic retinopathy.[99,100] Diabetic macular edema is probably caused by a breakdown of the inner blood-retina barrier,[101] but its exact origin is still not fully understood. The degree of retinal thickening has been found to be significantly correlated with visual acuity.[102] Furthermore, macular edema may induce a hyperopic shift in ocular refraction, since it implies a relative shortening in the axial length of the eye.

## 4. Acute hyperglycemia and the refractive properties of the eye

### *4.1 Transient refractive changes during acute hyperglycemia*

In the 19th century it was already recognized that changes in blood glucose

levels can influence visual acuity and ocular refraction in patients with diabetes mellitus.[103-106] Since then, both myopic shifts[106-112] and hyperopic shifts[113-127] have been reported. It has been suggested that myopia develops under hyperglycemic conditions, and that after treatment of the dysregulated diabetes mellitus the refraction will change towards more hyperopia or less myopia.[109,122,128-130]However, there are also studies that have reported hyperopic changes in refraction during acute episodes of hyperglycemia.[116,118,132-134] This lack of consensus may partly be explained by the fact that different analytical approaches were adopted in the studies mentioned above. Although the majority of investigators was interested in the response of the eye when elevated blood glucose levels were reduced to near-normal values, changes at the time of maximal acute hyperglycemia were also reported. Therefore, it is important to define the time-point of the refractive changes, i.e. whether they are present at the time of maximal acute hyperglycemia or after the initiation of treatment for acute hyperglycemia. Previous reports describe the refractive shifts at different time-points after the start of the study. Another explanation for the inconsistency in the literature on refractive changes during hyperglycemia could be the following: both hyperopic and myopic shifts could result from morphological changes in the image formation system of the eye. A decrease in the radius of curvature or the equivalent refractive index of the lens could induce a myopic or a hyperopic change in ocular refraction, respectively. It could be hypothesized that there is a balance between changes in the shape and the refractive index of the lens, which eventually determine the overall refractive outcome.[111,115,131,132] The effect of hyperglycemia on ocular refractive power can be dramatic when treatment is started, and may differ from the sort of changes that occur when the diabetes is under control. In most cases the refractive shifts with hyperglycemia are reversible once effective metabolic control is achieved. Therefore, it is not advisable to change or issue a new prescription for glasses for newly diagnosed patients or patients with poorly controlled diabetes.

*4.2 The lens and the sorbitol pathway*

The mechanisms underlying changes in the shape of the lens with accompanying shifts in refractive power during hyperglycemia are still unclear. Current opinion favors the view that the hydration of the lens changes as a result of osmotic changes. The glucose level of the aqueous humor varies directly with the glucose level of the blood.[135] As the concentration of glucose in the aqueous humor increases, the glucose level within the lens also increases, because the intracellular glucose level in the lens is not regulated by insulin.[136,137] The glucose in the lens is metabolized via the sorbitol pathway, which consists of two enzymes (aldose reductase and sorbitol dehydrogenase) which catalyze the conversion of glucose into its sugar

alcohol sorbitol and the further conversion of sorbitol to fructose. These sugar alcohols tend to accumulate within the lens fibres, because they are membrane impermeable.[138] Consequently, an osmotic gradient between the hypertonic lens and the aqueous humor is built up, resulting in an influx of water from the aqueous humor, producing lenticular swelling.[136] This may lead to a decrease in the radius of curvature and equivalent refractive index of the lens, resulting in changes in ocular refractive power.

## 5. Methods used in the present study

In order to accurately measure the refractive properties of the diabetic and healthy eye the following methods were applied in the present study: corrected Scheimpflug imaging, Hartmann-Shack aberrometry, and optical coherence tomography. These measurement methods will be explained in more detail in the following paragraphs.

### *5.1 Corrected Scheimpflug imaging*

The Scheimpflug camera, which can be regarded as a modified slit-lamp, produces a sharp image of the whole anterior eye segment. The Scheimpflug technique

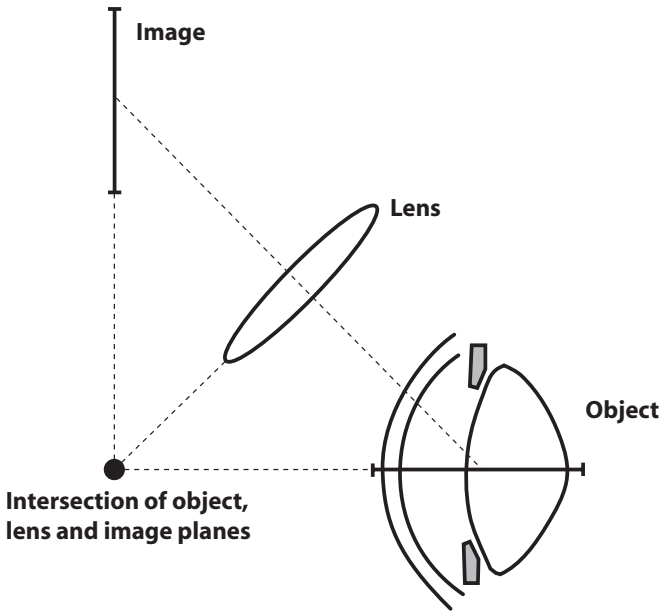



**Figure 6** *Diagram of the Scheimpflug principle: the object, lens, and image planes intersect in one line. This provides a sharp image of the anterior segment of the eye.*

is based on the principle that the image of an obliquely positioned object is formed in such a way that the object, lens, and image planes intersect in one line, thus increasing the depth of focus of the object plane. Figure 6 illustrates the Scheimpflug principle, which is achieved by tilting the image plane. Because of an increased depth of focus and the relatively high resolution of the Scheimpflug image, it is possible to detect small changes in the shape of the cornea and the lens. However, the image of the anterior eye segment, according to the Scheimpflug principle, is sensitive to two types of distortion. Type 1 distortion is the result of the geometry of the Scheimpflug camera. The image becomes distorted because the magnification is not constant over the image, since the image and object plane are not parallel to each other.[139] Type 2 distortion is due to the refraction at the various ocular surfaces.[140-142] For example, the anterior lens surface, as shown on a Scheimpflug image, has been refracted by the anterior and posterior corneal surface. The posterior lens surface is observed through both the cornea and the lens, and correction for type 2 image distortion has been shown to be necessary,[18,143] and has been described in detail by Dubbelman et al.[17,18,144] If these corrections are made, Scheimpflug imaging provides accurate measurements of the geometry of the anterior eye segment.[17,18,144]

*5.2 Hartmann-Shack aberrometry*

Hartmann-Shack aberrometry is a technique that measures not only the ocular refractive power (sphere and cylinder), but also minute imperfections (higher order aberrations) of an optical system. An aberrometer operates by focusing an extremely fine beam of infrared light (wavelength 780 nm) on the retina. When the light beam scatters back from the eye fundus, a 32 x 32 array of micro-lenses captures these rays of light. Corresponding to their focal points, each micro lens forms a spot on a charge-coupled device (CCD) camera. To reconstruct the wavefront of the eye, the spot images or Hartmann-Shack images are analyzed to evaluate the displacements of x and y positions of the central points of the spots from a perfect grid pattern.[145] Figure 7 presents a diagram of the Hartmann-Shack principle.

*5.3 Calculation of the equivalent refractive index of the lens*

The various layers of the lens have different refractive indices: the refractive index is highest at the very center, and lowest at the periphery of the lens.[8] In the present study we calculated the equivalent refractive index of the lens, which is an approximation of the average refractive index of the lens. This is possible by combining the data of the corrected Scheimpflug images on the geometry of the anterior eye segment, a measurement of the axial length of the eye, and a

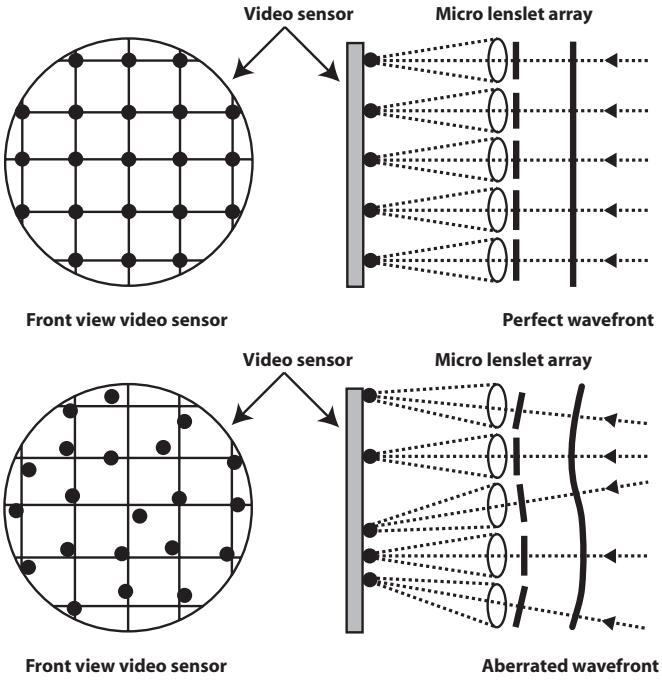



**Figure 7** *Diagram of the Hartmann-Shack principle: minute aberrations of the eye can be determined by comparing the measured wave-front with the wave-front of an optically perfect eye.*

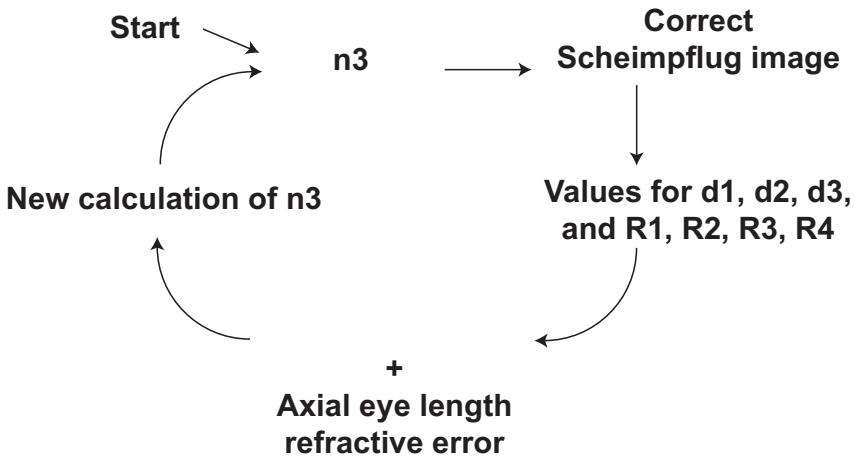



**Figure 8** *Iterative method to calculate the refractive index of the lens (n3). Parameters involved are: corneal thickness (d1), anterior chamber depth (d2), lens thickness (d3), radius anterior corneal surface (R1), radius posterior corneal surface (R2), radius anterior lens surface (R3), and radius posterior lens surface (R4) (after Dubbelman et al.*[18,144]

measurement of the refractive error by means of aberrometry. The equivalent refractive index could then be calculated through an iterative process (Fig 8), which has been developed by Dubbelman et al.[18,144]

*5.4 Optical coherence tomography*

Optical coherence tomography (OCT) is a non-invasive, transpupillary imaging technique which can visualize retinal structures in vivo with a high resolution. Cross-sectional images of the retina are produced through the optical back-scattering of light in a fashion analogous to B-scan ultrasonography. This makes it possible to differentiate the anatomic layers within the retina and to measure the thickness of the retina.[146]

## 6. General overview

In order to accurately determine the thickness and the shape of the cornea, and the thickness, shape and internal structure of the lens, we measured the anterior eye segment in patients with diabetes mellitus type 1 and type 2 and in healthy subjects by means of corrected Scheimpflug imaging (Chapters 2, 3, and 4). The influence of diabetes mellitus type 1 and type 2 on the thickness, radius of curvature, power, and asphericity of the cornea is described in Chapter 2. It was important to find out whether the thickness and shape of the cornea change with diabetes mellitus, in order to determine the contribution of the cornea in sustained diabetic refractive changes. Furthermore, Chapters 3 and 4 describe the influence of diabetes mellitus type 1 and type 2 on the thickness, radius of curvature, equivalent refractive index, power and internal structure of the crystalline lens. We studied the previously reported profound effect of diabetes mellitus on the thickness and shape of the lens, and added to this knowledge the influence of diabetes mellitus on the equivalent refractive index and the refractive power of the lens (Chapter 3). Furthermore, the origin of the increased size of the diabetic lens was investigated by analyzing the internal structure of the lens (Chapter 4).

In Chapters 5, 6, 7 and 8 the underlying mechanisms of blurred vision and refractive changes were investigated by measuring the geometry of the cornea and the lens, the ocular refractive error, and the retinal thickness of the eye during episodes of acute hyperglycemia. The ocular refraction and geometry of the eye of 25 patients with diabetes mellitus were measured during the presence and absence of hyperglycemia and subjective symptoms of blurred vision (Chapter 5). Chapter 6 describes changes in ocular refraction and the lens in a patient with newly diagnosed diabetes mellitus, acute severe hyperglycemia and symptoms of

blurred vision. Furthermore, the refractive properties of the healthy human eye were experimentally measured during acute induced hyperglycemia (Chapter 7), and the same procedure to induce acute hyperglycemia was used to investigate the effect of metabolic dysregulation on the thickness of the retina (Chapter 8). Finally, Chapter 9 provides information on therapeutic possibilities for the treatment of diabetic macular edema, a condition in which symptoms of blurred vision are frequently experienced.

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# Chapter 2

## The influence of chronic diabetes mellitus on the thickness and the shape of the anterior and posterior surface of the cornea

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## Abstract

*Purpose* To determine the influence of diabetes mellitus (DM) type 1 and type 2 on the thickness, radius of curvature, power, and asphericity of the cornea.

*Methods* In this observational cross-sectional study, 102 patients with DM type 1, 101 patients with DM type 2, and 69 healthy subjects were measured by means of Scheimpflug imaging to determine central corneal thickness and the radius and asphericity of the anterior and posterior corneal surfaces. Corneal power was calculated from these parameters. Several systemic parameters (e.g, duration of diabetes, glycated hemoglobin, blood glucose levels, and type of medication) and ocular comorbidity (e.g, stage of retinopathy) were recorded.

*Results* Patients with DM type 1 and 2 had significantly smaller posterior corneal radii ($P < 0.05$) than healthy subjects (men: 6.49/6.48/6.64 mm; women: 6.36/6.30/6.49 mm). As a result, the optical power of the posterior corneal surface of the patients with diabetes differed from that of the healthy subjects ($P < 0.01$; men: DM, 26.2 D; healthy, 26.0 D; women: DM, 26.3 D; healthy, 26.2 D). However, corneal thickness, anterior radius and asphericity, and overall corneal power did not differ significantly between the groups. Furthermore, none of the systemic factors or ocular comorbidity had any influence on the corneal thickness or shape.

*Conclusions* DM affects the posterior corneal radius, resulting in a small change in posterior corneal power. However, chronic DM does not seem to significantly influence the overall corneal power.

# Introduction

The optical components of the eye that are mainly responsible for the refraction of the incoming light are the cornea and the lens. Diabetes mellitus (DM) causes changes in the shape of the lens. These changes, which occur in the radius, thickness, and refractive index of the lens, are believed to be the origin of the refractive changes that are often observed in patients with diabetes.[1–4] In addition to diabetes-induced changes in the lens, various corneal changes caused by DM have also been reported. As a result of structural and functional abnormalities of the cornea, such as an impaired epithelial barrier function,[5,6] decreased endothelial function,[7,8] and altered endothelial cell morphology,[9–11] patients with DM may develop complications such as recurrent corneal erosions, superficial punctuate keratitis, decreased sensitivity,[12,13] delayed wound healing, and corneal edema after vitrectomy.[14,15] Because of this increased risk of corneal complications, refractive surgery, for example, is questionable in patients with DM.[16,17] Furthermore, in patients with chronic DM type 1 and type 2, an increased central corneal thickness (CCT) has been reported.[18–20] Lee et al[18] found that CCT was significantly increased in patients who had DM for > 10 years (595.9 ± 4.2 mm) compared with a healthy control group (567.8 ± 3.8 mm; $P < 0.001$) or patients who had DM for < 10 years (582.2 ± 3.7 mm; $P < 0.05$). However, other studies report that CCT is not increased in DM type 1 or type 2.[21,22]

No reports have yet been made with regard to the influence of DM on posterior and anterior corneal radius of curvature and asphericity. As a result, the long-term effect of DM on corneal shape is not known, and it is unclear whether the cornea could also play a role in explaining the refractive changes in patients with chronic DM. Therefore, the aim of this study was to measure corneal thickness, radius of curvature, power, and asphericity in patients with chronic DM type 1 and type 2 and compare these parameters to those of healthy subjects. In this study, Scheimpflug imaging is used because it allows an accurate measurement of the corneal thickness and also of the radius and asphericity of both the anterior and the posterior corneal surface. Furthermore, the influence of several systemic factors on the cornea, such as the duration of diabetes, glycated hemoglobin values, and actual blood glucose values, was also studied, as well as the stage of diabetic retinopathy and the use of insulin.

## Materials and methods

In this cross-sectional study, a total of 272 subjects (69 control subjects, 102 patients with DM type 1 and 101 patients with DM type 2) were measured in the Department of Ophthalmology at the VU University Medical Center in Amsterdam. Subjects with glaucoma, or a history of intraocular surgery and subjects, who had worn contact lenses in the previous 2 years, were excluded. Age, duration of diabetes, glycated hemoglobin levels, and the type of medication were recorded. Blood glucose levels were measured with a blood glucose analyzer (HemoCue Diagnostics BV, Oisterwijk, the Netherlands). Two independent ophthalmologists (BP, PR) used the EURODIAB classification system to determine the stage of diabetic retinopathy from two-field digital color 45° fundus photographs.23 For practical reasons, the EURODIAB levels of retinopathy were sub-divided into three categories; retinopathy absent (EURODIAB level 0), retinopathy present (EURODIAB levels 1, 2, 3) and retinopathy after photocoagulation or proliferative retinopathy (EURODIAB level 4 or 5). The diagnosis of DM type 1 or type 2 was established according to the guidelines issued by the World Health Organization.[24] The Medical Ethics Committee of the VU University Medical Center in Amsterdam approved the protocol of this study, and written informed consent was obtained from all participants, according to the tenets of the Declaration of Helsinki.

The right eye of each participant was studied. Refractive error was measured with an IRX3 aberrometer (Imagine Eye Optics, Paris, France), and calculated as: equivalent refractive error (ERE) = sphere + (cylinder / 2). The ERE varied between -9.6 and 5.8 D (mean ± SD: -1.0 ± 2.6 D) in the control group, between -10.3 and 4.0 D (mean ± SD: -1.2 ± 2.1) in the DM type 1 group and between -10.1 and 7.1 D (mean ± SD: -0.5 ± 2.6) in the DM type 2 group.

Images of the cornea were obtained with a Topcon SL-45 Scheimpflug camera, equipped with a charge coupled device (CCD) camera (St-9XE, SBIG astronomical instruments) with a range of 16 bits of grey values (512 x 512 pixels, pixel size 20 x 20 μm, magnification: 1x). All Scheimpflug images were taken along the optical axis. One series of three Scheimpflug images was made in both horizontal (0°) and vertical (90°) meridians. Ray-tracing was used to correct the images for distortion due to the geometry of the Scheimpflug camera and due to the refraction of the anterior corneal surface. Consequently, this provided an accurate measurement of the corneal thickness and the shape of the posterior surface of the cornea (Fig. 1). This method has been described in detail by Dubbelman et al.[25] Since the Scheimpflug images of the diabetic and control subjects were also used

to study the shape of the lens, 1.0% cyclopentolate and 5% phenylephrine eye-drops were administered to each right eye to obtain maximal pupillary dilation and paralysis of accommodation.

To provide a description of the asphericity of the cornea, the following conic of revolution[26-28] was used:

$$y = \frac{c(x - x_0)^2}{1 + \sqrt{1 - kc^2(x - x_0)^2}} + y_0 \qquad (1)$$

The curvature c = 1/r, r is the radius of curvature at the vertex (x0,y0). The conic constant k indicates how fast a surface steepens (k > 1) or flattens (k < 1) with distance from the apex. Therefore, the value of k describes the degree to which an aspherical surface differs from the equivalent spherical surface. The surface

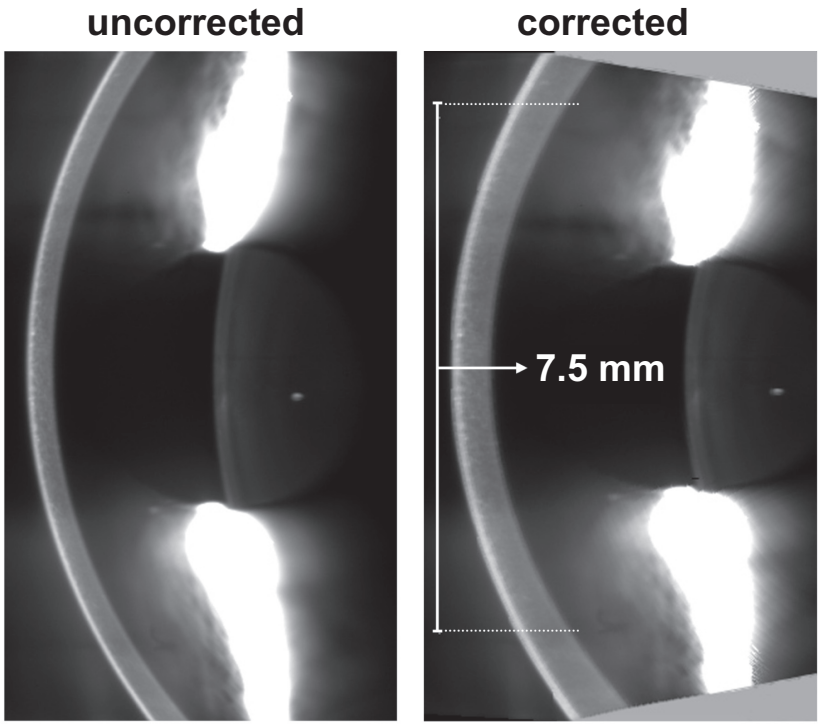


**Figure 1** *Corrected Scheimpflug imaging provides an accurate measurement of the thickness, shape and asphericity of the cornea; the aperture of 7.5 mm has been indicated in the corrected image. Note the change in the corneal thickness and the shape of the posterior surface after correction.*

represents a hyperboloid when k < 0, a paraboloid when k = 0, a prolate spheroid when 0 < k < 1, a circle when k = 1, and an oblate spheroid when k > 1. This conic of revolution was fitted for both anterior and posterior corneal surfaces at an aperture of 7.5 mm. Finally, in horizontal and vertical meridians, the corneal thickness, the radius at the vertex and the k value were determined.

The following formulas were used to calculate the power (P) of the anterior and the posterior surface of the cornea in diopters, with the refractive index of air ($n_0$), the cornea ($n_1$), and the aqueous humor ($n_2$), the anterior radius ($r_a$) and the posterior radius ($r_p$):

$$P_{anterior} = \frac{n_1 - n_0}{r_a} \quad (2)$$

$$P_{posterior} = \frac{n_2 - n_1}{r_p} \quad (3)$$

The overall corneal power (P) was calculated with the Lensmaker's equation,[29] with corneal thickness t:

$$P = P_{anterior} + P_{posterior} - \frac{t}{n_1} P_{anterior} P_{posterior} \quad (4)$$

Statistical analysis of corneal thickness, radius and asphericity in all participants was performed with independent Student's t-tests, linear regression and analysis of variance (ANOVA) with multiple comparisons, using the Bonferroni post hoc method. Multiple regression analysis was applied to adjust for age in the analysis of corneal asphericity, and to correct for gender in the analysis of corneal radius. A quadratic covariate (age-mean age)$^2$ was used in the statistical analysis for ERE, since ERE is known to slightly change with age.[30-32] Two-sided p-values < 0.05 were considered to be statistically significant. All analyses were performed with SPSS 12.0.1 software.

# Results

Table 1 presents the baseline characteristics of the three groups. Mean age was significantly different in the DM type 2 group compared to the control group and the DM type 1 group ($p < 0.001$). No statistically significant difference was found in ERE between the three groups ($p = 0.37$). The mean central corneal thickness (CCT) was 0.578 mm (SE 0.004) in the control group, 0.586 mm (SE 0.003) in the DM type 1 group, and 0.578 mm (SE 0.003) in the DM type 2 group. No statistically significant correlation was found between CCT and age and no significant differences in CCT were observed between the three groups ($p = 0.19$).

| | Control group (n = 69) | DM type 1 (n = 102) | DM type 2 (n = 101) |
|---|---|---|---|
| Age in years; ( range) | 36.6 ± 14.2; (18-65) | 39.9 ± 10.8; (18-60) | 56.4 ± 7.0; (36-65)* |
| Equivalent refractive error (Dpt) [a] | -1.02 ± 2.58 | -1.22 ± 2.12 | -0.52 ± 2.59 |
| Gender (male/female) (n) | 29 / 40 | 58 / 44 | 54 / 47 |
| Duration of diabetes (years) [b] | | 21.0 ± 11.7 | 8.8 ± 7.5** |
| Glycated hemoglobin (%) | | 8.1 ± 1.6 | 7.5 ± 1.4** |
| Actual blood glucose (mg/dl) | | 175 ± 83 | 143 ± 58** |
| Medication (n / total n) | | | |
| Insulin | | 102 / 102 | 59 / 101 |
| Other (oral anti-diabetics or diet) | | 0 / 102 | 42 / 101 |
| Retinopathy (n / total n) [c] | | | |
| Retinopathy absent | | | |
| EURODIAB 0 | | 52 / 102 | 64 / 101 |
| Retinopathy present | | | |
| EURODIAB 1 | | 12 / 102 | 13 / 101 |
| EURODIAB 2 | | 7 / 102 | 9 / 101 |
| EURODIAB 3 | | 1 / 102 | 3 / 101 |
| EURODIAB 5 | | 1 / 102 | 0 / 101 |
| Retinopathy after photocoagulation | | | |
| EURODIAB 4 | | 29 / 102 | 12 / 101 |

Data are presented as mean ± SD. [a] Equivalent refractive error was corrected for age in the three groups. [b] Duration of diabetes was corrected for age in the two diabetic groups. [c] Retinopathy was subdivided into three categories; retinopathy absent (EURODIAB level 0), retinopathy present (EURODIAB level 1,2,3), and retinopathy after photocoagulation or proliferative retinopathy (EURODIAB level 4 or 5). *Significantly different, compared to the control group and the DM type 1 group, $p < 0.001$. **Significantly different, compared to the DM type 1 group, $p < 0.001$.

**Table 1** *Baseline characteristics of the control group and the two diabetic groups*

| | Control group (n = 69) | | DM type 1 (n = 102) | | DM type 2 (n = 101) | |
|---|---|---|---|---|---|---|
| | males (n = 29) | females (n = 40) | males (n = 58) | females (n = 44) | males (n = 54) | females (n = 47) |
| *Anterior cornea* | | | | | | |
| mean radius (mm) | 7.86 ± 0.04 | 7.70 ± 0.03 | 7.87 ± 0.04 | 7.69 ± 0.03 | 7.82 ± 0.04 | 7.62 ± 0.03 |
| 0° | 7.90 ± 0.04 | 7.73 ± 0.03 | 7.89 ± 0.04 | 7.74 ± 0.03 | 7.83 ± 0.04 | 7.66 ± 0.04 |
| 90° | 7.83 ± 0.04 | 7.68 ± 0.03 | 7.85 ± 0.04 | 7.64 ± 0.04 | 7.80 ± 0.04 | 7.59 ± 0.03 |
| power (Diopters) | 47.8 ± 0.2 | 48.8 ± 0.2 | 47.8 ± 0.2 | 48.9 ± 0.2 | 48.1 ± 0.2 | 49.4 ± 0.2 |
| *Posterior cornea* | | | | | | |
| mean radius (mm) | 6.64 ± 0.04 | 6.49 ± 0.04 | 6.49 ± 0.04 | 6.36 ± 0.04 | 6.48 ± 0.04 | 6.30 ± 0.03 |
| 0° | 6.74 ± 0.04 | 6.56 ± 0.04 | 6.62 ± 0.04 | 6.51 ± 0.03 | 6.61 ± 0.04 | 6.41 ± 0.03 |
| 90° | 6.54 ± 0.05 | 6.43 ± 0.04 | 6.35 ± 0.04 | 6.22 ± 0.04 | 6.32 ± 0.04 | 6.18 ± 0.04 |
| power (Diopters) | -6.03 ± 0.04 | -6.17 ± 0.03 | -6.17 ± 0.04 | -6.27 ± 0.03 | -6.19 ± 0.04 | -6.36 ± 0.03 |
| *Overall cornea* | | | | | | |
| power (Diopters) | 41.8 ± 0.2 | 42.7 ± 0.2 | 41.7 ± 0.2 | 42.5 ± 0.2 | 42.0 ± 0.2 | 43.0 ± 0.2 |

**Table 2** *Radius (± SE) and power of the anterior and posterior surface of the cornea for males and females in the three groups*

The anterior and posterior corneal radius differed significantly between males and females in all three groups ($p < 0.01$ and $p < 0.05$, respectively); therefore, the analyses were performed with correction for gender. Values of the anterior and posterior radius and the power of the cornea of the males and females in the three groups are summarized in Table 2. Comparisons were made between the groups with regard to the 0º and 90º meridians, and the results appeared to be similar for both meridians. No significant difference in anterior radius and anterior corneal power was found between the three groups. However, two-way analysis of variance revealed a significant difference in mean posterior radius and power of the cornea between the three groups ($p < 0.001$). Table 3 shows that the mean posterior radius was significantly smaller and that the power of the posterior cornea was significantly larger in the two diabetic groups, compared to the control group. However, the power of the whole cornea was not affected by DM (Table 3).

Asphericity is expressed in the conic constant (k-value), which is an indication of how rapidly a surface flattens ($k < 1$) or steepens ($k > 1$) with distance from the apex. Simple linear regression showed that in the control group the k-value of both corneal surfaces was age-dependent.33 With age, the k-value of the anterior corneal surface increased ($p = 0.03$), whereas the k-value of the posterior surface decreased ($p = 0.002$). Therefore, corrections for age had to be made.

| | Difference in the means (± SE) | 95% Confidence Interval for the difference in the means | P-value |
|---|---|---|---|
| *Mean posterior radius (mm)* | | | |
| Control group - DM type 1 | 0.14 ± 0.04 | 0.05 to 0.23 | 0.001 |
| Control group - DM type 2 | 0.18 ± 0.04 | 0.09 to 0.28 | < 0.001 |
| DM type 1 - DM type 2 | 0.04 ± 0.04 | -0.05 to 0.13 | 0.82 |
| *Posterior power (Diopters)* | | | |
| Control group - DM type 1 | 0.14 ± 0.04 | 0.04 to 0.23 | 0.001 |
| Control group - DM type 2 | 0.18 ± 0.04 | 0.08 to 0.27 | < 0.001 |
| DM type 1 - DM type 2 | 0.04 ± 0.04 | -0.04 to 0.13 | 0.75 |
| *Overall power (Diopters)* | | | |
| Control group - DM type 1 | 0.19 ± 0.21 | -0.32 to 0.70 | > 0.99 |
| Control group - DM type 2 | -0.13 ± 0.21 | -0.64 to 0.39 | > 0.99 |
| DM type 1 - DM type 2 | -0.32 ± 0.20 | -0.79 to 0.16 | 0.33 |

**Table 3** *Results of multiple regression analysis of the posterior radius and power, corrected for gender, when comparing the three groups; differences in the means are presented with standard errors*

Mean anterior asphericity was 0.88 (SE 0.01) in the DM type 1 group, 0.88 (SE 0.01) in the DM type 2 group, and 0.88 (SE 0.01) in the control group. Anterior asphericity did not differ between the three groups. This was also the case for the posterior asphericity. Mean posterior asphericity was 0.69 (SE 0.02) in the DM type 1 group, 0.72 (SE 0.02) in the DM type 2 group, and 0.69 (SE 0.02) in the control group. No significant difference was found when comparing the three groups.

Figure 2 provides an illustration of the marginal influence of DM on the shape of the cornea. In the present study, it was found that the radius of the posterior corneal surface was 0.14 mm (DM type 1) and 0.18 mm (DM type 2) smaller compared to that of the control group. This results in a thickening of the diabetic cornea in the periphery, because the CCT and the anterior corneal radius did not change. At a distance of 3.75 mm from the apex of the cornea, the peripheral thickening is approximately 20 μm and 26 μm for the DM type 1 group and the DM type 2 group, respectively.

In order to determine associations between the corneal parameters (CCT, radius and asphericity) and several systemic factors, such as duration of DM, levels of glycated hemoglobin, actual blood glucose levels, and use of insulin, simple linear regression analysis was performed for each of the variables in the two diabetic groups. No associations were found between the systemic factors and the

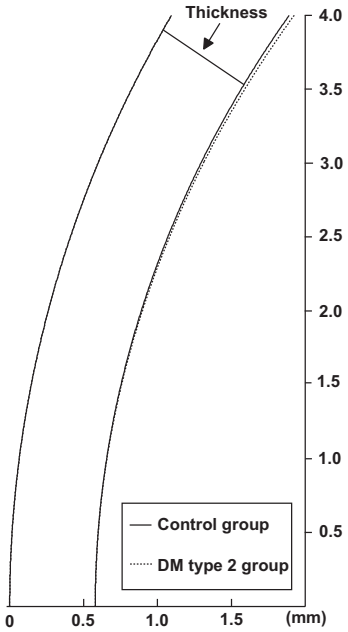


**Figure 2** *Illustration of the change in posterior corneal radius due to diabetes, resulting in a peripheral thickening of the cornea; the mean corneal shape is indicated for the control group (solid line), and for the DM type 2 group (dashed line). The central corneal thickness and the anterior corneal radius did not change.*

corneal parameters. It was also found that the level of retinopathy (retinopathy absent, retinopathy present and retinopathy after photocoagulation or proliferative retinopathy) did not significantly influence any of the corneal parameters.

## Discussion

The aim of the present study was to determine the influence of DM on the shape, thickness and power of the cornea by measuring these corneal parameters in patients with chronic DM type 1 and type 2, and compare them to those of healthy subjects. Several studies have investigated the effect of hyperglycaemia on refraction, but there seems to be no agreement on the exact cause of refractive change in unstable diabetes. It has been reported that refractive changes in patients with chronic DM are caused by alterations in the lens,[1-4] but the exact contribution of the cornea to these refractive changes is still unknown. Corneal topographic parameters were measured in patients who received intensive treatment for acute severe hyperglycemia by Sonmez et al.[34] They concluded

that changes in these corneal topographic parameters might be a potential source of error for refractive and cataract surgery during the treatment period of acute hyperglycemia. In patients with chronic DM, this study is the first in which corneal shape has been measured by means of corrected Scheimpflug imaging. It is important to correct the Scheimpflug images for distortion due to the geometry of the camera and refraction of the anterior corneal surface in order to obtain an accurate measurement of the corneal thickness and posterior corneal surface.[25] The anterior corneal shape did not seem to be affected by DM, but the posterior corneal radius decreased due to the influence of DM, and this resulted in a small, but significant change in posterior corneal power. However, the posterior corneal power contributes little to the overall refractive state of the eye, and even in the total corneal power (both anterior and posterior) no significant difference was found between the diabetic groups and the control group. Therefore, chronic DM does not seem to significantly influence the overall corneal power.

In this study, the CCT of the two diabetic groups did not differ from that of the control group. These results are in agreement with the findings of Inoue et al, who found no significant differences in CCT between 99 subjects with DM type 2 and 97 healthy subjects.[10] In smaller study groups, Keoleian et al.[21] and Ziadi et al.[22] also reported no differences in CCT between subjects with DM and healthy subjects. In the present study, CCT appeared not to be dependent on various systemic parameters such as duration of DM, glycated hemoglobin, actual blood glucose levels, and use of insulin. In 81 subjects with DM type 1, Busted et al also reported no significant correlations between diabetes duration, blood glucose levels or use of insulin and CCT.[19] However, in contrast to the present study they found an association between the level of retinopathy and CCT. In diabetic subjects with proliferative retinopathy, CCT was 566 µm compared to 544 µm and 527 µm in diabetic subjects without retinopathy and healthy subjects, respectively. Lee et al. reported that CCT increased significantly with increasing duration of DM in 200 diabetic subjects.[18] Mean CCT was 596 µm, 582 µm and 567 µm in subjects with DM of more than 10 years, subjects with DM of less than 10 years, and healthy subjects, respectively. A main difference between the present study and the studies mentioned above were the measuring methods (Scheimpflug imaging versus ultrasound pachymetry). In order to perform ultrasound pachymetry, the velocity of sound in the cornea is needed. It could be that DM causes a change in this velocity of sound, because the different corneal layers are known to be affected by DM.[5,8,9] This could result in a difference between the CCT of healthy subjects and the CCT of subjects with DM.

Several studies have shown that DM causes changes in corneal endothelial cell morphology, similar to those induced by aging.[35,36] It could therefore be

hypothesized that DM causes premature aging of the eye. In healthy subjects, corneal asphericity was found to be age-dependent.[33] Consequently, in diabetic subjects it could be assumed that asphericity would be affected more than in healthy subjects. This study shows that this is not the case, because no significant change in the asphericity of the anterior or the posterior corneal surface was found. DM only has a significant influence on the radius of the posterior corneal surface. Nonetheless, this influence is so small that it does not change the optical power of the diabetic cornea.

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# Chapter 3

## The influence of diabetes mellitus type 1 and 2 on the thickness, shape and equivalent refractive index of the human crystalline lens

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## Abstract

*Purpose:* To study the influence of diabetes mellitus (DM) type 1 and type 2 on the thickness, radius of curvature, equivalent refractive index and power of the crystalline lens.

*Methods:* Lens thickness and the radius of the anterior and posterior surfaces of the lens were measured in 114 patients with DM type 1, 112 patients with DM type 2 and 75 healthy control subjects by means of corrected Scheimpflug imaging. Ocular refractive error was determined with Hartmann-Shack aberrometry. The equivalent refractive index and the power of the lens were calculated from these parameters. Several systemic parameters (e.g. duration of DM, glycated hemoglobin, capillary blood glucose levels, and type of medication) and ocular comorbidity (e.g. level of diabetic retinopathy) were recorded.

*Results:* The lenses of the patients with DM type 1 were significantly thicker and more convex, compared to those of the control group ($p < 0.001$). Furthermore, there was a significant decrease in the equivalent refractive index of their lenses, compared to the control group. No difference in lens parameters was found between the patients with DM type 2 and the control group. In the DM type 1 group, the duration of DM was an important determinant of lens biometry; the independent effect of the duration of DM per year on lens thickness, anterior radius, posterior radius and equivalent refractive index was respectively 95%, 88%, 207%, and 45% of the effect of age per year. Lens power and ocular refractive error were not affected by DM type 1 or type 2.

*Conclusions:* The results of the present study show that DM type 1 has a major impact on lens biometry. Furthermore, the difference in effect of DM type 1 and type 2 on lens biometry may indicate a fundamental difference in pathogenesis. The decrease in equivalent refractive index of the lens appeared to compensate for the profound increase in lens convexity in patients with DM type 1, resulting in no significant change in lens power or ocular refraction with the duration of DM.

# Introduction

The human lens continues to grow throughout life, due to the addition of new lens fibers. As a result, the lens becomes thicker and more convex with age.[1,2] In patients with diabetes mellitus (DM) the lens has been found to become even thicker and more convex, compared to that of healthy subjects.[3-11] In patients with DM type 1, Sparrow et al.[5] found that the duration of DM is a powerful determinant of lens biometry. After correction for the effect of age, they reported that the independent effect of the duration of DM per year on lens thickness and curvature was respectively 68% and 88% of the effect of age per year.

The normal increase in convexity of the lens with age could be expected to result in an increase in lens power, and thus a tendency towards myopia. Nevertheless, in the healthy eye no such tendency could be observed and it was even found that there was a hyperopic shift in refractive error.[12,13] This paradoxical occurrence of an increase in lens convexity with no myopic shift in ocular refractive error has been called the "lens paradox".[14] An explanation for this lens paradox was found in a decrease in the refractive index of the lens with age, which compensates for the more convex shape of the lens with age.[2, 15-18]

As mentioned above, the increase in convexity of the diabetic lens with the duration of DM has been reported to be very large. Nevertheless, as in healthy subjects, large myopic shifts with age have not been consistently observed in patients with DM. Fledelius[19] reported a myopic shift in patients with DM, compared to subjects with no DM. However, in the Beaver Dam Eye Study and in a study of a large rural South Indian population, a tendency towards hyperopia was found in patients with DM.[20,21] Furthermore, no influence of DM on ocular refraction was observed in the Blue Mountains Eye Study.[22,23] Therefore, the question that arises is whether the change in shape of the diabetic lens is perhaps smaller than previously reported, or that the large change in shape of the lens is compensated by a decrease in the equivalent refractive index, similar to that in the healthy eye. A decrease in the equivalent refractive index of the lens would prevent the diabetic eye from becoming more myopic with increasing age and duration of DM.

In order to answer this question, an accurate measurement of the biometry of the lens is necessary to make it possible to calculate the equivalent refractive index of the lens. This measurement can be obtained with corrected Scheimpflug imaging,[2, 24] in which the distortion due to the refraction of the front and back surface of the cornea and the front surface of the lens is taken into account by individual ray-tracing. The correction of Scheimpflug images has been shown to

be important, because the refraction that occurs at the various ocular interfaces, and the distortion due to the geometry of the Scheimpflug camera, produce a distorted image of the anterior eye segment.[2, 24, 26]

Therefore, the aim of the present study was to accurately measure lens biometry in subjects with DM type 1 and type 2 by means of corrected Scheimpflug imaging, in order to study the influence of DM on the thickness and shape of the lens. We also calculated the equivalent refractive index of the lens from the Scheimpflug parameters, in combination with the equivalent refractive error and axial eye length measurements.[1, 24] This, together with the calculation of the power of the lens, made it possible to investigate a compensation mechanism for the changes in lens biometry caused by DM. All lens parameters (thickness, anterior and posterior radius, equivalent refractive index and power) were compared to those of control subjects. Finally, in the two DM groups we investigated the influence of several systemic factors, such as the duration of DM, glycated hemoglobin (HbA1c), capillary blood glucose levels, the level of diabetic retinopathy (DRP), and the use of insulin, on lens biometry.

## Materials and methods

In this cross-sectional study, the right eye of a total of 301 subjects (75 control subjects, 114 patients with DM type 1 and 112 patients with DM type 2) was measured at the Department of Ophthalmology of the VU University Medical Center in Amsterdam. The diagnosis of DM type 1 or type 2 was established according to the guidelines issued by the World Health Organization.[27] Participants with cataract, glaucoma, a history of intraocular surgery, or ocular pathology other than DRP were excluded. Age, duration of DM, HbA1c, and the type of medication were recorded. Capillary blood glucose levels were measured with a blood glucose analyzer (HemoCue Diagnostics BV, Oisterwijk, the Netherlands) before the ocular measurements were made. The Medical Ethics Committee of the VU University Medical Center in Amsterdam approved the protocol of the study, and written informed consent was obtained from all participants, according to the tenets of the Declaration of Helsinki.

*Ocular measurements*

The right eye of each participant was measured after the administration of 1.0% cyclopentolate and 5% phenylephrine eye-drops to obtain maximal pupillary dilation and paralysis of accommodation. Images of the lens were obtained with a Topcon SL-45 Scheimpflug camera, equipped with a charge-coupled device

(CCD) camera (St-9XE, SBIG astronomical instruments, Santa Barbara, USA) with a range of 16 bits of grey values (512 x 512 pixels, pixel size 20 x 20 μm, magnification: 1x). One series of three Scheimpflug images was made in the vertical (90°) meridian along the optical axis. Ray-tracing was used to correct the images for distortion due to the geometry of the Scheimpflug camera and the refraction of the different ocular surfaces. The method used to correct Scheimpflug images has been described in detail by Dubbelman et al. (Fig 1).[2] By combining the measurements of the corneal thickness (d1), the depth of the anterior chamber (ACD), the anterior (R1) and posterior (R2) radius of the cornea, the lens thickness (d3) and the anterior (R3) and posterior (R4) radius of the lens, the axial length of the eye, and the ocular refraction, it is possible to calculate the equivalent refractive index of the lens (n lens) by means of an iterative process.[2, 24]

The following formulas were applied to calculate the power (P) of the anterior and the posterior surface of the lens in diopters (D), with the refractive indices of the aqueous humor (n2), the lens ($n_{lens}$), the vitreous (n4), and the radius of the anterior (R3) and the posterior (R4) surface of the lens:

$$P_{anterior} = \frac{n_{lens} - n_2}{R3} \qquad (1)$$

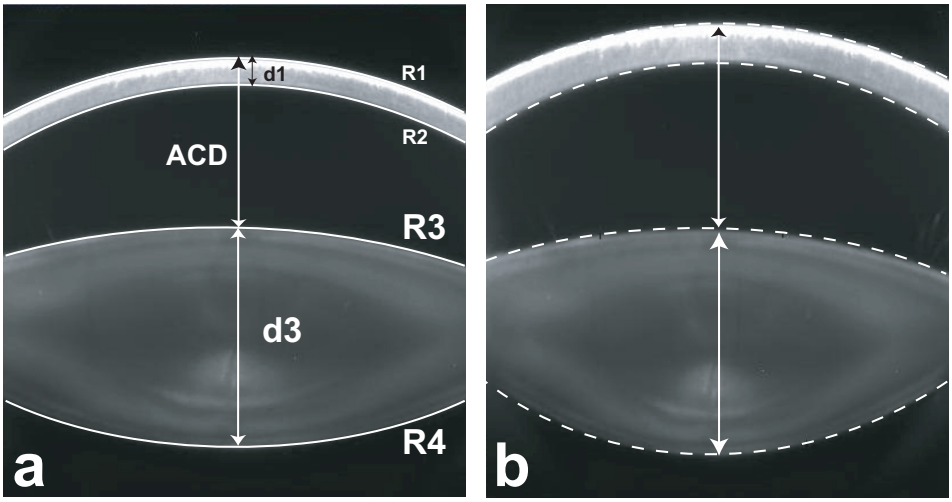


**Figure 1** *Uncorrected (a) and corrected (b) Scheimpflug images of an 25 year old female. Note the thicker cornea (d1), lens (d3) and the increased anterior chamber depth (ACD) after correction for the distortions due to the geometry of the Scheimpflug camera and the refraction of the various ocular surfaces. R1 = anterior radius cornea, R2 = posterior radius cornea, R3 = anterior radius of the lens, R4 = posterior radius of the lens.*

$$P_{posterior} = \frac{n_4 - n_{lens}}{R4} \quad (2)$$

The lens power (P) was calculated with the Lensmaker equation,[28] with lens thickness (d3):

$$P = P_{anterior} + P_{posterior} - \frac{d3}{n_{lens}} P_{anterior} P_{posterior} \quad (3)$$

In some older participants and participants who had DM for a long time, the posterior surface of the lens was not visible. Therefore, d3, R4, $n_{lens}$, and lens power could only be determined in 67 of the 75 control subjects, in 55 of the 114 patients with DM type 1, and in 32 of the 112 patients with DM type 2. The other parameters (R3 and ACD) could be measured in all 301 subjects. The ocular refractive error was measured with an IRX3 aberrometer (Imagine Eye Optics, Paris, France), and calculated as: equivalent refractive error = sphere + (cylinder / 2). The axial length of the eye was measured with an IOL-master (Carl Zeiss Inc., North America). The ACD was determined by measuring the distance from the anterior surface of the cornea to the anterior surface of the lens.

The level of DRP was graded from two-field digital color 45° fundus photographs by two independent ophthalmologists (BP, PR) according to the EURODIAB classification system.[29] For practical reasons, the EURODIAB levels of retinopathy were sub-divided into three categories; retinopathy absent (EURODIAB level 0), retinopathy present (EURODIAB levels 1, 2, 3) and retinopathy after photocoagulation or proliferative retinopathy (EURODIAB level 4 or 5).

*Statistical analysis*

First of all, preliminary analysis of the lens biometry was performed by means of simple linear regression of the lens parameters against age in each group separately. The linearity of the effect of age on the lens parameters was determined from normal probability plots of regression-standardized residuals; the age-effect was linear in each group. Multiple linear regression analysis was then applied to test the influence of various independent variables (such as duration of DM, HbA1c or capillary blood glucose levels) on the lens parameters in the DM groups. Furthermore, multiple linear regression analysis was also performed to study significant differences between the three groups. The independent variable

age and/or duration of DM was added to adjust for the effect of age and/or the duration of DM. A difference in regression slopes between the groups was tested by adding a product-term to the model. In the analysis of the equivalent refractive error, a quadratic covariate (age-mean age)2 was added to the model, since the equivalent refractive error is known to change slightly with age.[12, 20, 22] All data were approximately normally distributed, and two-sided p-values $< 0.05$ were considered to be statistically significant. All analyses were performed with SPSS 14.0 software.

## Results

The baseline characteristics of the three groups are presented in Table 1. The mean age in the two diabetic groups differed significantly from that of the control group ($p < 0.001$). No statistically significant difference was found in the equivalent refractive error or axial eye length between the three groups. There was a significant difference in the duration of DM, HbA1c and blood glucose levels between the two DM groups.

Preliminary simple linear regression analyses demonstrated the important and significant effect of age on lens biometry and ACD in the three groups. This effect has been shown in Figures 2 to 6. From these graphs it can also be seen that the slopes of the regression lines of the lens parameters of the DM type 1 group are steeper than those of the control group or the DM type 2 group. These preliminary results were confirmed by the multiple regression analyses, in which adjustments were made for the effect of age. DM type 1 appeared to be a powerful and significant determinant of lens biometry. After adjustment for age, the lenses of the patients with DM type 1 were significantly thicker, were more convex, and had a lower equivalent refractive index and ACD than those of the control group (Table 2).

Furthermore, a significant difference in the regression slopes of lens thickness d3 (95% CI: 0.001 to 0.018; $p = 0.021$), anterior radius R3 (95% CI: -0.064 to -0.009; $p = 0.009$), posterior radius R4 (95% CI: -0.043 to -0.002; $p = 0.031$), equivalent refractive index nlens (95% CI: -0.001 to -0.0001; $p = 0.006$) and ACD (95% CI: -0.017 to -0.001; $p = 0.025$) was found between the DM type 1 group and the control group. DM type 2 had no significant effect on the lens parameters or ACD (Table 2), and the regression slopes of the lens parameters (d3, R3, R4, n lens, and ACD) in the DM type 2 group did not differ from those of the control group. To investigate whether the difference in lens parameters was entirely due to the influence of DM, comparisons with adjustments for age and

| | Control group (n = 75) | DM type 1 (n = 114) | DM type 2 (n = 112) |
|---|---|---|---|
| Age in y; ( range) | 36.8 ± 13.5;(18-64) | 41.0 ± 11.6;(18-65)* | 58.5 ± 8.6; (36-76)* |
| Gender (male/female) (n) | 32 / 43 | 62 / 52 | 62 / 50 |
| Equivalent refractive error (D)[a] | -0.94 ± 2.64 | -0.62 ± 2.48 | 0.20 ± 2.72 |
| Axial eye length (mm) | 24.0 ± 1.2 | 23.6 ± 1.0 | 23.5 ± 0.8 |
| Duration of diabetes (y)[a] | | 22.5 ± 12.0 | 9.0 ± 7.4*** |
| Glycated hemoglobin (%) | | 8.0 ± 1.5 | 7.5 ± 1.5** |
| Capillary blood glucose (mmol/l) | | 9.6 ± 4.5 | 8.0 ± 3.4*** |
| Medication (n / total n) | | | |
| Insulin | | 114 / 114 (100%) | 65 / 112 (58%) |
| Other (oral anti-diabetics or diet) | | 0 / 114 (0%) | 47 / 112 (42%) |
| Retinopathy (n / total n)[b] | | | |
| Retinopathy absent | | | |
| EURODIAB 0 | | 56 / 114 (49%) | 76 / 112 (67%) |
| Retinopathy present | | | |
| EURODIAB 1 | | 13 / 114 (11%) | 12 / 112 (11%) |
| EURODIAB 2 | | 9 / 114 (8%) | 9 / 112 (8%) |
| EURODIAB 3 | | 1 / 114 (0.9%) | 3 / 112 (3%) |
| Retinopathy after photocoagulation or proliferative retinopathy | | | |
| EURODIAB 4 | | 34 / 114 (30%) | 12 / 112 (11%) |
| EURODIAB 5 | | 1 / 114 (0.9%) | 0 / 112 (0%) |

Data are presented as mean ± SD. [a]Comparisons between the groups in equivalent refractive error and duration of diabetes were adjusted for age. [b]Retinopathy was sub-divided into three categories; retinopathy absent (EURODIAB level 0), retinopathy present (EURODIAB level 1,2,3), and retinopathy after photocoagulation or proliferative retinopathy (EURODIAB level 4 or 5). * Significantly different compared to the control group, $p = 0.04$ (DM type 1) and $p < 0.001$ (DM type 2). ** Significantly different compared to the DM type 1 group, $p = 0.02$. *** Significantly different compared to the DM type 1 group, $p < 0.01$.

**Table 1** *Baseline characteristics of the control group and the two DM groups (DM type 1 and type 2)*

duration of DM were made between the three groups. No significant differences in lens parameters or ACD were found between the three groups after correction for age and duration of DM.

In the DM type 1 group the duration of DM was found to have a significant influence on the lens parameters d3, R3, R4, n lens, and ACD ($p < 0.05$) (Table 3). In this group, the independent effect of the duration of DM per year on d3, R3, R4, n lens, and ACD was 95%, 88%, 207%, 45%, and 75% of the effect of age per year, respectively. The important effect of the duration of DM on a DM type 1 lens is illustrated in Figure 7, which shows a 37-year age-effect and an additional 31-year duration of DM effect on lens biometry. In the DM type 2 group, a significant effect of the duration of DM on R3 was found (Table 3). The effect of the duration of DM on the lens parameters was equal in males and

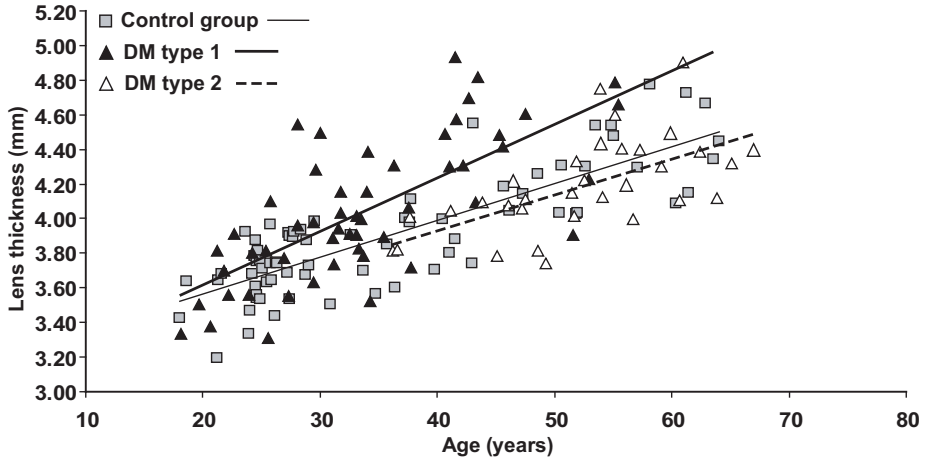


**Figure 2** *Graph of preliminary data of the lens thickness (d3) against age in the three groups. Slopes are presented with standard errors (± SE), r = regression coefficient. Control group: d3 = 3.14 (± 0.07) + 0.021 (± 0.002) * age, n = 67, r = 0.83, p < 0.001. DM type 1: d3 = 3.00 (± 0.15) + 0.031 (± 0.004) * age, n = 55, r = 0.71, p < 0.001. DM type 2: d3 = 3.10 (± 0.29) + 0.021 (± 0.006) * age, n = 32, r = 0.59, p = 0.001.*

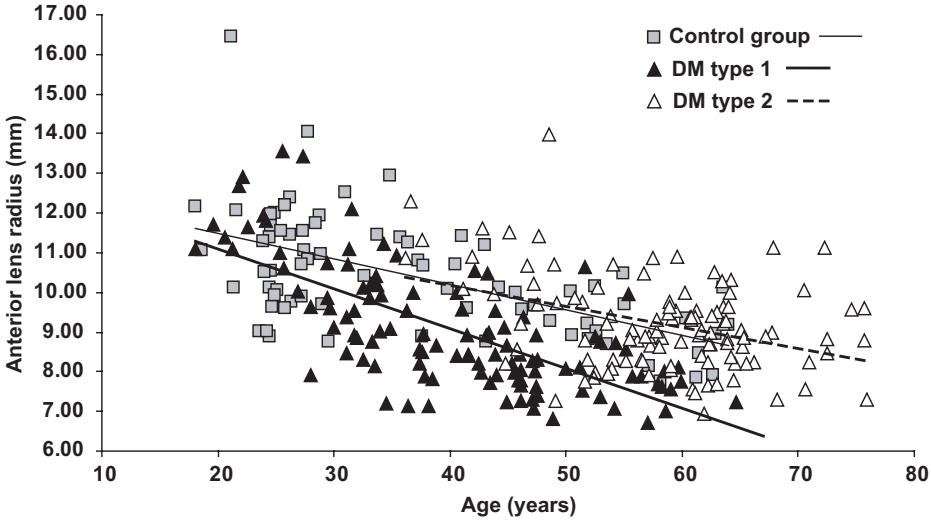


**Figure 3** *Graph of preliminary data of the anterior lens radius (R3) against age in the three groups. Slopes are presented with standard errors (± SE), r = regression coefficient. Control group: R3 = 12.79 (± 0.41) - 0.064 (± 0.010) * age, n = 75, r = 0.58, p < 0.001. DM type 1: R3 = 13.11 (± 0.40) - 0.101 (± 0.010) * age, n = 114, r = 0.70, p < 0.001. DM type 2: R3 = 12.27 (± 0.72) - 0.053 (± 0.012) * age, n = 112, r = 0.38, p < 0.001.*

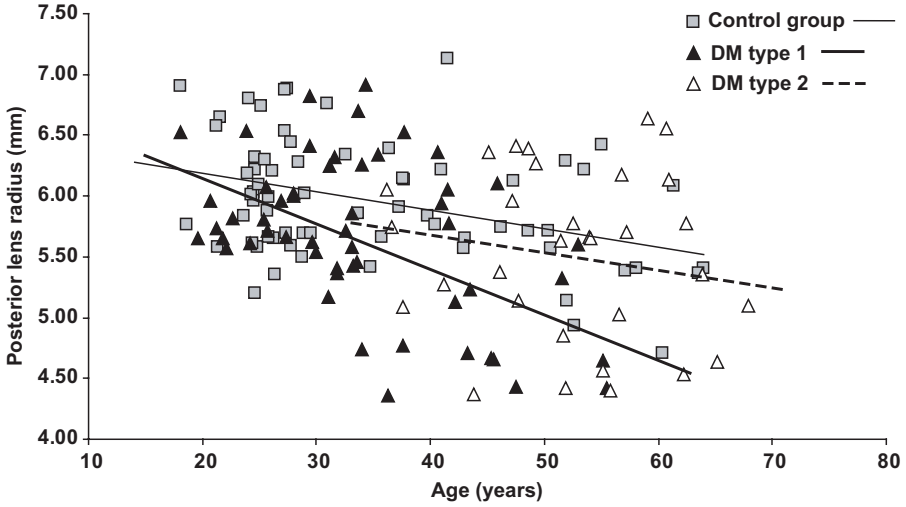


**Figure 4** *Graph of preliminary data of the posterior lens radius (R4) against age in the three groups. Slopes are presented with standard errors (± SE), r = regression coefficient. Control group: R4 = 6.49 (± 0.17) - 0.015 (± 0.005) * age, n = 67, r = 0.38, p = 0.002. DM type 1: R4 = 6.89 (± 0.33) - 0.037 (± 0.009) * age, n = 55, r = 0.48, p < 0.001. DM type 2: R4 = 6.27 (± 0.74) - 0.015 (± 0.014) * age, n = 32, r = 0.19, p = 0.29.*

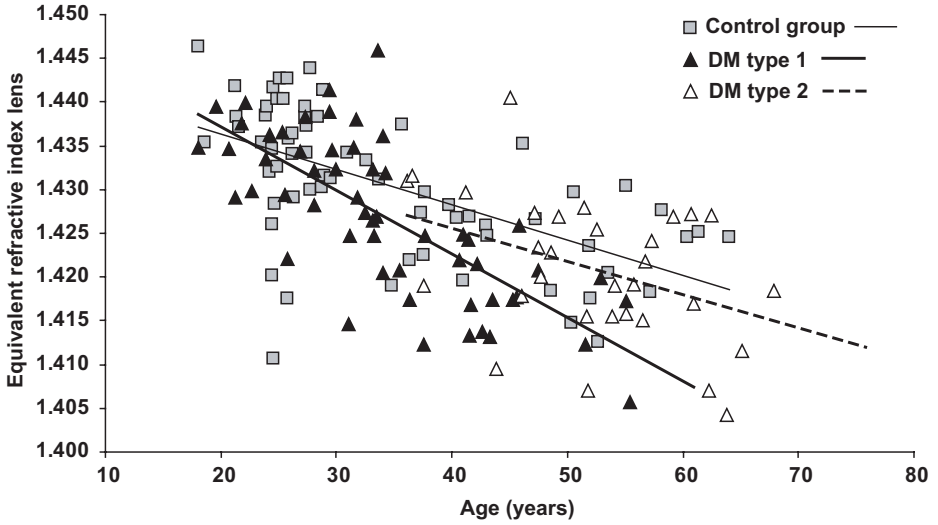


**Figure 5** *Graph of preliminary data of the equivalent refractive index (nlens) of the lens against age in the three groups. Slopes are presented with standard errors (± SE), r = regression coefficient. Control group: nlens = 1.444 (± 0.003) - 0.0004 (± 0.0001) * age, n = 67, r = 0.58, p < 0.001. DM type 1: nlens = 1.452 (± 0.003) - 0.0007 (± 0.0001) * age, n = 55, r = 0.74, p < 0.001. DM type 2: nlens = 1.441 (± 0.008) - 0.0004 (± 0.0001) * age, n = 32, r = 0.44, p = 0.012.*

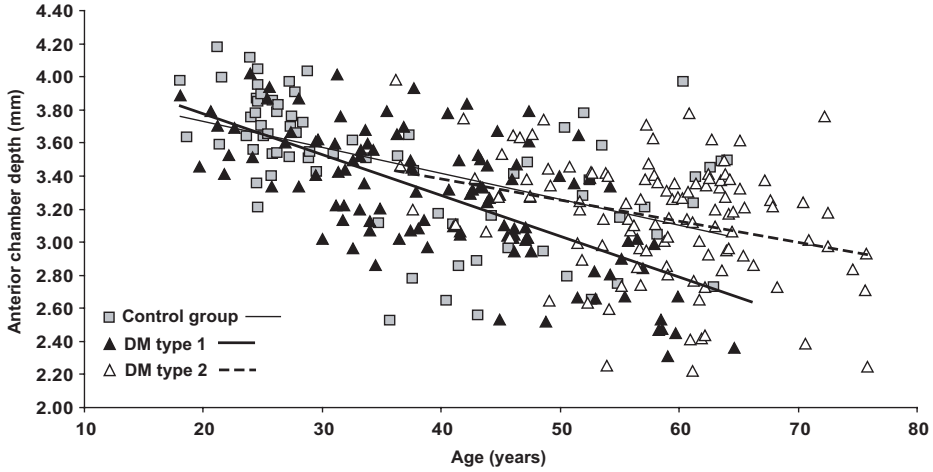


**Figure 6** *Graph of preliminary data of the anterior chamber depth (ACD) against age in the three groups. Slopes are presented with standard errors (± SE), r = regression coefficient. Control group: ACD = 4.04 (± 0.12) - 0.016 (± 0.003) * age, n = 75, r = 0.53, p < 0.001. DM type 1: ACD = 4.27 (± 0.11) - 0.025 (± 0.003) * age, n = 112, r = 0.68, p < 0.001. DM type 2: ACD = 3.90 (± 0.22) - 0.013 (± 0.004) * age, n = 114, r = 0.31, p = 0.001.*

females in the two DM groups.

No significant effect of age on the lens power (Fig 8) or the equivalent refractive error could be demonstrated in any of the three groups. Furthermore, neither the lens power nor the equivalent refractive error differed between the groups. No significant association was found between the duration of DM and lens power or equivalent refractive error.

In order to determine associations between the lens biometry and various systemic factors, such as HbA1c, capillary blood glucose levels, and use of insulin, multiple regression analysis was performed for each of these variables in the two DM groups. HbA1c and capillary blood glucose levels had no significant influence on the various lens parameters. In the DM type 2 group there was no difference in the lens parameters of patients who used insulin, patients who took oral medication, and patients who were on a diet. After adjustment for age only, R3 in the DM type 1 group was significantly decreased in patients with DRP after photocoagulation or proliferative DRP (EURODIAB 4 or 5), compared to patients with no DRP (mean difference [± SE] = 0.82 [± 0.25] mm, 95% CI = 0.21 to 1.43 mm, p = 0.005) or with mild DRP (EURODIAB 1, 2, or 3) (mean difference [± SE] = 1.08 [± 0.24] mm, 95% CI = 0.51 to 1.65 mm, p < 0.001). In the DM type 2 group, R3 was only significantly decreased after adjustment for age in patients with DRP after photocoagulation or proliferative DRP (EURODIAB

| | Mean values for both groups (± SE) | Difference in the means (± SE) | 95% Confidence Interval for the difference in the means[a] | P-value[a] |
|---|---|---|---|---|
| ***d3 (mm)*** | | | | |
| Control group and DM type 1* | 3.95 ± 0.03 and 4.15 ± 0.03 | -0.20 ± 0.04 | -0.30 to -0.09 | **< 0.001** |
| Control group and DM type 2 | 3.95 ± 0.03 and 3.85 ± 0.05 | 0.10 ± 0.06 | -0.05 to 0.25 | **0.287** |
| ***R3 (mm)*** | | | | |
| Control group - DM type 1* | 9.72 ± 0.14 and 8.61 ± 0.11 | 1.11 ± 0.17 | 0.69 to 1.52 | **< 0.001** |
| Control group - DM type 2 | 9.72 ± 0.14 and 10.12 ± 0.13 | -0.40 ± 0.22 | -0.92 to 0.12 | **0.196** |
| ***R4 (mm)*** | | | | |
| Control group - DM type 1* | 5.89 ± 0.07 and 5.52 ± 0.08 | 0.37 ± 0.11 | 0.11 to 0.63 | **0.003** |
| Control group - DM type 2 | 5.89 ± 0.07 and 5.79 ± 0.12 | 0.09 ± 0.15 | -0.27 to 0.46 | **> 0.99** |
| $n_{lens}$ | | | | |
| Control group - DM type 1* | 1.429 ± 0.001 and 1.425 ± 0.001 | 0.004 ± 0.001 | 0.001 to 0.007 | **0.007** |
| Control group - DM type 2 | 1.429 ± 0.001 and 1.428 ± 0.001 | 0.001 ± 0.002 | -0.003 to 0.005 | **> 0.99** |
| ***ACD (mm)*** | | | | |
| Control group - DM type 1* | 3.29 ± 0.04 and 3.16 ± 0.03 | 0.13 ± 0.05 | 0.11 to 0.25 | **0.027** |
| Control group - DM type 2 | 3.29 ± 0.04 and 3.37 ± 0.04 | -0.08 ± 0.06 | -0.23 to 0.07 | **0.597** |

d3 = lens thickness; R3 = anterior lens radius; R4 = posterior lens radius; n lens = equivalent refractive index of the lens; ACD = anterior chamber depth. SE = standard err of the means. [a] Bonferroni post hoc corrections were applied to these data. * Significantly different compared to the control group, $p < 0.05$.

**Table 2** *Differences in the various lens parameters and anterior chamber depth, adjusted for age, when comparing the DM groups (DM type 1 and type 2) with the control group*

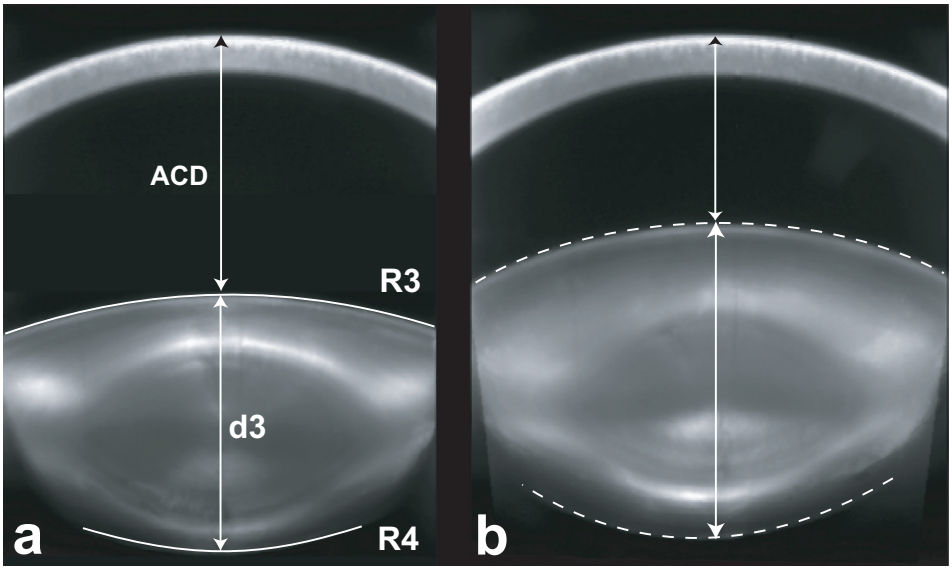


**Figure 7** *The 37-year age-effect in a healthy lens (left Scheimpflug image) and the 37-year age-effect with an additional 31-year duration of DM effect in a DM type 1 lens (right Scheimpflug image). With increasing duration of DM, the lens (d3) becomes thicker and more convex (R3 and R4), and the depth of the anterior chamber (ACD) decreases.*

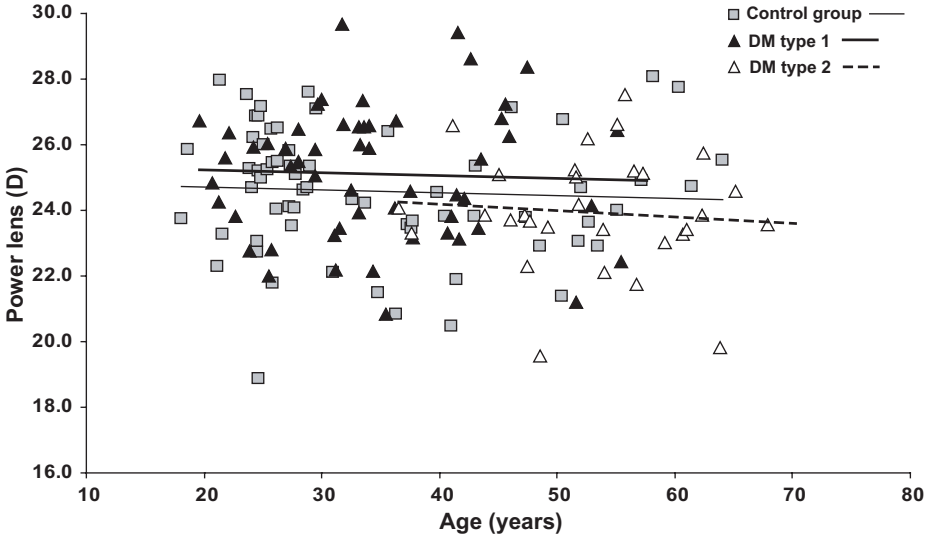


**Figure 8** *Graph of preliminary data of the power (P) of the lens against age in the three groups. Slopes are presented with standard errors (± SE), r = regression coefficient. Control group: P = 24.95 (± 0.73) - 0.010 (± 0.020) * age, n = 67, r = 0.07, p = 0.61. DM type 1: P = 25.15 (± 1.05) - 0.009 (± 0.030) * age, n = 55, r = 0.001, p = 0.99. DM type 2: P = 24.76 (± 2.06) - 0.015 (± 0.039) * age, n = 32, r = 0.07, p = 0.70.*

| | DM type 1 | | | | DM type 2 | | | | Control group | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Slope duration (95% CI)** | **n** | **R** | **p** | **Slope duration (95% CI)** | **n** | **R** | **p** | **Slope age (95% CI)** | **Ratio** |
| **d3 (mm)** | 0.020 (0.012 to 0.027) | 55 | 0.83 | <0.01 | 0.002 (-0.016 to 0.021) | 32 | 0.59 | 0.80 | 0.021 (0.018 to 0.025) | **0.95** |
| **R3 (mm)** | -0.056 (-0.075 to -0.036) | 114 | 0.78 | <0.01 | -0.035 (-0.063 to -0.007) | 112 | 0.44 | 0.01 | -0.064 (-0.085 to -0.043) | **0.88** |
| **R4 (mm)** | -0.031 (-0.049 to -0.014) | 55 | 0.62 | <0.01 | 0.005 (-0.047 to 0.056) | 32 | 0.20 | 0.86 | -0.015 (-0.024 to -0.006) | **2.07** |
| **$n_{lens}$** | $-1.81 \times 10^{-4}$ ($-0.36$ to $-0.02 \times 10^{-4}$) | 55 | 0.76 | 0.04 | $-0.64 \times 10^{-4}$ ($-6.07$ to $4.78 \times 10^{-4}$) | 32 | 0.44 | 0.81 | $-4.0 \times 10^{-4}$ ($-5.29$ to $-2.57 \times 10^{-4}$) | **0.45** |
| **ACD (mm)** | -0.012 (-0.018 to -0.007) | 114 | 0.69 | <0.01 | -0.007 (-0.015 to -0.002) | 112 | 0.34 | 0.12 | -0.016 (-0.022 to -0.010) | **0.75** |

Slopes are presented with 95% confidence intervals (95% CI). Lens parameters in the diabetic groups were analyzed with adjustment for age, duration of DM slopes were obtained from multiple regression analysis. n = number of subjects included, R = multiple regression coefficient, the ratio was calculated as: (slope duration DM type 1 group) / (slope age control group).

**Table 3** *The independent effect of the duration of DM per year on the various lens parameters and the anterior chamber depth (ACD). The ratio was calculated as (slope duration DM type 1 group) / (slope age control group). The independent effect of the duration of DM type 1 per year on lens thickness (d3), anterior lens radius (R3), posterior lens radius (R4), equivalent refractive index of the lens ($n_{lens}$), and ACD was respectively 95%, 88%, 207%, 45% and 75% of the effect of age per year.*

4 or 5), compared to patients with mild DRP (EURODIAB 1, 2, or 3) (mean difference [± SE] = 0.61 [± 0.25] mm, 95% CI = 0.01 to 1.22 mm, p = 0.045). In both diabetic groups, the tests for linear trend were significant (DM type 1: $p < 0.001$ and DM type 2: $p = 0.008$), which means that R3 decreases as the severity of DRP increases. However, R3 or any of the other lens parameters of patients in the two DM groups were not affected by the level of DRP after adjustment for age and duration of DM.

## Discussion

The aim of the present study was to study the influence of DM on the thickness, shape, equivalent refractive index, and power of the lens by measuring these parameters in patients with DM type 1 and type 2, and to compare them with those of control subjects. The results of this study confirm the previous findings that DM type 1 has a profound effect on lens biometry. Furthermore, it adds to this knowledge the calculation of the equivalent refractive index of the lens, which was found to decrease significantly with age and duration of DM. It was also found that DM type 1 appeared to have a large impact on lens biometry, whereas DM type 2 did not affect the lens thickness, shape or equivalent refractive index.
Corrected Scheimpflug imaging[2, 24] was used to measure the lens biometry. It is important to correct the Scheimpflug images, because of the distortion due to the geometry of the camera and the refraction of the different ocular surfaces. This method has been shown to be accurate and reproducible in both in vivo and in vitro method validation experiments.[1, 2, 24]

Several studies have investigated the effect of DM type 1 on the thickness and/or shape of the lens.[3-5, 7-11] In the present study, an increase in average lens thickness of 0.2 mm was found in the DM type 1 group, which is in agreement with the results of Fledelius et al.[4] and Pierro et al..[9] Furthermore, the duration of DM had an important effect on the thickness and shape of the lens. The independent effect of the duration of DM on lens thickness and the anterior and posterior radius was 95%, 88%, and 207%, respectively, of the age-effect per year. Sparrow et al. reported 68%, 88% and 52% for the lens thickness, anterior and posterior radius, respectively.[5] The difference between the percentages for lens thickness and posterior radius could be due to the fact that Sparrow et al. used uncorrected Scheimpflug imaging, which could possibly have resulted in an underestimation of the lens thickness, and especially the posterior radius.

Despite the significant changes in lens biometry that were found in the DM type 1 group, ocular refraction did not change significantly with the duration

of DM. This is in contrast to the findings of Fledelius et al., who explained a myopic shift in DM with an increase in lens thickness.[4] In the present study the equivalent refractive index of the lens was calculated, and it was found to decrease significantly with age in the control group, and to decrease even more with age and duration of DM in the DM type 1 group. Therefore, the additional decrease in equivalent refractive index of the lens appeared to compensate for the profound increase in lens convexity due to DM type 1. The fact that the lens power was not affected by the duration of DM, and also did not differ between the groups, confirms this finding.

The origin of the decrease in equivalent refractive index of the lens remains unclear. It has been suggested that the water content of the healthy lens increases with age,[30] and that this could result in a decrease in refractive power. This could also be true for the diabetic lens. Furthermore, the increase in the dimensions of the diabetic lens may be due to an abnormality in the growth of the lens, a swelling of the lens, or a decrease in central compaction of the mature lens fibers. The growth of the healthy lens has been reported to be almost entirely due to an increase in one of the zones (C2) of the cortex.[31-33] A close analysis of the size of the alternating light and dark zones in the cortex and the size of the nucleus of the diabetic lens could possibly identify the cause of the increase in dimensions of the lens in patients with DM, i.e., if the rate of production of the lens fibers was enhanced, an increase in zone C2 of the cortex would occur. On the other hand, if cellular or extracellular overhydration occurred, resulting in a swelling of the lens as a whole or an increase in the size of the individual lens fibers, there would be an increase in all the different zones of the lens.

Surprisingly, no significant differences in lens biometry were found between the DM type 2 group and the control group, and no significant effect of the duration of DM on the lens could be determined, except for the anterior lens radius. These results agree with the findings of Sparrow et al., who observed a significant effect of the duration of DM on lens biometry in a DM type 1 group, but not in a DM type 2 group.[6] They suggested that this was because the exact duration of the disease was unknown in DM type 2. Nonetheless, the duration of DM type 2 is generally under-estimated, which would even amplify any genuine relationship of lens biometry with duration of DM. In the present study the posterior lens radius (and thus the lens thickness and the equivalent refractive index of the lens) was not easy to examine because of the thickening of the lens with age. This resulted in less measurements of DM type 2 lenses. However, the anterior chamber depth could be examined in all DM type 2 patients, and no change was found with the duration of DM. This indicates that any effect of the duration of DM on lens thickness in the DM type 2 group would have been minor. Furthermore, it can be

concluded that DM type 1 and type 2 most likely have a different impact on lens biometry.

All patients with DM type 1, and 58% of the patients with DM type 2, used insulin. The effect of insulin on lens biometry was investigated in the DM type 2 group, but no association was found between the lens parameters and the use of insulin in this group. Despite the fact that in vitro studies have shown that insulin can stimulate mitogenesis of the epithelial cells of the lens, and that it is capable of inducing hypertrophy in epithelial tissues,[34,35] there is no agreement on the effect of insulin on lens biometry in the results of clinical studies. Pierro et al.[9] reported a lack of correlation between lens thickness and insulin dosage in insulin-dependent DM patients, and Sparrow et al.[5] observed an increase in the anterior clear zone of the lens with an increase in the daily insulin dose. Furthermore, in the present study the effect of DM control on lens biometry was determined by means of HbA1c and capillary blood glucose levels. No significant association was found between blood glucose levels and lens biometry, which is in accordance with the findings of Pierro et al..[9] However, it could be that a more prolonged follow-up of the blood glucose levels could provide evidence for an association between DM control and lens biometry.

A relationship between the level of retinopathy and lens biometry was found in both DM groups. A longer duration of DM increases the risk of developing retinopathy,[36,37] and with a longer duration of DM the lens thickness and convexity have been found to increase. This was likewise concluded by Pierro et al.[9] and Sparrow et al..[5] However, after adjusting for both age and duration of DM, the association between the level of retinopathy and lens biometry disappeared. This indicates that the association was presumably entirely due to the influence of the duration of DM, and not a diffusion of a growth factor from the posterior eye segment, as hypothesized by Sparrow et al..[6]

In conclusion, the results of the present study indicate that DM type 1 has a major impact on lens biometry. The substantial differences in effect on lens biometry between DM type 1 and type 2 may indicate a fundamental difference in pathogenesis. In patients with DM type 1, the decrease in equivalent refractive index of the lens appeared to compensate for the profound increase in lens convexity, resulting in no significant change in lens power or ocular refraction with the duration of DM.

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# Chapter 4

## Changes in the internal structure of the human crystalline lens with diabetes mellitus type 1 and 2

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## Abstract

*Purpose:* To investigate the effect of diabetes mellitus (DM) type 1 and type 2 on the internal structure of the lens.

*Design:* Observational cross-sectional study

*Methods:* Scheimpflug photography was used to image the lens of the right eye of 213 patients with DM (type 1: 107, type 2: 106) and 75 healthy control subjects. The densitogram of the Scheimpflug image was used to indicate the nucleus and the different layers of the cortex of the lens. Lenses with cataract were excluded.

*Results:* The nucleus and the different cortical layers of the DM type 1 lenses were significantly thicker, compared to those of the control group ($p < 0.001$). A significant association was found between the duration of DM type 1 and both the anterior and posterior cortex, its different layers, and the nucleus ($p < 0.001$). The increase in the anterior and posterior cortex with the duration of DM was comparable to that of the nucleus. No important differences in the internal structure of the lens were found between the patients with DM type 2 and the control group.

*Conclusions:* DM type 1 has a significant effect on the internal structure of the lens. The difference in effect of DM type 1 and type 2 on internal lens structure suggests an essential difference in pathogenesis. Furthermore, the results of the present study may indicate that the increase in the size of the lens with DM type 1 is the result of a generalized swelling of the lens, affecting all its different parts.

# Introduction

It is well-known that the human lens continues to grow throughout life, and that it becomes more convex and thicker with age.[1-3] In patients with diabetes mellitus (DM), the lens has been reported to become even thicker and more convex with age, compared to that in healthy subjects.[4-12] After adjustment for the effect of age, the independent effect of the duration of DM per year on lens thickness was more than 70% of the effect of age per year.[6,7]

The physiological thickening of the normal lens with age has been reported to be primarily due to an increase in the anterior and posterior cortex of the lens.[13-16] This was investigated by means of Scheimpflug photography, which provides a detailed image of the various anatomic regions of the lens (i.e. the cortex and the nucleus, as well as alternating light and dark areas within the anterior and posterior cortex).[17] These different light and dark areas can be categorized according to the Oxford Clinical Cataract Classification and Grading System.[13,18] In this system the cortical areas are divided into four zones: C1 to C4. Zones C1 and C3 are zones of high light scatter, whereas zones C2 and C4 are zones of low light scatter (Fig 1). It appeared that the increase in the cortex of the normal lens with age was entirely the result of an increase in one particular zone (C2) of the anterior and posterior cortex.[13,14,16]

The origin of the profound increase in the dimensions of the lens in DM has not yet been explained. Sparrow et al. found that the increase in lens biometry in patients with DM type 1 was due to an increase in both the cortex and the nucleus of the lens, and they observed that the cortex of the diabetic lens was affected more than the nucleus.[6] This effect was markedly less apparent in patients with DM type 2.[7] However, these studies did not investigate the influence of DM on the different cortical zones of the lens. Knowledge about changes in the internal structure of the lens with DM could provide insight into the cause of the increase in the size of the diabetic lens. For example, an increase in the C2 zone of the cortex of the lens, as observed in the physiologically ageing lens, could imply an enhanced rate of lens fiber production. On the other hand, an increase in all different zones of the lens could be the result of cellular or extracellular swelling of the lens. Furthermore, in order to examine the thickness of the different layers within the lens, an accurate measurement of the lens is necessary. This can be obtained with corrected Scheimpflug imaging, which takes into account the distortion caused by the geometry of the Scheimpflug camera and the refraction of the cornea and the lens itself.[2,3,19]

The aim of the present study was to investigate the various cortical zones

and the nucleus of the crystalline lens in patients with DM type 1 and 2, and in healthy control subjects, by means of corrected Scheimpflug imaging.[2,3] In the two diabetic groups we also investigated the influence on the internal structure of the lens of several systemic factors, such as the duration of DM, glycated hemoglobin (HbA1c), capillary blood glucose, the level of diabetic retinopathy (DRP), and the use of insulin.

## Methods

In the present study, the right eye of 288 subjects (75 healthy control subjects, 107 patients with DM type 1 and 106 patients with DM type 2) was examined at the Department of Ophthalmology of the VU University Medical Center in Amsterdam. The diagnosis of DM type 1 or type 2 was determined according to the guidelines published by the World Health Organization.[20] The baseline characteristics of the three groups are presented in Table 1. Subjects with cataract, glaucoma, a history of intraocular surgery, or ocular pathology other than DRP were excluded from the study. Capillary blood glucose levels were measured with a blood glucose analyzer (HemoCue Diagnostics BV, Oisterwijk, the Netherlands). The Medical Ethics Committee of the VU University Medical Center in Amsterdam approved the protocol of this study, and all participants have given their written informed consent, in accordance with the tenets of the Declaration of Helsinki.

*Ocular measurements*

1.0% Cyclopentolate and 5% phenylephrine eye-drops were administered to obtain maximal pupillary dilation and paralysis of accommodation. Images of the lens were obtained with a Topcon SL-45 Scheimpflug camera, equipped with a charge-coupled device (CCD) camera (St-9XE, SBIG Astronomical Instruments, Santa Barbara, USA) with a range of 16 bits of grey values (512 x 512 pixels, pixel size 20 x 20 μm, magnification: 1x). One series of three Scheimpflug images was made in the vertical (90°) meridian along the optical axis. The initial stage in the analysis of the Scheimpflug images was to identify the different zones within the lens. It was not possible to measure each zone in the lens accurately for all 288 subjects, and therefore the number of measurements differed for each zone. This was mainly because the posterior region of the lens was difficult to visualize in some older participants and in patients who had had DM for a long time. The Oxford Clinical Cataract Classification and Grading System was used to distinguish the different layers in the anterior and posterior cortex of the lens

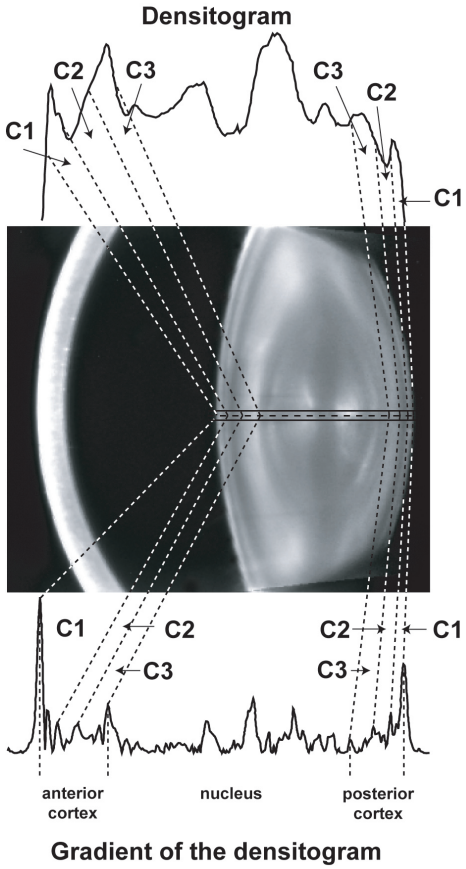


**Figure 1** *Scheimpflug image of a 32-year old healthy male. According to the Oxford Classification System, the different anterior and posterior cortical zones (C1 – C3) and the nucleus can be defined from the local maximums of the gradient of the densitogram. In the present study the anterior cortex is represented by a summation of zones C1, C2, and C3. The same holds true for the posterior cortex. The nucleus is defined as the region between the anterior and posterior C3 zones.*

(Fig 1).[13] This system makes use of the gradient of a densitogram, indicated in the lower part of Figure 1. The densitogram itself (upper part of Figure 1) consists of the grey values of the Scheimpflug image along a sagittal strip of 8 pixels ( 1 pixel = ± 0.025 mm) on either side of a line through the vertex of the anterior lens surface. The gradient of the densitogram represents the rate of change of the densitogram, and from the maxima of this gradient the different layers in the anterior and posterior cortex could be determined. Zone C1 consists of a narrow dark (C1α, or anterior clear zone) and light (C1β, or line of disjunction) zone behind the lens capsule. For the sake of convenience, no distinction was made between these two sub-zones within the C1 zone in the present study. Zone

C2 is a zone of low light scatter and the subsequent C3 zone is a zone of high light scatter. In the present study the nucleus was defined as the area between the anterior and posterior C3 zone, because the C4 low light scatter zone was difficult to distinguish. Furthermore, the anterior cortex is a summation of the anterior C1 to C3 zones, and the same holds true for the posterior cortex. After the different cortical zones had been determined, the Scheimpflug image was corrected for distortion due to the geometry of the Scheimpflug camera and due to the refraction of the different ocular surfaces, by means of ray-tracing.[2,3]
The level of DRP was determined, from two-field digital color 45° fundus photographs, by two independent ophthalmologists (BP, PR) who used the EURODIAB classification system.[21] For practical reasons, the EURODIAB levels of DRP were sub-divided into three categories; DRP absent (EURODIAB level 0), DRP present (EURODIAB levels 1, 2, 3) and DRP after photocoagulation and/or proliferative DRP (EURODIAB level 4 or 5).

*Statistical analysis*
Firstly, preliminary analysis was carried out by means of simple linear regression of the various zones of the lens to test the influence of age on the lens zones in each group separately. The linearity of the effect of age on the lens zones was determined from normal probability plots of regression-standardized residuals; the age-effect was linear in each group. Multiple linear regression analysis was then performed to analyze the effect of other covariates (such as duration of DM, HbA1c or capillary blood glucose levels) on the internal structure of the lens in the two DM groups. Multiple linear regression analysis was also performed to study differences between the three groups. The independent variables of age and/or duration of DM were added to the model to adjust for the effect of age and/or the duration of DM. Differences in regression slopes between the groups were investigated by adding a product-term to the model. All data were approximately normally distributed, and two-sided p-values $< 0.05$ were considered to be statistically significant. All analyses were performed with SPSS 14.0 software.

## Results

The mean age of the control group differed significantly from that of the DM type 2 group ($p < 0.001$), but was comparable to that of the DM type 1 group (Table 1). Furthermore, the duration of DM was significantly longer in the DM type 1

| | Control group (n = 75) | DM type 1 (n = 107) | DM type 2 (n = 106) |
|---|---|---|---|
| Age in yrs; ( range) | 36.8 ± 13.5; (18-64) | 40.3 ± 10.8; (18-65) | 58.1 ± 8.4; (36-76)* |
| Gender (male/female) (n) | 32 / 43 | 61 / 46 | 58 / 48 |
| Duration of diabetes (y)[a] | | 22.5 ± 11.6 | 9.0 ± 7.4** |
| Glycated hemoglobin (%) | | 8.1 ± 1.6 | 7.5 ± 1.5** |
| Capillary blood glucose (mmol/l) | | 9.5 ± 4.5 | 7.9 ± 3.3** |
| Medication (n / total n) | | | |
| Insulin | | 107 / 107 (100%) | 62 / 106 (58%) |
| Other (oral anti-diabetics or diet) | | 0 / 107 (0%) | 44 / 106 (42%) |
| Retinopathy (n / total n)[b] | | | |
| Retinopathy absent | | | |
| EURODIAB 0 | | 54 / 107 (51%) | 72 / 106 (68%) |
| Retinopathy present | | | |
| EURODIAB 1 | | 12 / 107 (11%) | 10 / 106 (9%) |
| EURODIAB 2 | | 8 / 107 (7%) | 9 / 106 (9%) |
| EURODIAB 3 | | 1 / 107 (1%) | 3 / 106 (3%) |
| Retinopathy after photocoagulation or proliferative retinopathy | | | |
| EURODIAB 4 | | 31 / 107 (29%) | 12 / 106 (11%) |
| EURODIAB 5 | | 1 / 107 (1%) | 0 / 106 (0%) |

Data are presented as mean ± SD. [a]Comparisons between the groups in duration of DM were adjusted for age. [b]Retinopathy was sub-divided into three categories; retinopathy absent (EURODIAB level 0), retinopathy present (EURODIAB level 1,2,3), and retinopathy after photocoagulation or proliferative retinopathy (EURODIAB level 4 or 5). * Significantly different compared to the control group, $p < 0.001$. ** Significantly different compared to the DM type 1 group, $p < 0.01$.

**Table 1** *Baseline characteristics of the control group and the two DM groups (DM type 1 and type 2)*

group, compared to the DM type 2 group ($p < 0.01$). The metabolic control of DM was slightly worse in the DM type 1 group than in the DM type 2 group (HbA1c: $p = 0.009$ and capillary blood glucose level: $p = 0.004$) (Table 1).

Preliminary analysis showed that age appeared to have an important effect on the internal structure of the lens in all three groups. This is illustrated in Figures 2 and 3, which show graphs of the effect of age on the anterior and posterior cortex and the nucleus of the lens (Fig 2), and on the cortical zones of the lens (Fig 3) in the three groups. In the control group the lens thickness was found to increase with age, primarily because of an increase in the anterior and posterior cortex of the lens (Fig 2). This increase was approximately 1.6 times greater in the anterior cortex than in the posterior cortex. Furthermore, it was entirely due to an increase in the C2 zone of the cortex (Fig 3). From these graphs it can also be seen that the slopes of the regression lines of all the different lens zones of the DM type 1

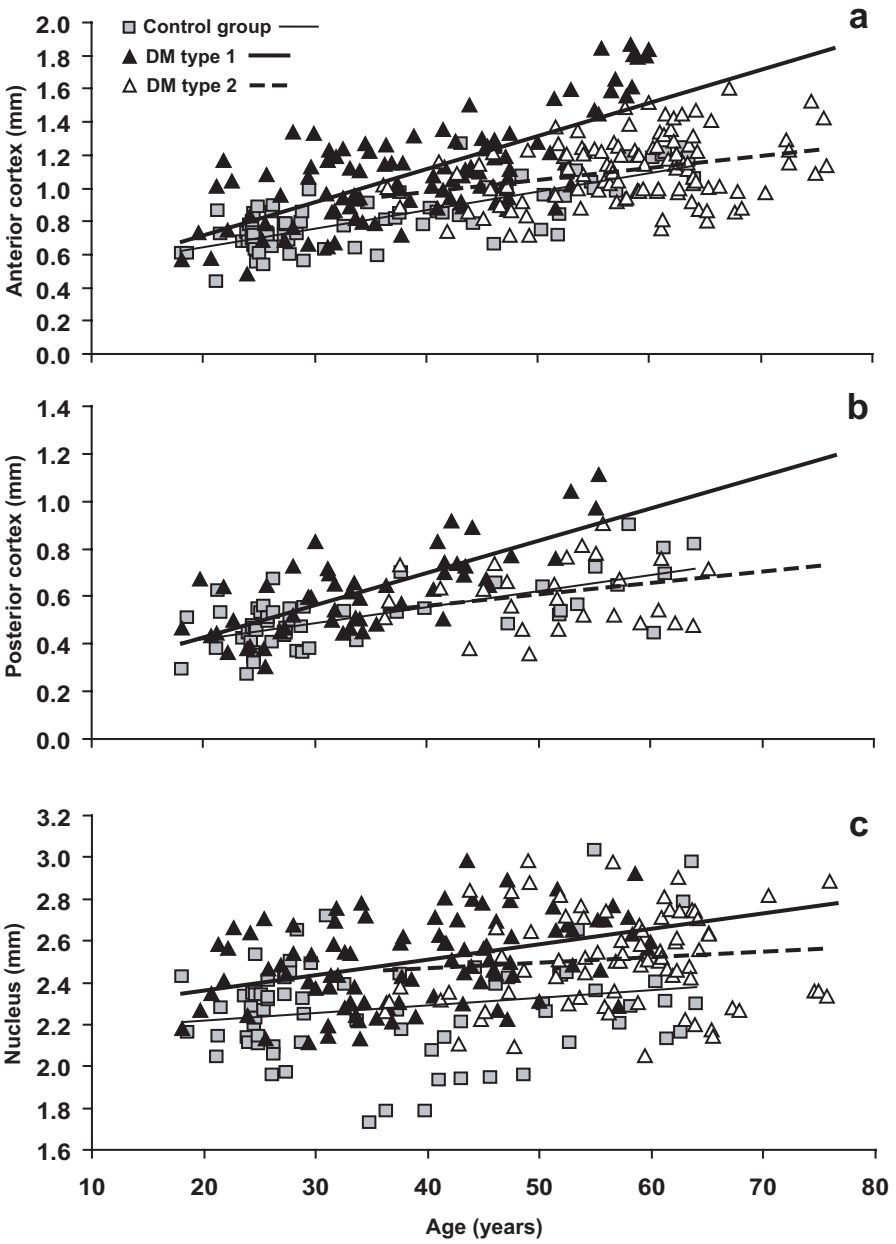


**Figure 2** *Preliminary graphs of the effect of age on the anterior (a) and posterior (b) cortex, and the nucleus (c) of the lens in the control group and the two DM groups. See Figure 1 for the classification of the different zones of the lens. In the control group the anterior and posterior cortex increased significantly with age (anterior cortex [± standard error] = 0.43 [± 0.04] + 0.011 [± 0.001]*age, n = 75, r = 0.78, p < 0.001; posterior cortex [± standard error] = 0.29 [± 0.04] + 0.007 [± 0.001]*age, n = 55, r = 0.67, p < 0.001).*

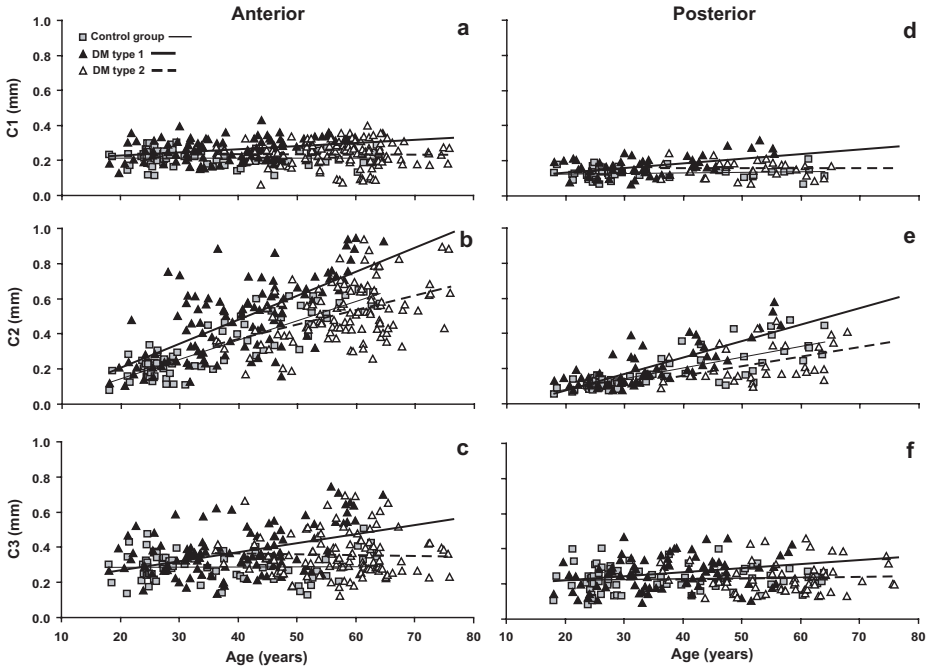


**Figure 3** *Preliminary graphs of the effect of age on the C1, C2, and C3 zones of the anterior (a-c) and posterior cortex (d-f) of the lens in the control group and the two DM groups. See Figure 1 for the classification of the different zones of the lens. In the control group the C2 zones of the anterior and posterior cortex increased significantly with age (anterior C2 [± standard error] = -0.07 [± 0.03] + 0.011 [± 0.001]*age, n = 75, r = 0.88, p < 0.001; posterior C2 [± standard error] = -0.04 [± 0.02] + 0.006 [± 0.001]*age, n = 65, r = 0.79, p < 0.001).*

group are steeper than those of the control group or the DM type 2 group.

The multiple regression analyses supported the preliminary results. After adjustment for age, both the anterior and posterior cortex, and also the nucleus of the lens in the DM type 1 group, appeared to be significantly thicker than in the control group (Table 2). Furthermore, the zones C1, C2 and C3 of the anterior and posterior cortex of the lens were significantly increased in the DM type 1 group, compared to the control group (Table 2). A product-term added to the multiple regression analysis showed that the regression slopes of the anterior cortex (95% CI: 0.005 to 0.014; $p < 0.001$) and the posterior cortex (95% CI: 0.002 to 0.011; $p = 0.003$) differed significantly in the DM type 1 group and the control group. A differentiation of zones C1 – C3 within the anterior and posterior cortex showed that there was a significant difference in the regression slopes of the C1 zone (95% CI: 0.0003 to 0.003; $p = 0.017$) and the C3 zone (95% CI: 0.002 to 0.009;

| Internal regions lens (mm) | Mean values (± SE) | Difference (± SE) | 95% CI[a] | P-value[a] |
|---|---|---|---|---|
| *C1 anterior (mm)* | | | | |
| Control group - DM type 1* | 0.22 ± 0.01 and 0.27 ± 0.01 | 0.05 ± 0.01 | 0.03 to 0.07 | < 0.001 |
| Control group - DM type 2 | 0.22 ± 0.01 and 0.22 ± 0.01 | 0.01 ± 0.01 | -0.03 to 0.02 | > 0.99 |
| *C2 anterior (mm)* | | | | |
| Control group - DM type 1* | 0.44 ± 0.02 and 0.55 ± 0.01 | 0.11 ± 0.02 | 0.06 to 0.16 | < 0.001 |
| Control group - DM type 2 | 0.44 ± 0.02 and 0.38 ± 0.02 | -0.05 ± 0.03 | -0.01 to 0.11 | 0.154 |
| *C3 anterior (mm)* | | | | |
| Control group - DM type 1* | 0.31 ± 0.01 and 0.39 ± 0.01 | 0.09 ± 0.02 | 0.04 to 0.13 | < 0.001 |
| Control group - DM type 2 | 0.31 ± 0.01 and 0.33 ± 0.01 | 0.03 ± 0.02 | -0.08 to 0.02 | 0.540 |
| *Total anterior (mm)[b]* | | | | |
| Control group - DM type 1* | 0.95 ± 0.02 and 1.20 ± 0.02 | 0.25 ± 0.03 | 0.17 to 0.32 | < 0.001 |
| Control group - DM type 2 | 0.95 ± 0.02 and 0.95 ± 0.02 | -0.01 ± 0.04 | -0.08 to 0.10 | > 0.99 |
| *Nucleus (mm)* | | | | |
| Control group - DM type 1* | 2.32 ± 0.03 and 2.53 ± 0.02 | 0.21 ± 0.03 | 0.13 to 0.29 | < 0.001 |
| Control group - DM type 2* | 2.32 ± 0.03 and 2.45 ± 0.03 | 0.14 ± 0.04 | 0.04 to 0.24 | 0.004 |
| *C1 posterior (mm)* | | | | |
| Control group - DM type 1* | 0.13 ± 0.01 and 0.17 ± 0.01 | 0.04 ± 0.01 | 0.02 to 0.06 | < 0.001 |
| Control group - DM type 2 | 0.13 ± 0.01 and 0.14 ± 0.01 | 0.01 ± 0.01 | -0.04 to 0.02 | > 0.99 |
| *C2 posterior (mm)* | | | | |
| Control group - DM type 1* | 0.20 ± 0.01 and 0.24 ± 0.01 | 0.04 ± 0.01 | 0.01 to 0.08 | 0.010 |
| Control group - DM type 2* | 0.20 ± 0.01 and 0.13 ± 0.02 | -0.07 ± 0.01 | -0.12 to -0.02 | 0.003 |
| *C3 posterior (mm)* | | | | |
| Control group - DM type 1* | 0.23 ± 0.01 and 0.27 ± 0.01 | 0.03 ± 0.01 | 0.001 to 0.07 | 0.038 |
| Control group - DM type 2 | 0.23 ± 0.01 and 0.22 ± 0.01 | -0.02 ± 0.02 | -0.03 to 0.06 | 0.946 |
| *Total posterior (mm)[b]* | | | | |
| Control group - DM type 1* | 0.55 ± 0.02 and 0.65 ± 0.02 | 0.10 ± 0.02 | 0.04 to 0.16 | < 0.001 |
| Control group - DM type 2 | 0.55 ± 0.02 and 0.50 ± 0.03 | -0.05 ± 0.03 | -0.04 to 0.13 | 0.501 |

SE = standard error of the means. [a] Adjustment for multiple comparisons were made by means of the Bonferroni post hoc method. [b] Total = a summation of C1, C2, and C3. * Significantly different compared to the control group, $p < 0.05$.

**Table 2** *Differences in the internal lens parameters, adjusted for age, when comparing the DM groups (DM type 1 and type 2) with the control group*

$p < 0.001$) of the anterior cortex, and in all zones of the posterior cortex (C1 95% CI: 0.001 to 0.004; $p = 0.003$, C2 95% CI: 0.001 to 0.006; $p = 0.016$, C3 95% CI: 0.0004 to 0.005; $p = 0.046$) in the DM type 1 group and the control group. No difference was found in the regression slopes of the nucleus between the DM type 1 group and the control group. To investigate whether the difference in lens zones was entirely due to the influence of DM, comparisons with adjustments for age and duration of DM were made between the three groups, but no significant differences in thickness of the lens zones were found. Figure 4 is a schematic drawing of the effect of DM type 1 on the lens; all zones of the DM type 1 lens are

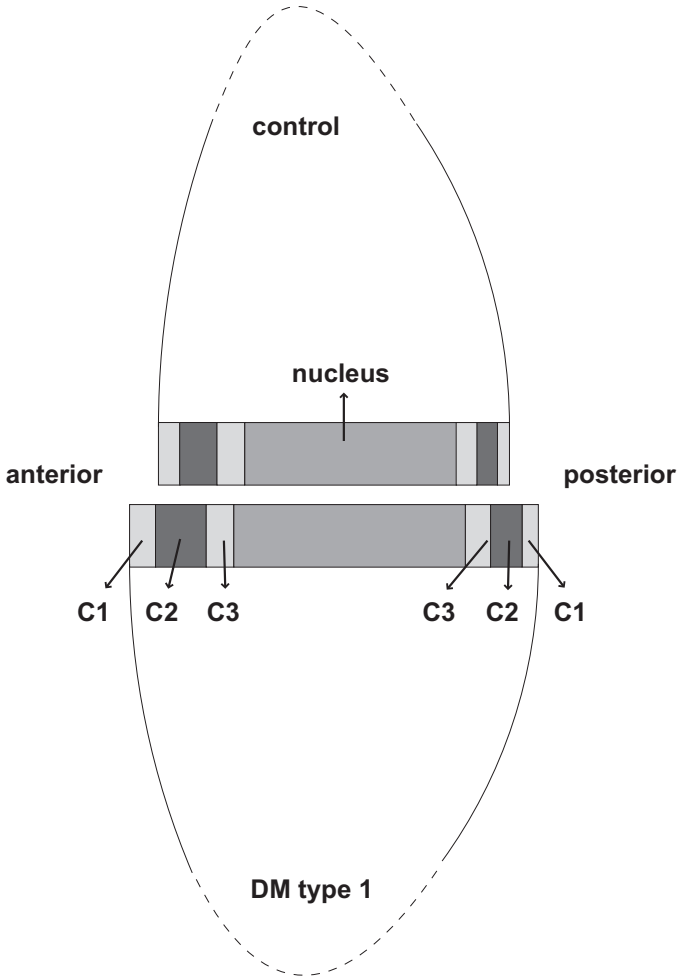


**Figure 4** *Schematic drawing of the cortex, its various zones, and the nucleus of the lens of a 41-year old healthy control subject (upper part) and a 41-year old subject with a 22.5-year duration of DM type 1 (lower part) to indicate the increase in size of all zones of the diabetic lens, compared to those of the control lens.*

increased in size, compared to the control lens. The curvature and the thickness of the control lens and the DM type 1 lens are similar to the outcomes of the Scheimpflug measurements in the present study, representing the average values for a 41-year old healthy control subject and a 41-year old patient who had DM type 1 for 22.5 years. However, hypothetical lens equators (dotted lines) have been added to the drawing, because these parts of the lens are obscured by the iris and can not be seen on a Scheimpflug image.

Unlike DM type 1, DM type 2 had little effect on the cortex and the nucleus of the lens. The patients with DM type 2 had a small increase in nuclear thickness,

| Lens regions (mm) | DM type 1 | | | | DM type 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Slope duration (95% CI) | n | R | p | Slope duration (95% CI) | n | R | p |
| *Anterior cortex* | | | | | | | | |
| **C1 zone** | 0.002 (0.001 to 0.003) | 107 | 0.43 | 0.002 | 0.001 (-0.001 to 0.003) | 106 | 0.11 | 0.268 |
| **C2 zone** | 0.006 (0.003 to 0.009) | 107 | 0.74 | < 0.001 | 0.002 (-0.002 to 0.006) | 106 | 0.44 | 0.346 |
| **C3 zone** | 0.005 (0.003 to 0.008) | 107 | 0.43 | 0.010 | 0.0004 (-0.003 to 0.003) | 106 | 0.03 | 0.981 |
| **Total**[a] | 0.008 (0.004 to 0.012) | 107 | 0.75 | < 0.001 | 0.003 (-0.002 to 0.008) | 106 | 0.33 | 0.280 |
| *Nucleus* | 0.009 (0.005 to 0.012) | 96 | 0.54 | < 0.001 | -0.001 (-0.008 to 0.005) | 77 | 0.12 | 0.710 |
| *Posterior cortex* | | | | | | | | |
| **C1 zone** | 0.002 (0.0002 to 0.003) | 55 | 0.31 | 0.023 | -0.001 (-0.004 to 0.003) | 32 | 0.06 | 0.781 |
| **C2 zone** | 0.005 (0.002 to 0.008) | 57 | 0.45 | < 0.001 | 0.0005 (-0.006 to 0.007) | 33 | 0.03 | 0.878 |
| **C3 zone** | 0.002 (0.0003 to 0.004) | 79 | 0.26 | 0.020 | 0.0001 (-0.003 to 0.003) | 59 | 0.01 | 0.924 |
| **Total**[a] | 0.008 (0.005 to 0.012) | 55 | 0.53 | < 0.001 | -0.002 (-0.014 to 0.009) | 32 | 0.08 | 0.687 |

Duration slopes are adjusted for age in a multiple regression analysis. [a] Total = a summation of C1, C2, and C3. n = number of subjects included, R = multiple regression coefficient, p = probability level, significant if $p < 0.05$.

**Table 3** *The independent effect of the duration of DM per year on the various cortical zones of the lens and the nucleus in the two DM groups*

but also a small decrease in the C2 zone of the posterior cortex of the lens, compared to the control group (Table 2). No significant difference was found in the anterior cortex or zones C1 and C3 of the posterior cortex of the lens between the DM type 2 group and the control group, and there was also no difference in the regression slopes of the various lens zones between these two groups.

The anterior and posterior cortex, and the nucleus of the lens in the DM type 1 group were significantly affected by the duration of DM (Table 3). In the DM type 1 group the lens thickness was found to increase with the duration of DM, due to an increase in the anterior and posterior cortex, and in the nucleus of the lens.

This increase was the same in the anterior and posterior cortex and the nucleus (Table 3). The effect of the duration of DM on the lens zones was the same for males and females in the DM type 1 group. No significant effect of the duration of DM on the various lens zones was found in the DM type 2 group (Table 3).

The metabolic control of DM (i.e. HbA1c and capillary blood glucose levels) had no influence on the various zones of the lens in the two DM groups. In the DM type 2 group the various lens zones were not affected by the use of insulin. Furthermore, the internal structure of the lens did not differ in patients with different levels of DRP in the two DM groups.

## Discussion

The aim of the present study was to investigate the various zones within the human crystalline lens in patients with DM type 1 and type 2, and to compare them to those of healthy control subjects. The results showed that DM type 1 had a profound effect on the internal structure of the lens. In patients with DM type 1 the cortex, the different cortical zones (C1, C2, and C3), and the nucleus of the lens were significantly thicker than those of the control group. Furthermore, the duration of DM type 1 was an important determinant of internal lens structure; both the anterior and the posterior cortex, as well as the nucleus increased with an increasing duration of DM. It was also found that, in contrast to the effect of DM type 1 on the lens, DM type 2 had very little effect on the different zones of the lens.

Measurements of the internal structure of the lens were performed with corrected Scheimpflug imaging. The correction of the Scheimpflug images is important, because of the distortion of the images that is inherent to Scheimpflug photography. Both in vivo and in vitro validation experiments have shown that this method is accurate and reproducible.[2,22] The different layers of the lens were classified according to the Oxford Clinical Cataract Classification and Grading System[13], and the thickness of these layers was objectively determined by pointing out the maxima of the gradient of the densitogram of each Scheimpflug image. This method has been described in detail by Dubbelman et al.,[16] who measured the change in the internal structure of the lens with age and accommodation in a group of 102 healthy subjects. In that study, and in an earlier Scheimpflug study,[14] it was found that the physiological thickening of the lens with age was the result of an increase in the thickness of the anterior and posterior cortex, which was entirely caused by an increase in the C2 zone. This was also found in the healthy control group in the present study.

The origin of the profound increase in the dimensions of the lens with DM type 1 still remains unclear. It could be hypothesized that there is an increased growth of the individual lens fibers. An enhanced production rate of lens fibers could have been stimulated by the use of insulin, which has been reported to induce mitogenesis of the epithelial cells of the lens.[23,24] However, if this hypothesis was plausible, one would expect the size of the cortical C2 zone to be enlarged, since only this particular zone is known to increase in size with age in the healthy lens.[13,14,16] However, it could also be that the increased thickening of the diabetic lens is due to cellular or extracellular overhydration. This would cause an increase in the size of the individual lens fibers and, as a result, the swelling of the lens as a whole, i.e. an increase in the thickness of all the different zones of the lens. The results of the present study seem to support this second theory of lens swelling more than the first hypothesis of enhanced growth. We found a general increase in all the different layers of the lens with DM type 1, and the use of insulin did not seem to have any effect on the lens zones. It is reasonable to assume that a swelling of the lens or its individual lens fibers is the result of an influx of water in the lens. Indirect evidence for this might be provided by the measurement of a decrease in the equivalent refractive index of the lens, which has been observed in a large group of patients with long-term DM type 1 (Wiemer, unpublished data, 2007). It is further supported by a case-report of a patient with DM and severe hyperglycemia, in whom so-called sugar-cracks, or fluid-filled cavities within the lens interstitium were observed.[25] It was hypothesized that these sugar-cracks were most likely the result of overhydration of the lens, which could have been caused by an increase in the osmotic pressure within the lens, due to the accumulation of glucose and its metabolic products within the lens.[8,26]

No important effect of DM type 2 on the different zones of the lens was found in the present study, which agrees with the findings of Sparrow et al..[7] Therefore, DM type 1 and DM type 2 appear to have a different impact on the lens. It is unlikely that the fact that the exact duration of DM is not known in patients with DM type 2 would have reduced the possible effect of DM type 2 on the lens. In general, the duration of DM type 2 is under-estimated, so this would even amplify any true association of the internal structure of the lens with the duration of DM.

We found no significant association between the metabolic control of DM and the internal structure of the lens. In a previous study of lens thickness and blood glucose Pierro et al. also found no relationship between lens biometry and metabolic parameters.[10] However, it could be possible that more prolonged monitoring of the blood glucose levels could provide evidence for a correlation between the metabolic control of DM and the internal structure of the lens, because the present study had a cross-sectional design. Furthermore, no relationship was

found between the level of retinopathy and the internal structure of the lens. Earlier studies have reported findings; Sparrow et al.[7] noted that with proliferative retinopathy the cortex of the lens in DM type 2 was increased, and Pierro et al.[10] found that lens thickness was associated with the level of retinopathy in DM type 1.

In conclusion, the results of the present study show that DM type 1 has a profound effect on the internal structure of the lens. It appears that DM type 1 and DM type 2 have different underlying pathophysiological mechanisms, since there was dissimilarity in their effect on the internal lens structure. Furthermore, the increase in lens dimensions with DM type 1 seems to be the result of a generalized swelling of the lens, affecting all its different parts.

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# Chapter 5

## Measuring the refractive properties of the diabetic eye during blurred vision and hyperglycemia using aberrometry and Scheimpflug imaging

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## Abstract

*Purpose:* To measure refraction and geometry of the diabetic eye during the presence and absence of hyperglycemia and blurred vision, using aberrometry and Scheimpflug imaging.

*Methods:* Aberrometry and Scheimpflug imaging were used to examine ocular refraction and higher order aberrations, as well as the shape of the cornea and the lens, in 25 patients with diabetes mellitus. From these parameters, the equivalent refractive index of the lens was calculated. Using paired t-tests, comparisons were made between a first series of measurements (visit 1), in the presence of blurred vision and hyperglycemia (> 10.0 mmol/l), and a second series of measurements (visit 2) under normal conditions.

*Results:* Mean difference in blood glucose between visit 1 and visit 2 was 5.9 mmol/l (SD 3.1) ($p < 0.0001$). Both small hyperopic and myopic shifts of equivalent refractive error (ERE) were found in 9 patients (mean absolute difference ERE: 0.38 D [SD 0.12]; $p = 0.02$). Furthermore, higher order aberrations (RMS error) were slightly increased in 4 patients (mean difference RMS error: 0.07 μm [SD 0.02]; $p = 0.04$) during visit 1, compared to visit 2. No significant changes could be observed in the shape of the cornea or lens in any of the patients. No significant correlations were found between the changes in blood glucose and the measured parameters of the diabetic eyes.

*Conclusions:* The present study suggests that subjective symptoms of blurred vision during hyperglycemia are not necessarily caused by changes in the refractive properties of the diabetic eye.

# Introduction

Symptoms of blurred vision due to metabolic dysregulation are a well-known feature of diabetes mellitus (DM). It is generally believed that this blurred vision in patients with DM is caused by a variation in blood glucose levels, which induces changes in ocular refractive error. However, there seems to be no consensus in the literature with regard to the direction and origin of these refractive changes. Myopic shifts (Duke-Elder 1925; Turtz & Turtz 1958; Birnbaum & Leu 1975; Gwinup & Villarreal 1976; Fledelius et al. 1990; Mantyjarvi 1988; Furushima et al. 1999), as well as hyperopic shifts (Huggert 1954; Varma et al. 1980; Planten 1975; Planten et al. 1978; Eva et al. 1982; Kluxen & Scholz 1987; Imai & Matsuda 1992; Saito et al. 1993; Okamoto et al. 2000; Herse 2005; Giusti 2003; Sonmez et al. 2005; Tai et al. 2006) have often been reported in patients with severe acute hyperglycemia, or during intensive treatment of acute metabolic dysregulation. Already in 1925, Duke-Elder described a myopic shift in hyperglycemic condition and a hyperopic shift after a rapid decrease in blood glucose levels. He stated that these refractive changes were most likely caused by changes in the lens. A change in lens thickness could actually be measured during hyperglycemia in more recent studies in which ultrasound biometry was used. After inducing acute hyperglycemia in 7 healthy subjects, Furushima et al. (1999) found an increase in lens thickness of 1 mm and a myopic shift of -2 diopters. Kato et al. (2000) reported a significant increase in lens thickness (0.3 mm) after rapid control of hyperglycemia. Nevertheless, it is often assumed that a change in the refractive index of the lens could also play a role in explaining the refractive changes in patients with DM. Planten et al. (1975) found 1 to 3 diopters of hyperopia in 23 diabetic patients with acute hyperglycemia. They suggested that this hyperopia was caused by changes in the refractive indices of the different layers of the lens, because they found no changes in the thickness or position of the lens. Using Scheimpflug photography, Kluxen et al. (1987) reported a maximum of 6 diopters hyperopia in one patient with severe hyperglycemia. They measured an increase in lens thickness of 0.4 mm, and suggested a decrease in the refractive index of the lens. Saito et al. (1993) performed measurements with slit-lamp photography and ultrasound biometry in five patients with newly diagnosed DM. They suggested that the refractive index of the lens decreased, due to water influx, and that this caused hyperopia (max. 4.9 diopters) and lens swelling (max. 0.3 mm) after control of acute metabolic dysregulation. Okamoto et al. (2000) found hyperopia (max. 3.8 diopters), but no changes in lens thickness in 14 diabetic patients. As a result, it was also assumed that there was a decrease in the refractive index of

the lens. This was also hypothesized by Tai et al. (2006), who reported hyperopia (max. 2 diopters) in 8 out of 24 diabetic patients, but no change in ocular biometry, measured with Orbscan II and ultrasound biometry. However, no studies have yet investigated how acute hyperglycemia affects the shape and refractive index of the lens.

In previous studies focusing on blurred vision in patients with DM, the refractive error of the eye has usually been described in terms of sphere and cylinder only. Various other optical errors (higher order aberrations) were generally not taken into account, although they are known to affect visual acuity (Applegate et al. 2003). Furthermore, Shahidi et al. (2004) reported an increase in the higher order aberrations in 22 patients with chronic DM. No studies have yet investigated the influence of acute hyperglycemia on the higher order aberrations of the eye.

It is still unclear whether the higher order aberrations and the shape and refractive index of the lens could also play a role in explaining blurred vision in patients with DM. The aim of the present study was to evaluate the mechanism underlying blurred vision and refractive changes in DM, using aberrometry and corrected Scheimpflug imaging (Dubbelman & van der Heijde 2001). With aberrometry it is possible to detect small changes in refraction and higher order ocular aberrations. Furthermore, corrected Scheimpflug imaging makes it possible to measure the exact shape of the lens, from which the equivalent refractive index of the lens can be calculated (Dubbelman et al. 2005). In the present study, the refractive error and the higher order aberrations, as well as the shape of the cornea and the lens were accurately measured during the presence and absence of hyperglycemia and subjective symptoms of blurred vision.

## Materials and methods

Between May 2005 and December 2006, 229 patients with DM type 1 or type 2, who visited the Department of Ophthalmology at the VU University Medical Center in Amsterdam, were questioned about the presence of subjective symptoms of blurred vision. Capillary blood glucose levels were determined with a blood glucose analyzer (HemoCue Diagnostics BV, Oisterwijk, the Netherlands). Patients with subjective complaints of blurred vision and elevated blood glucose levels (> 10.0 mmol/l) were included in the study. These patients were measured during two visits; during the first visit (visit 1) the measurements were performed when subjective symptoms of blurred vision and elevated blood glucose levels were present. The patients were then instructed to return for another series of measurements (visit 2) when the blurred vision had disappeared and the blood

glucose levels were lower (< 10.0 mmol/l). The mean follow-up time between visit 1 and visit 2 (when the blurred vision and hyperglycemia were absent) was 51 days (SD 64). Changes in ocular biometry with age over this short period of time are negligible (Dubbelman & van der Heijde 2001; Dubbelman et al. 2006; Jonsson et al. 2006; Olsen et al. 2007). Age, DM type 1 or type 2, duration of diabetes, glycated hemoglobin levels (HbA1c), and type of medication were recorded. Patients with cataract, glaucoma, macular edema, or a history of intraocular surgery were excluded. The Medical Ethics Committee of the VU University Medical Center in Amsterdam approved the study protocol, and written informed consent was obtained from all participants, according to the tenets of the Declaration of Helsinki.

*Ophthalmological measurements*

The right eye of each patient was studied after administration of 1.0% cyclopentolate and 5.0% phenylephrine eye-drops to obtain maximal pupillary dilation and paralysis of accommodation. Refractive error and higher order aberrations were measured with an IRX3 aberrometer (Imagine Eye Optics, Paris, France), which performs wavefront analysis of the eye according to the Hartmann-Shack principle. This aberrometer operates by focusing an extremely fine beam of infrared light (780 nm) on the retina. When the light beam scatters back from the fundus through the pupil, a 32 x 32 array of micro lenses captures these rays of light. Corresponding to their focal points each micro lens forms a spot on a CCD camera. To reconstruct the wavefront of the eye, the spot images or Hartmann-Shack images are analyzed, using a software program that has been developed to evaluate the displacements of x and y positions of the central points of the spots from a perfect grid pattern (Liang et al. 1994). During both visits, the mean pupil diameter was measured at 5.0 mm, and two series of three aberrometry measurements were made of each patient. The equivalent refractive error of each eye was calculated as: equivalent refractive error (ERE) = sphere + (cylinder / 2). A refractive change of more than 0.2 diopters (D) was considered to be significant, according to the accuracy of the aberrometer at a 5 mm pupil size (Cheng et al. 2003; Salmon & van de Pol 2005). Furthermore, the higher order aberrations of each eye were summarized in root mean square (RMS) errors, including the third up to the sixth Zernike orders (Thibos et al. 2002). The RMS errors are expressed in micrometers (μm).

In order to determine ocular geometry, images of the cornea and lens were obtained with a Topcon SL-45 Scheimpflug camera, the film of which was replaced by a charge-coupled device (CCD) camera (St-9XE, SBIG astronomical instruments) with a range of 16 bits of grey values (512 x 512 pixels, pixel size

20 x 20 μm, magnification: 1x). Two series of three Scheimpflug images were made in the vertical (90°) meridian during both visits. Ray-tracing was applied to correct the images for distortion due to the geometry of the Scheimpflug camera and due to the refraction of the anterior surface of the cornea and the lens (Dubbelman & van der Heijde 2001). Consequently, this made it possible to obtain an accurate measurement of the corneal thickness (d1), anterior (R1) and posterior (R2) corneal radii of curvature, lens thickness (d3) and the anterior (R3) and posterior (R4) radii of curvature of the lens. This method for the correction of Scheimpflug images has been validated and described in detail by Dubbelman et al (2005).

The equivalent refractive index of the lens (n lens) can be calculated by combining measurements of refractive error, intraocular distances, and the radii of the cornea and lens (Figure 1). Therefore, axial eye-length was also measured in those patients whose posterior lens surface was clearly visible on the Scheimpflug images. The axial eye-length was measured with the IOL master (Carl Zeiss Inc., North America). The anterior chamber depth (d2) was determined with Scheimpflug imaging by measuring the distance from the anterior surface of the cornea to the anterior surface of the lens. The equivalent refractive index of the lens was calculated by means of an iterative process, which has been described by Dubbelman et al (2005).

Finally, two independent ophthalmologists (BP, PR) used the EURODIAB classification system to determine the stage of diabetic retinopathy from two-field

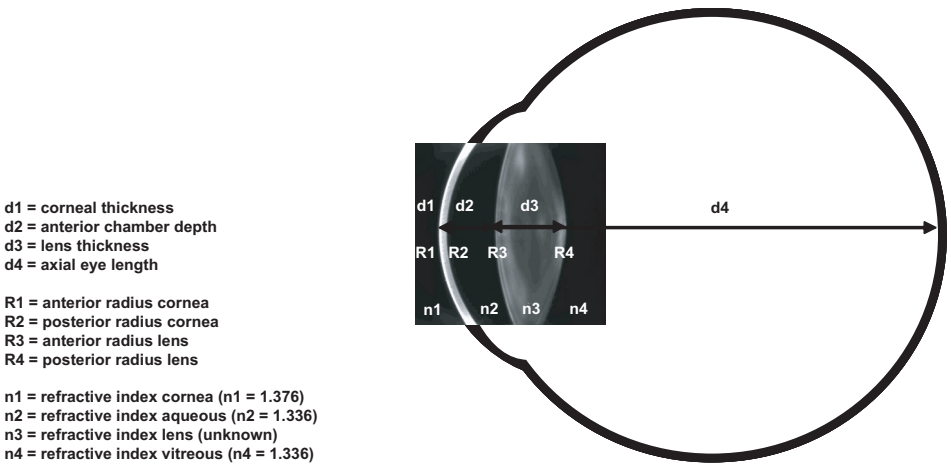



**Figure 1** *Schematic eye with the parameters that were included for the calculation of the equivalent refractive index of the lens using corrected Scheimpflug imaging, aberrometry and axial eye-length measurements.*

| Pat. No | Gender | Type of DM | Age[a] (years) | Duration of diabetes[a] (years) | HbA1c[a] (%) | Therapy | Retinopathy[b] (EURODIAB) | Difference in capillary blood glucose between visits 1 and 2 (mmol/l) | Time between visits (days) |
|---|---|---|---|---|---|---|---|---|---|
| **1** | M | 2 | 46.6 | 11.7 | 12.4 | Insulin/ OAD[c] | 0 | 12.8 | 4 |
| **2** | F | 2 | 76.6 | 35.6 | 7.1 | Insulin | 0 | 9.1 | 0 |
| **3** | F | 1 | 44.9 | 33.6 | 7.9 | Insulin | 4 | 1.4 | 161 |
| **4** | M | 1 | 33.1 | 29.9 | 8.0 | Insulin | 4 | 5.1 | 47 |
| **5** | F | 2 | 51.6 | 10.1 | 8.3 | Insulin | 0 | 12.8 | 4 |
| **6** | M | 1 | 46.1 | 35.5 | 8.2 | Insulin | 4 | 4.3 | 223 |
| **7** | M | 1 | 18.1 | 9.0 | 7.3 | Insulin | 0 | 6.7 | 37 |
| **8** | M | 1 | 45.6 | 25.0 | 9.2 | Insulin | 5 | 8.2 | 26 |
| **9** | F | 2 | 60.7 | 17.1 | 12.7 | OAD | 2 | 2.8 | 29 |
| **10** | M | 1 | 43.5 | 39.0 | 7.8 | Insulin | 4 | 6.5 | 91 |
| **11** | F | 1 | 33.3 | 25.5 | 7.6 | Insulin | 2 | 9.3 | 212 |
| **12** | M | 2 | 57.9 | 8.9 | 7.2 | Insulin/ OAD | 0 | 2.5 | 7 |
| **13** | F | 1 | 32.5 | 20.8 | 7.7 | Insulin | 2 | 2.5 | 121 |
| **14** | M | 1 | 19.6 | 9.8 | 12.0 | Insulin | 0 | 6.7 | 29 |
| **15** | M | 1 | 51.4 | 40.9 | 9.3 | Insulin | 4 | 7.3 | 0 |
| **16** | M | 1 | 46.2 | 33.0 | 8.0 | Insulin | 1 | 4.3 | 7 |
| **17** | M | 1 | 52.5 | 24.7 | 7.5 | Insulin | 2 | 4.9 | 18 |
| **18** | M | 2 | 67.2 | 19.2 | 7.0 | Insulin | 4 | 3.9 | 11 |
| **19** | M | 1 | 21.2 | 12.0 | 9.0 | Insulin | 0 | 2.8 | 29 |
| **20** | F | 2 | 56.6 | 2.3 | 7.9 | Insulin/ OAD | 0 | 2.8 | 0 |
| **21** | M | 1 | 37.9 | 34.9 | 9.5 | Insulin | 4 | 6.6 | 40 |
| **22** | M | 2 | 51.8 | 10.2 | 7.9 | Insulin | 0 | 6.6 | 37 |
| **23**[d] | M | 2 | 55.7 | 0.1 | | OAD | 3 | 2.7 | 77 |
| **24** | F | 1 | 37.4 | 26.3 | 8.0 | Insulin | 4 | 9.9 | 0 |
| **25** | F | 2 | 77.9 | 0.1 | 6.1 | Insulin/ OAD | 0 | 3.5 | 69 |
| **Mean (SD)** | | | 46.6 (15.6) | 20.6 (12.7) | 8.5 (1.7) | | | 5.8 (3.2) * | 51 (64) |

[a] at the first visit.
[b] EURODIAB level 0 = retinopathy absent; EURODIAB levels 1 and 2 = non-proliferative diabetic retinopathy present; EURODIAB level 3 = moderate non-proliferative diabetic retinopathy present; EURODIAB level 4 = photocoagulated diabetic retinopathy; EURODIAB level 5 = proliferative diabetic retinopathy.
[c] OAD = Oral Anti-Diabetic drugs.
[d] No data on HbA1c for this patient.
* Significant difference between visit 1 and visit 2, $p < 0.0001$ (paired t-test).

**Table 1** *Characteristics of the 25 patients with diabetes mellitus, who were included in the present study.*

45° digital color fundus photographs (Aldington et al. 1995; Higgins et al. 2007; Olafsdottir et al. 2007).

## Results

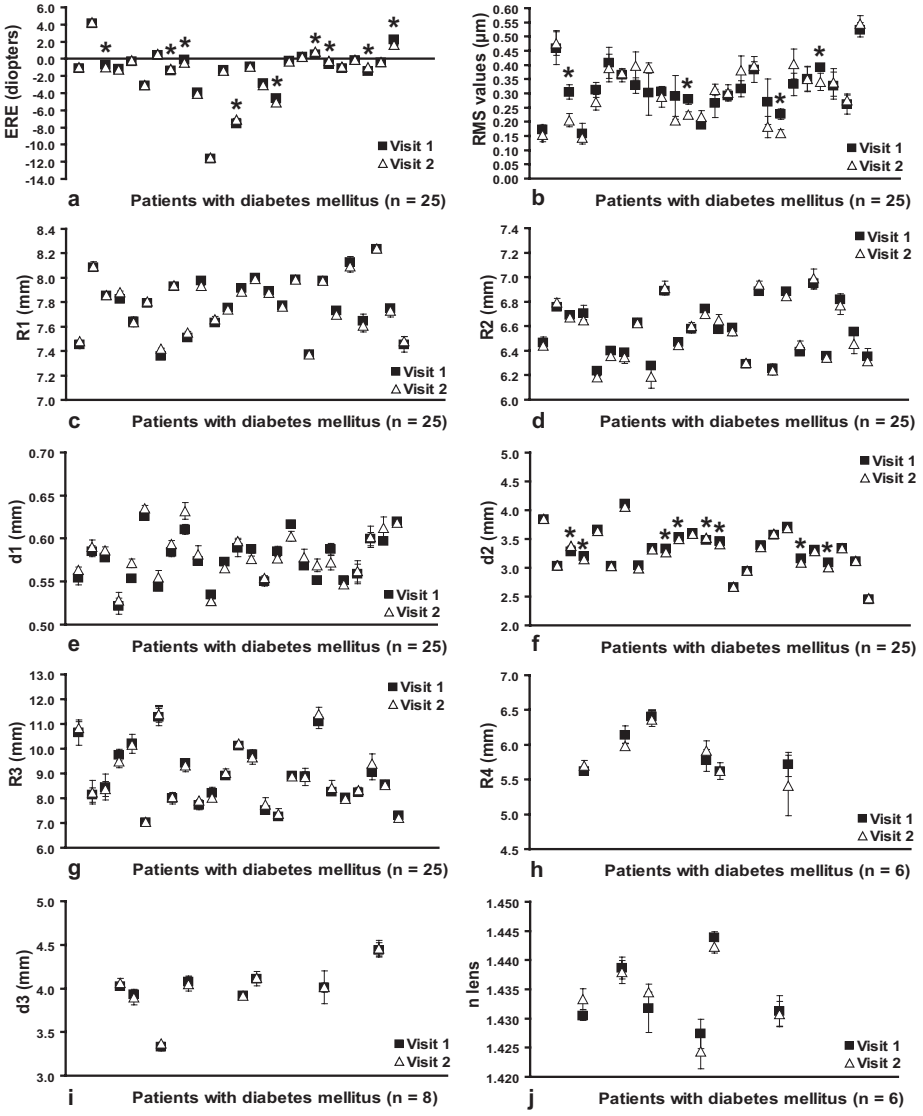
Of the 229 patients with DM who were questioned and whose blood glucose was measured at baseline, 25 patients with both subjective complaints of blurred vision and hyperglycemia were included in the study (10.9 %). Excluded from the study were 42 patients who had hyperglycemia but no complaints of blurred vision, 2 patients with blurred vision and no hyperglycemia, and 160 patients with normal blood glucose and no blurred vision. Table 1 summarizes the characteristics of the 25 diabetic patients (type 1: N=15; type 2: N=10) (9 females and 16 males). At visit 1 (when blurred vision and hyperglycemia were present), the mean age was 46.6 years (SD 15.6) and the mean duration of DM was 20.6 years (SD 12.7). The mean capillary blood glucose levels were 14.1 mmol/l (SD 3.5) at visit 1 and 8.1 mmol/l (SD 2.5) at visit 2. These blood glucose levels differed significantly between visit 1 and visit 2 (mean difference: 5.9 mmol/l (SD 3.1 and 95% CI 4.7 – 7.2); $p < 0.0001$ (paired t-test)), but there was no significant difference in the glycated hemoglobin levels (HbA1c).

Figure 2 presents graphs of the measured parameters of the right eyes of the

| Patient | ERE during visit 1 | ERE during visit 2 | Absolute difference in the means | 95% confidence intervals | P value | Change in ERE during blurred vision |
|---|---|---|---|---|---|---|
| **3** | -0.73 ± 0.07 | -0.95 ± 0.06 | 0.22 ± 0.09 | 0.11 – 0.32 | 0.006 | **hyperopic** |
| **8** | -1.37 ± 0.05 | -1.15 ± 0.04 | 0.21 ± 0.06 | 0.14 – 0.28 | 0.0009 | **myopic** |
| **9** | -0.13 ± 0.06 | -0.46 ± 0.04 | 0.33 ± 0.07 | 0.25 – 0.42 | 0.0002 | **hyperopic** |
| **13** | -7.53 ± 0.13 | -7.07 ± 0.06 | 0.47 ± 0.14 | 0.31 – 0.63 | 0.001 | **myopic** |
| **16** | -4.64 ± 0.12 | -5.04 ± 0.13 | 0.41 ± 0.17 | 0.21 – 0.61 | 0.007 | **hyperopic** |
| **19** | 0.47 ± 0.02 | 0.82 ± 0.11 | 0.35 ± 0.11 | 0.22 – 0.48 | 0.002 | **myopic** |
| **20** | -0.67 ± 0.16 | -0.26 ± 0.08 | 0.41 ± 0.17 | 0.21 – 0.61 | 0.003 | **myopic** |
| **23** | -1.42 ± 0.16 | -0.97 ± 0.03 | 0.45 ± 0.16 | 0.26 – 0.63 | 0.003 | **myopic** |
| **25** | 2.23 ± 0.22 | 1.63 ± 0.08 | 0.60 ± 0.23 | 0.33 – 0.86 | 0.022 | **hyperopic** |

Data are presented as mean ± SD. P-values < 0.05 were considered to be statistically significant (t-test)

**Table 2** *The equivalent refractive error (ERE); small statistically significant differences were found in 9 of the 25 patients with diabetes mellitus between the two visits.*




Data are presented as mean ± SD. P-values < 0.05 were considered to be statistically significant (t-test)

* Significantly different compared to visit 1, p < 0.05

**Figure 2** *Graphs of the optical properties of the right eyes of 25 patients with DM during visit 1 (in the presence of subjective blurred vision and hyperglycemia) and during visit 2 (in the absence of subjective blurred vision and hyperglycemia). Equivalent refractive error ERE (a); Higher order aberrations RMS (b); Anterior radius cornea R1 (c); Posterior radius cornea R2 (d); Corneal thickness d1 (e); Anterior chamber depth d2 (f); Anterior radius lens R3 (g); Posterior radius lens R4 (h); Lens thickness d3 (i); Refractive index lens nlens (j).*

25 diabetic patients during visit 1 and visit 2. A comparison of both visits made it clear that a small significant difference in ERE (> 0.2 D) could be observed in 9 of the 25 patients: 4 patients had a hyperopic shift and 5 patients became more myopic during hyperglycemia (mean absolute difference in ERE: 0.38 D (SD 0.13 and 95% CI 0.29 – 0.47); p = 0.02 (t-test)) (Figure 2a and Table 2). Furthermore, higher order aberrations (RMS errors) were slightly, but significantly increased in 4 of the 25 patients (mean increase in RMS error: 0.07 μm (SD 0.02 and 95% CI 0.04 – 0.09); p = 0.04) at visit 1, compared to visit 2 (Figure 2b). The mean differences in ERE and RMS errors between the two visits were not dependent on the difference in blood glucose levels during the two visits.

No significant change in corneal thickness or in anterior or posterior corneal radius was observed in any of the patients between visit 1 and visit 2 (Figures 2c, 2d and 2e). A small, but significant change in the anterior chamber depth (mean change of d2: 0.06 mm (SD 0.02 and 95% CI 0.04 – 0.08); p = 0.02) was found in 8 patients, in 3 of whom the change of ERE was significant (Figure 2f). There was no significant difference in the anterior radius of the lens, the posterior radius of the lens or the lens thickness between visit 1 and visit 2 in any of the 25 patients (Figures 2g, 2h and 2i). To obtain maximal mydriasis in this diabetic study group was difficult. As a result, the posterior surface of the lens was visible in 8 of the 25 patients and a posterior radius of the lens could be determined in 6 patients. Therefore, calculation of the equivalent refractive index of the lens was possible for those 6 patients, 3 of whom had a significant change in ERE. Nevertheless, no significant change was found in the equivalent refractive index of the lens between visit 1 and visit 2 in any of the patients (Figure 2j). Finally, no significant correlation could be found between the difference in capillary blood glucose levels during the two visits and the mean difference in the shape of the cornea or lens, or the equivalent refractive index of the lens during the two visits.

## Discussion

Several studies have reported on the effect of hyperglycemia on ocular refractive error, but there seems to be no agreement on the direction and exact origin of refractive alterations in patients with DM. Changes in the shape and refractive index of the lens have been assumed to play a causal role in the diabetic refractive changes, but these parameters have not been measured before, due to limitations of the measurement instruments. Moreover, higher order aberrations have not yet been studied during hyperglycemia. Therefore, in the present study, the higher order aberrations of the diabetic eye, as well as the shape of the cornea and the

lens, were measured during the presence and absence of symptoms of blurred vision and hyperglycemia, in order to explain the mechanism underlying blurred vision in patients with DM.

Of a total of 229 patients who were screened for the present study, 10.9 % had both hyperglycemia and complaints of blurred vision. However, only small changes in ERE were found in 9 of the 25 patients included in the study. This is in contrast to the findings of other studies, which reported larger changes in ERE during hyperglycemia than were found in the present study. However, these studies included patients with more serious and longer lasting hyperglycemia. In 5 newly diagnosed diabetic patients, who had more elevated average plasma glucose levels (22.6 mmol/l) than the patients in the present study (14.1 mmol/l), Saito et al. (1993) reported hyperopic shifts of maximal 4.9 diopters. Tai et al. (2006) found a hyperopic shift of 2 diopters in 8 diabetic patients with average glucose levels of 19.0 mmol/l. Moreover, it has been demonstrated by Okamoto et al. (2000) that the degree of hyperopia is correlated to the rate of reduction of the blood glucose levels. It could hypothesized that longer phases of elevated blood glucose levels, resulting in higher glucose levels in the aqueous humour, are necessary to induce formation of higher sorbitol levels in the lens which then could cause tissue swelling. Therefore, it could be that in the present study a higher and more prolonged blood glucose level was needed to induce a larger change in ERE.

In the present study, ERE and higher order aberrations were measured for a pupil size of 5 mm. For this pupil size the accuracy of the aberrometer to measure ERE is estimated to be 0.2 D (Cheng et al. 2003; Salmon & van de Pol 2005). In 9 of 25 patients a significant change in ERE of on average 0.38 D was found. The depth of focus at a pupil size of 5 mm is approximately 0.4 D (Atchison & Smith 2000), which is within the same range as the change in ERE. It must be noted that under physiological conditions the mean pupil size is approximately 3 mm which results in a depth of focus of approximately 0.7 D (Atchison & Smith 2000; Charman 1991). Furthermore, the repeatability of measuring subjective ERE has been reported to be 0.74 D (Leinonen et al. 2006). Therefore, the results of the present study indicate that it is unlikely that the blurred vision during hyperglycemia was caused by the small refractive changes.

Only a minimal increase in the higher order aberrations (0.07 μm) could be measured in 4 diabetic patients. According to Applegate et al. (2003), an increase in the RMS error of 0.07 μm should hardly decrease visual acuity. Therefore, the observed changes in RMS error in the present study were too small to directly affect visual acuity and cause symptoms of blurred vision.

Small changes in ERE were observed, but no changes in the geometry of

the cornea and lens were found in the present study. This is in agreement with the results of several other studies, in which no changes were found in ocular biometry. Planten et al. (1975) reported 1 to 3 diopters of hyperopia in 23 diabetic patients with acute hyperglycemia, but no changes in lens thickness measured with ultrasound biometry. Moreover, Okamoto et al. (2000) found hyperopia of maximal 3.8 diopters, with no changes in lens thickness. Finally, Tai et al. (2006) reported hyperopia of maximal 2 diopters, but they could not determine any change in ocular biometry. In contrast to previous studies, the shape of the lens was measured during hyperglycemia in the present study. In the shape of the lens no significant change was found which could provide an explanation for the symptoms of blurred vision in patients with DM. In 8 patients, 3 of whom had significant changes in ERE, only small, but significant changes in anterior chamber depth were found. This result is in agreement with the findings of Tai et al. (2006), who also reported small, significant changes in anterior chamber depth during hyperglycemia.

Although several previous studies hypothesized that DM affects the refractive index of the lens, in the present study there was no evidence of changes in the equivalent refractive index due to hyperglycemia. However, the equivalent refractive error of the lens could only be calculated in 6 patients, due to poor visualization of the posterior side of the lens. This was caused by a combination of the thickness of the diabetic lens and difficult mydriasis, both of which are well-known diabetic complications (Sparrow et al. 1990; Sparrow et al. 1992; Alio et al. 1989).

Although significant differences were found between the visits in the present study, it must be noted that these changes should be interpreted in the light of the high accuracy and precision of the methods that have been used. Only marginal changes were found in refractive error and higher order aberrations of the diabetic eyes, which did not seem to be large enough to explain the complaints of blurred vision. This leads to the conclusion that the symptoms of blurred vision due to hyperglycemia should also be attributed to other factors. It could be that changes in other visual areas (e.g. retina or optical cerebral cortex) cause subjective complaints of blurred vision, or that more serious and long-lasting hyperglycemia is needed to induce changes in ERE, higher order aberrations or shape of the cornea and lens which could cause blurred vision.

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# Chapter 6

## Blurred vision and severe acute hyperglycemia: a change in both the shape and the refractive index of the lens

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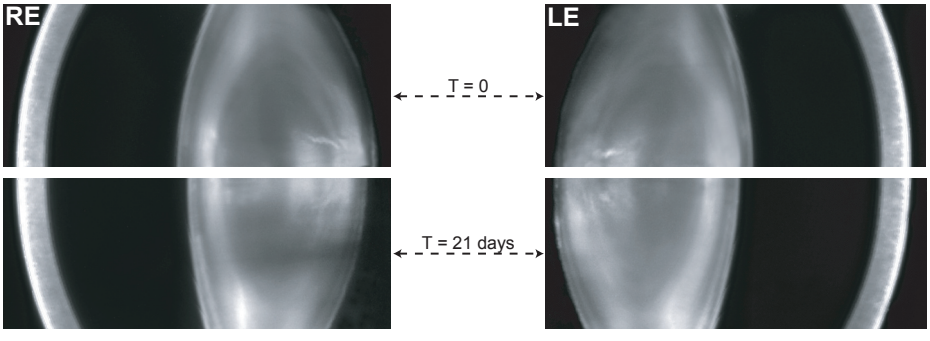
*Submitted for publication*

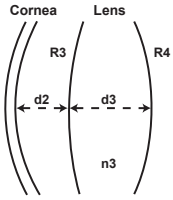
A 27-year old man with no history of ophthalmologic disease was diagnosed with diabetes mellitus after persistent genital infections and severe weight-loss. At the time of the diagnosis his serum blood glucose level was 28.7 mmol/L (glycated hemoglobin level 16.0 %), but insulin treatment reduced this level to 8.2 mmol/L within seven days. Four days after he had been diagnosed with diabetes mellitus he developed subjective symptoms of blurred vision and needed glasses to watch television. These symptoms led to his referral to our ophthalmology department. At that time his cycloplegic objective refraction (spherical equivalent) was +2.44 diopters (RE) and +2.23 diopters (LE). Slit-lamp examination revealed no opacities or abnormalities in the anterior eye segment, and fundoscopic evaluation of the retina showed no symptoms of diabetic retinopathy or other abnormalities. The axial eye length was measured and corrected Scheimpflug images of the anterior eye segment were obtained, in order to accurately measure the shape of the cornea and the lens,[1] and to calculate the equivalent refractive index of the lens.[2] Three weeks after diagnosis his blood glucose levels were well under control (serum blood glucose: 6.8 mmol/L) and the symptoms of blurred vision had disappeared; cycloplegic objective refraction was +1.17 diopters (RE) and +1.29 diopters (LE). Comparisons at follow-up showed that during metabolic dysregulation there were hyperopic shifts in ocular refraction of +1.27 diopters (RE) and +0.94 diopters (LE). Furthermore, corrected Scheimpflug images of both eyes showed that the lens thickness had increased, and that the anterior surface of the lens was more convex (Figure). The equivalent refractive index of the lens in both eyes had decreased (Figure). No changes could be observed in the shape of the cornea, the shape of the posterior lens surface, or the axial eye length.

Blurred vision, due to a variation in blood glucose levels, is a well-known complication of diabetes mellitus. It has been suggested that the predominant cause of refractive changes during hyperglycemia is a change in the shape and/or the refractive index of the lens.[3,4] However, previous studies have not been able to demonstrate this, due to a lack of available measurement methods. By means of corrected Scheimpflug imaging we found a change in both the shape and the refractive index of the lens. This may explain the fact that both myopic[5] and hyperopic[6] shifts have been reported in patients with diabetes and metabolic dysregulation. A small change in the shape of the lens, accompanied by a relatively large change in equivalent refractive index of the lens, as observed in this patient, appears to result in a hyperopic shift of refraction during hyperglycemia. Alternatively, if there is a large change in the shape of the lens, in combination with a small change in the equivalent refractive index, a myopic shift of refraction will predominate. Therefore, it seems that there is a delicate balance between changes in the shape and the equivalent refractive index of the lens during hyperglycemia,

which will eventually determine the overall refractive outcome.




| RE | T = 0 | T = 7 days | T = 21 days |
|---|---|---|---|
| d2 | 2.74 (0.01) | 2.85 (0.01) | 2.92 (0.01) |
| d3 | 4.18 (0.01) | 4.06 (0.01) | 3.95 (0.002) |
| R3 | 9.14 (0.03) | 10.49 (0.04) | 10.82 (0.14) |
| R4 | 5.93 (0.06) | 5.84 (0.04) | 5.80 (0.06) |
| n3 | 1.421 (0.0004) | 1.428 (0.002) | 1.434 (0.001) |
| SE | 2.44 (0.23) | 1.48 (0.06) | 1.17 (0.04) |




| LE | T = 0 | T = 7 days | T = 21 days |
|---|---|---|---|
| d2 | 2.74 (0.01) | 2.90 (0.01) | 2.96 (0.02) |
| d3 | 4.17 (0.01) | 4.01 (0.01) | 3.89 (0.06) |
| R3 | 9.15 (0.08) | 10.31 (0.10) | 10.59 (0.15) |
| R4 | 5.63 (0.03) | 5.73 (0.02) | 5.77 (0.01) |
| n3 | 1.417 (0.002) | 1.427 (0.001) | 1.430 (0.002) |
| SE | 2.23 (0.16) | 1.72 (0.05) | 1.29 (0.01) |

**Figure** *Corrected Scheimpflug images of the right (RE) and left eye (LE) at time T = 0 days, when blurred vision and hyperglycemia were present, and at T = 21 days, when vision and blood glucose levels had returned to normal. An increase in the thickness and the anterior convexity of the lens can be observed in the images that were taken at T = 0. The values (with standard errors of the mean) of the various lens parameters and the refractive error at different times are presented in tables for the RE and LE. The diagram shows the various parameters: d2 (depth of the anterior chamber in mm), d3 (lens thickness in mm), R3 (anterior radius of curvature lens in mm), R4 (posterior radius of curvature lens in mm), n3 (equivalent refractive index lens), and SE (spherical equivalent in diopters).*

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# Chapter 7

## Refractive properties of the healthy human eye during acute hyperglycemia

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## Abstract

*Purpose:* To measure the refractive properties of the healthy human eye during acute hyperglycemia by means of Scheimpflug imaging and Hartmann-Shack aberrometry.

*Methods:* Acute hyperglycemia was induced in five healthy subjects (2 males, 3 females, mean age 24.8 years (SD 4.6)) by means of an oral glucose tolerance test (OGTT) after subcutaneous somatostatin injection. Before and every 30 minutes after the OGTT measurements with Scheimpflug imaging and Hartmann-Shack aberrometry were performed. The main outcome measures were the thickness and shape of the lens, and the ocular refractive error and higher order aberrations. The equivalent refractive index of the lens was calculated from these parameters. Measurements at baseline and during hyperglycemia were analyzed by means of Wilcoxon signed rank sum tests.

*Results:* During hyperglycemia (mean blood glucose level at baseline: 4.0 mmol/l; mean maximal blood glucose level: 18.4 mmol/l) no changes could be found in the refractive properties within the group. In one subject, a hyperopic shift (0.4 D) was observed, together with a more convex shape of the anterior lens surface and a decrease in the equivalent refractive index of the lens.

*Conclusions:* The present study shows that hyperglycemia generally does not cause changes in the refractive properties of the healthy eye. Nevertheless, in one subject a hyperopic shift accompanied by a change in shape and refractive index of the lens was measured. This finding could provide an explanation for the mechanism underlying the refractive changes that are often observed during hyperglycemia.

## Introduction

Transient refractive changes, due to a variation in blood glucose levels, are well-known complications of diabetes mellitus (DM). Both myopic shifts [2, 6, 9, 20, 28, 33] and hyperopic shifts [8, 15, 11, 22, 29, 34] have been reported in patients with DM after several days or weeks of hyperglycemia. It has been suggested that the predominant cause of the refractive changes is a change in the thickness of the lens [13, 14, 16, 22, 26], or shape of the lens [18] and/or a change in its refractive index [21, 24, 26, 30]. Two studies have been conducted in which hyperglycemia was induced under controlled circumstances to investigate refractive changes during hyperglycemia. Firstly, Gwinup et al. [12] administered glucose intravenously to ten patients with DM. A myopic shift of maximal -0.75 D was measured with autorefractometry. Secondly, Furushima et al. [10] induced hyperglycemia in 7 healthy, young subjects through somatostatin injections and an oral glucose load. They measured a large change in ocular refraction (-2.0 diopters (D)) and thickness of the lens (1.0 mm) with autorefractometry and ultrasound biometry. The results of these two studies indicated that induced hyperglycemia can cause changes in refraction and that these changes appeared to be larger in healthy subjects.

In the study of Furushima et al. [10], only the thickness of the lens was measured, and there is no information about the change in the shape and the refractive index of the lens due to acute hyperglycemia. Therefore, the aim of the present study was to induce hyperglycemia in healthy subjects under controlled circumstances, and accurately measure ocular geometry and refraction by means of corrected Scheimpflug imaging and Hartmann-Shack aberrometry, in order to investigate the mechanism underlying refractive changes during hyperglycemia. From the ocular geometry and refraction, in combination with the measurement of the axial length of the eye, it is also possible to calculate the equivalent refractive index of the lens [4, 5].

## Materials and methods

Five healthy Caucasian subjects (2 males and 3 females) were recruited for this study. Mean age was 24.8 years (SD 4.6 and range 21.2 - 32.6) and mean body mass index (BMI) was 24.2 kg/m2 (SD 3.2 and range 21.4 - 29.7). The Medical Ethics Committee of the VU University Medical Center in Amsterdam approved the study protocol, and written informed consent was obtained from all subjects

after the nature of the study had been explained. Subjects with a history of diabetes mellitus (or a fasting plasma glucose > 5.5 mmol/l), a BMI of > 30 kg/m2, visual acuity of < 0.5 (Snellen), or a history of ocular pathology were excluded from the study.

*Procedure to induce hyperglycemia*

After a 10-hour overnight fast, the subjects received a subcutaneous injection of 100 µg synthetic somatostatin (Sandostatin, Novartis, Basel, Switzerland) in order to suppress the endogenous insulin secretion during glucose loading. Each subject had an oral glucose tolerance test (OGTT) (glucose 75 g) 30 minutes after the somatostatin injection. Blood glucose levels were measured with a blood glucose analyzer (HemoCue Diagnostics BV, Oisterwijk, the Netherlands). Endogenous insulin levels were determined with immunometric assays (Luminescence, Bayer Diagnostics, Mijdrecht, the Netherlands) in the Laboratory of Endocrinology of the Department of Clinical Chemistry in the VU University Medical Center. The subjects remained in a fasting state during the entire procedure.

*Measurement of ocular parameters*

Before and 120 minutes after the OGTT 1.0% cyclopentolate and 5.0% phenylephrine eye-drops were administered to the right eye of the subjects. Hartmann-Shack aberrometry was performed with an IRX3 aberrometer (Imagine Eye Optics, Paris, France) and Scheimpflug imaging was performed with a Topcon SL-45 Scheimpflug camera, in which the film was replaced by a charge-coupled device (CCD) camera (St-9XE, SBIG astronomical instruments) with a range of 16 bits of grey values (512 x 512 pixels, pixel size 20 x 20 µm, magnification: 1x). Before and every 30 minutes after the OGTT, three measurements were made with each apparatus. To obtain accurate measurements of the shape of the lens, ray-tracing was performed to correct the Scheimpflug images for the distortion that is inherent to this technique [4, 5]. By combining the measurements of the corneal thickness (d1), the depth of the anterior chamber (ACD), the anterior (R1) and posterior (R2) radius of the cornea, the lens thickness (d3) and the anterior (R3) and posterior (R4) radius of the lens, the axial length of the eye, and ocular refraction, it was possible to calculate the equivalent refractive index of the lens (n lens) by means of an iterative process [5]. The axial length of the eye was measured with an IOL-master (Carl Zeiss Inc., North America). The equivalent refractive error (ERE) was calculated as: ERE = sphere + (cylinder / 2). Furthermore, the higher order aberrations (HOA) of each eye were analyzed at a pupilsize of 5.7 mm and they were summarized in root mean square errors, including the third up to the eighth Zernike orders [31].

Measurements at baseline and during hyperglycemia were compared in the whole group by means of Wilcoxon signed rank sum tests. A refractive change of more than 0.2 D and a change in HOA of more than 0.025 μm were considered to be meaningful, according to the precision (defined as 95% confidence interval) for measuring the ERE and HOA of the aberrometer [3, 27]. Error analysis indicated that a change in R1, R2, d1, ACD, d3, R3, R4, and n lens of more than 0.05 mm, 0.05 mm, 0.02 mm, 0.14 mm, 0.15 mm, 0.30 mm and 0.40 mm, and 0.007 respectively, could be considered as significant, according to the precision of corrected Scheimpflug imaging [4]. In each subject individually, the significance of a change was determined from the precision of the measurements and the difference in the ocular parameters at baseline and during hyperglycemia. P-values $\leq 0.05$ were considered statistically significant.

## Results

Figure 1 shows the changes in blood glucose after the OGTT. In all subjects the mean blood glucose levels rose from 4.0 mmol/l (range 3.4 to 4.5 mmol/l) to 18.4 mmol/l (range 16.1 to 22.0 mmol/l) in 126 minutes (range 90 to 210 minutes) after the OGTT. Subject 01 had a delayed elevation of blood glucose level and therefore this subject received a second 75 g oral glucose load at time = 30 minutes.

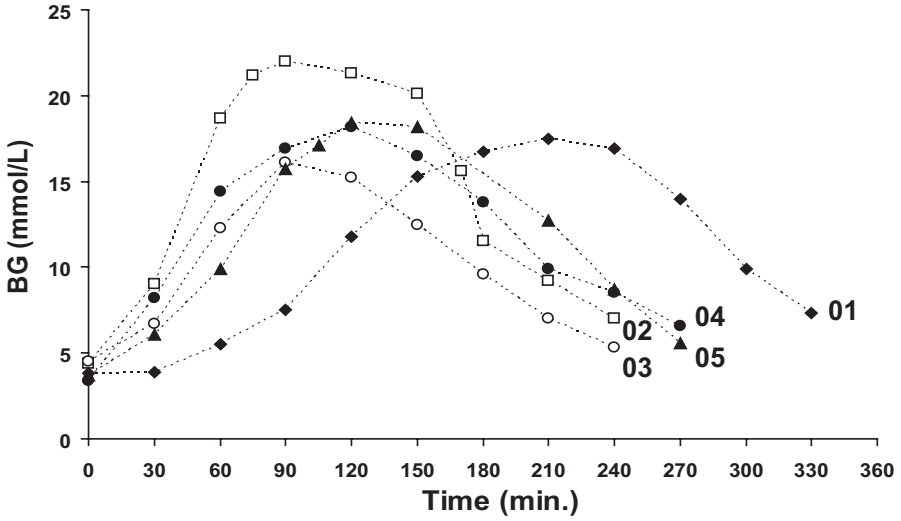


**Figure 1** *Changes in blood glucose (BG) levels in the five subjects after the administration of somatostatin and glucose; the oral glucose load (75 g) was administered at time = 0 minutes.*

Furthermore, venous blood samples of subject 01 were taken from the antecubital vein, which was kept open with 0.9 % saline (100 cl). Endogenous insulin was suppressed by the subcutaneous injection of somatostatin during the glucose load to a mean value of 2.1 pmol/l (range 0.4 to 4.5 pmol/l), and remained below basal secretion level (< 110.0 pmol/l) for 147 minutes (range 75 to 270 minutes).

No significant change in ERE was found in the whole group or in four of the subjects individually. In subject 01 a hyperopic shift in ERE of 0.4 D was measured during hyperglycemia ($p < 0.001$). There was no significant change in the HOA in the group or in any of the subjects individually. No changes in

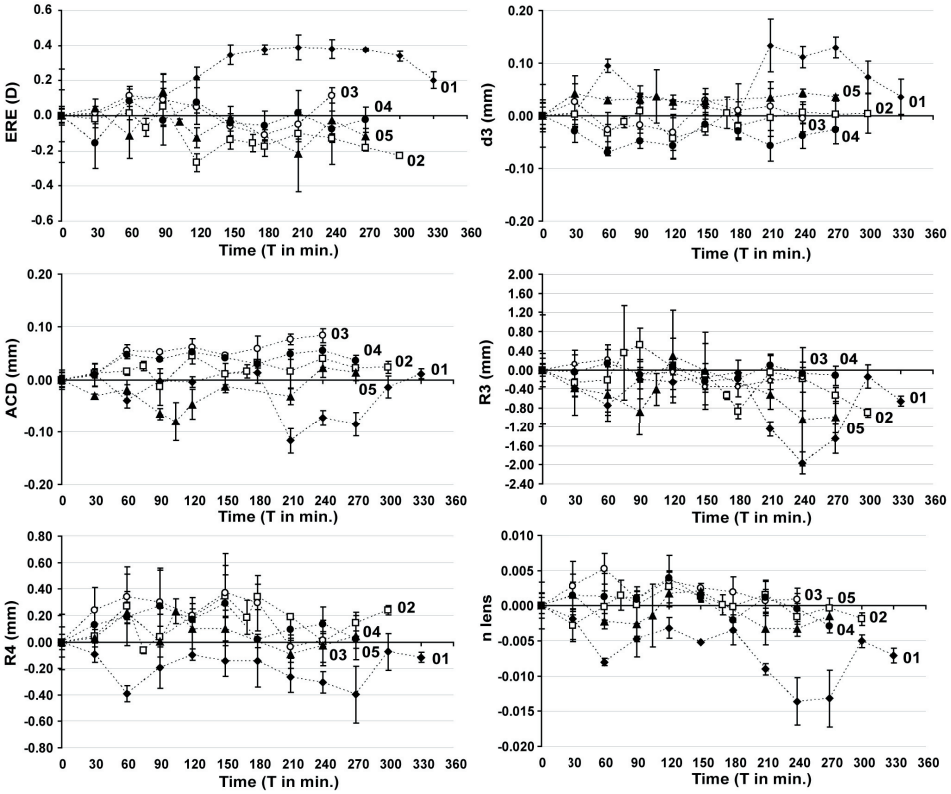


**Figure 2** *Graphs of the normalized equivalent refractive error (ERE), lens thickness (d3), anterior chamber depth (ACD), anterior (R3) and posterior (R4) radius of the lens, and the refractive index of the lens (n lens) of the five subjects. Data are normalized by subtracting the value at baseline from the measured value in each subject. In subject 01 a hyperopic shift of 0.4 D, an increase in R3 and decrease in n lens were found during hyperglycemia at T = 240 minutes ($p < 0.01$). The oral glucose load was administered at T = 0.*

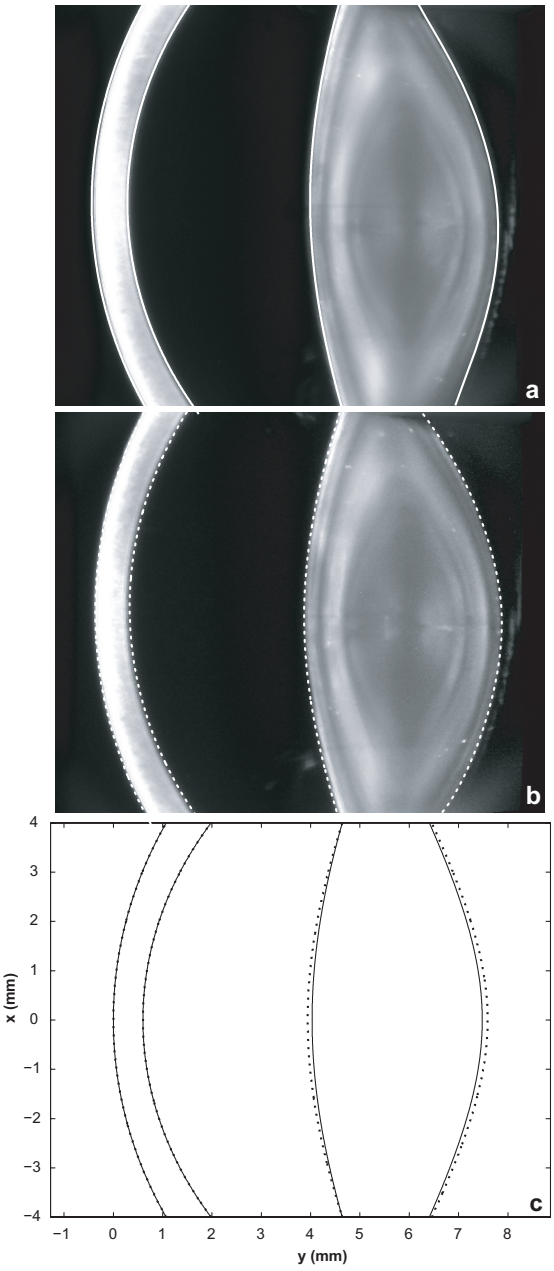


**Figure 3** *Corrected Scheimpflug images of the right eye of subject 01: (a) at baseline time = 0 minutes, the shape of the cornea and lens are indicated with a solid line; (b) during hyperglycemia at time = 240 minutes after the first oral glucose load, the shape of the cornea and lens are indicated with a line of dashes; (c) a drawing of the changes in the shape of the lens in hyperglycemic condition (line of dashes) compared to the normal condition (solid line).*

corneal thickness (d1), corneal shape (R1 and R2), anterior chamber depth (ACD), lens thickness (d3), or posterior lens shape (R4) were found in the group or in any of the subjects individually. In the whole group and in four subjects, no changes were found in the anterior radius of the lens (R3) or refractive index (n lens). However, in subject 01, the R3 and n lens changed significantly during hyperglycemia, compared to normal conditions; R3 decreased from 11.65 to 9.69 mm (mean decrease R3 = 1.96 mm; $p < 0.001$) and n lens decreased from 1.436 to 1.422 (mean decrease n lens = 0.014; $p = 0.003$). Figure 2 presents graphs of the normalized ERE, ACD, d3, R3, R4 and n lens of the five subjects. Figure 3 shows two corrected Scheimpflug images and a schematic drawing of the lens of subject 01, in order to illustrate the small differences in lens geometry during hyperglycemia compared to baseline. In all subjects, both hematological and ocular parameters normalized within 6 hours after the OGTT.

## Discussion

Refractive changes occur frequently in patients with DM. The underlying mechanism is still unclear and therefore the aim of the present study was to measure ocular refraction and geometry during hyperglycemia, in an attempt to identify a possible explanation for these refractive changes. The effect of reproducible hyperglycemia was studied in healthy subjects without the systemic effects of DM. An OGTT in combination with a somatostatin injection was used to induce hyperglycemia. In an earlier study, this was shown to induce large changes in the refractive error and lens thickness [10]. Somatostatin inhibits insulin secretion [7] and to our knowledge, there are no reports of refractive errors or changes in the lens due to this agent.

In general and in four of the five subjects individually, no changes in ocular refraction or geometry were found during hyperglycemia. It could be that a more prolonged and severe hyperglycemia is needed to induce changes in refractive error or geometry of the eye. Glucose within the lens is metabolized via the sorbitol pathway, which consists of two enzymes that catalyze the conversion of glucose into its sugar alcohol sorbitol and the further conversion of sorbitol to fructose. These sugar alcohols tend to accumulate within the lens, because they penetrate cell membranes poorly. This accumulation of sugar alcohols causes the lens to swell. This process might have taken longer than the observation period of the present study. Furthermore, the subjects measured in the present study were young and it could be that their lenses, which still have a fast metabolic reaction capacity, tolerate short hyperglycemic stress without swelling.

These results are not in accordance with the findings of Furushima et al. [10], who observed a large myopic shift (-2 D) and a large increase in the thickness of the lens (1 mm) during hyperglycemia in healthy subjects. One main difference between the present study and the Furushima et al. study are the methods that were used to measure ocular refraction (aberrometry versus autorefractometry) and ocular geometry (corrected Scheimpflug imaging versus ultrasound biometry). However, the precision of aberrometry and autorefractometry are comparable for the measurement of defocus, astigmatism and, consequently, the equivalent refractive error [3, 27, 32]. Furthermore, the precision of corrected Scheimpflug imaging and ultrasound biometry are comparable as well. It could be that the difference in ethnicity (Caucasian subjects in the present study versus Asian subjects in the Furushima study) caused the inconsistency between the two studies, since Asian people generally have a more myopic ocular refraction than Caucasian subjects [12, 36].

In the present study, small but significant changes in ocular refraction and lens geometry were found in one subject. A hyperopic shift of 0.4 D was found, in combination with an increase in anterior convexity of the lens. A combination of hyperopia and an increase in lens thickness during hyperglycemia has been described by Kluxen et al. [18], who found a 6 D hyperopic shift and a 0.4 mm increase in lens thickness in a diabetic patient with hyperglycemia. Saito et al. [26] reported hyperopic shifts (1.1 to 4.9 D) and an increase of approximately 0.2 mm in the thickness of the lens in five diabetic subjects during hyperglycemia. Therefore, it has been suggested that hyperglycemia causes a change in the refractive index of the lens [18, 21, 24, 26, 30]. The results of the present study support this hypothesis; in subject 01 a decrease in the equivalent refractive index of the lens was calculated during hyperglycemia. It could be suggested that if the change in the shape of the lens is small, hyperopia will predominate during hyperglycemia due to a decrease in the refractive index of the lens. Alternatively, if the change in the shape of the lens is large in comparison to the decrease in the refractive index of the lens, the overall refractive error will result in myopia. The controversy in the literature with regard to refractive changes during hyperglycemia could be explained by this underlying mechanism of a balance between changes in the shape or the refractive index of the lens, which eventually determine the overall refractive outcome [17, 20, 25, 34].

It is surprising that in only one subject, a change in refraction and ocular parameters could be determined. It must be noted that the procedures for inducing hyperglycemia and monitoring blood glucose were, to some extent, different for subject 01, compared to the other subjects. Because of a delayed elevation in blood glucose level, a second oral glucose load (150 g instead of 75 g glucose)

was administered. Nevertheless, the maximum blood glucose value of subject 01 did not exceed that of the other subjects and the endogenous insulin level was adequately suppressed during the glucose loading. Furthermore, in order to obtain sufficient blood samples 0.9 % saline had to be administered to keep the antecubital vein open. Therefore, it could not be excluded that the administration of saline contributed to the refractive change and alterations in the lens of subject 01. However, no studies have yet reported any refractive change due to saline administration.

The change in refractive error in patients with hyperglycemia could also be caused by a change in the shape of the cornea. However, previous research has shown that hyperglycemia has no influence on the shape of the anterior corneal surface [9, 21, 26, 29]. The results of the present study also agree with these findings. No change in the anterior or posterior corneal radius was found during hyperglycemia. Therefore, the cornea does not seem to play a role in the explanation of refractive changes during hyperglycemia. This also applies for the higher order aberrations. Applegate et al. [1] reported that an increase in the higher order aberrations could cause a decrease in visual acuity. However, no changes in the higher order aberrations were found in any of the subjects in the present study. Therefore, it can be assumed that blurred vision in hyperglycemia cannot be explained by changes in the higher order aberrations of the eye.

In sum, under the conditions of the present experiment induced hyperglycemia generally did not cause changes in the refractive properties of the healthy human eye. However, there were interindividual variations, as illustrated by subject 01, who had a hyperopic shift of refraction and a change in shape and equivalent refractive index of the lens during hyperglycemia. This could provide an explanation for the mechanism underlying the refractive changes often experienced by patients with DM and hyperglycemia.

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# Chapter 8

## The effect of acute hyperglycemia on retinal thickness and ocular refraction in healthy subjects

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## Abstract

*Purpose* To quantify the retinal thickness and the refractive error of the healthy human eye during hyperglycemia by means of optical coherence tomography (OCT) and Hartmann-Shack aberrometry.

*Methods* Hyperglycemia was induced in five healthy subjects who were given a standard oral glucose tolerance test (OGTT) after a subcutaneous injection of somatostatin. Main outcome parameters were the central, pericentral and peripheral thickness of the fovea, measured by means of optical coherence tomography (OCT3). Ocular refractive error was determined with Hartmann-Shack aberrometry. Measurements at baseline and during maximal hyperglycemia were analyzed, and a change was considered clinically significant if the difference between the measurements exceeded the threshold of 50 μm for retinal thickness and 0.2 D for refractive error.

*Results* During hyperglycemia (mean blood glucose level at baseline: 4.0 mmol/l; mean maximal blood glucose level: 18.4 mmol/l) no significant changes could be found in the central, pericentral, or peripheral foveal thickness in any of the five subjects. One of the subjects had a hyperopic shift of 0.4 D, but no significant change in refractive error was found in any of the other subjects.

*Conclusions* The present study shows that in healthy subjects induced hyperglycemia does not affect retinal thickness, but it can cause a small hyperopic shift of refraction.

# Introduction

Patients with diabetes mellitus (DM) often experience subjective symptoms of blurred vision associated to hyperglycemia. The nature and origin of this phenomenon are still unclear. Blurred vision during hyperglycemia could be a result of transient refractive alterations due to changes in the lens [5, 12, 15, 25, 27, 36, 37], but it could also be caused by changes in the retina. Macular edema, or retinal thickening due to abnormal fluid accumulation within the macula, is a common cause of visual loss [1, 14, 22]. The degree of retinal thickening has been found to be significantly correlated with visual acuity [24]. Furthermore, a change in retinal thickness, resulting in a change in axial eye length, could also induce a change in ocular refractive error. For instance, it can be calculated that with a 50 μm increase in retinal thickness, the ocular refractive error becomes 0.15 D more hyperopic [30].

Several studies have demonstrated that retinal thickness is affected by DM [2, 7, 8, 18, 21, 23, 26, 32, 33, 35, 38]. In general, an increase in retinal thickness has been reported in patients with long-term DM and advanced stages of retinopathy [7, 8, 18, 32, 33, 35]. However, in diabetic patients with and without minimal diabetic retinopathy a decrease in retinal thickness has been observed [2, 23]. In healthy subjects, it has been shown that the average retinal thickness did not change during normo-insulinaemic hyperglycemia [13].

It is unclear whether the thickness of the different retinal areas, such as the foveal area, the pericentral foveal area, and the peripheral foveal area, changes during acute hyperglycemia and suppression of insulin. A change in retinal thickness and/or ocular refractive error could explain the subjective symptoms of blurred vision in patients with DM and hyperglycemia. Therefore, in the present study the effect of hyperglycemia on retinal thickness and ocular refractive error was investigated in healthy subjects during suppression of endogenous insulin. Retinal thickness was measured by means of optical coherence tomography (OCT), which is a non-invasive technique that provides cross-sectional retinal images, and produces an objective measurement of the retinal thickness, independent of the refractive status of the eye [10, 11, 29]. Furthermore, aberrometry was used to measure the ocular refractive error. This technique makes it possible to detect small changes in ocular refraction [19].

## Materials and methods

Five healthy subjects (2 males and 3 females) participated in the study. The mean age of the subjects was 24.8 years (range 21.2 - 32.6), and their mean Body Mass Index (BMI) was 24.2 kg/m2 (range 21.4 - 29.7). The subjects were screened during a first visit, which included medical history-taking, a physical examination (measurement of visual acuity, weight, height and blood pressure) and collecting a fasting blood sample. Exclusion criteria were a history of DM (or a fasting plasma glucose > 5.5 mmol/l), a BMI of > 30 kg/m2, elevated blood pressure (> 140 / 85 mmHg), a visual acuity of < 0.5 (Snellen) or a history of ocular pathology. The investigators of the ocular parameters (NW and MD) were not informed about the blood glucose levels. Furthermore, the investigators who induced hyperglycemia (EE and SS) were not informed about the results of the ocular measurements. The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam, and written informed consent was obtained from all subjects after the purpose and nature of the study had been explained to them.

*Procedure to induce hyperglycemia*

After a 10-hour overnight fast, the subjects were given a subcutaneous injection of a low dose (100 µg) of synthetic somatostatin (Sandostatin, Novartis, Basel, Switzerland) in order to suppress endogenous insulin secretion. Each subject underwent an oral glucose tolerance test (OGTT) (75 g glucose) 30 minutes after the somatostatin injection, and blood glucose levels were measured with a blood glucose analyzer (HemoCue Diagnostics BV, Oisterwijk, the Netherlands). Endogenous insulin levels were measured by means of immunometric assays (Luminescence, Bayer Diagnostics, Mijdrecht, the Netherlands) in the Endocrinology Laboratory at the Department of Clinical Chemistry of the VU University Medical Center. The subjects remained in fasting state during the entire procedure.

*Ocular measurements*

Retinal thickness was measured with the Stratus OCT (Model 3000, Carl Zeiss Meditec, Dublin, CA, USA), which combines a low coherence scanning interferometer (wavelength 820 nm) with a video camera to visualize the fundus of the eye. The fast macular thickness OCT scan protocol was used to obtain 6 cross-sectional macular scans, 6 mm in length, which are positioned at equally spaced angular orientations (300) centred on the fovea. The cross-

sectional images were analyzed with OCT3 mapping software that uses an edge-detection technique to locate the vitreoretinal interface and the anterior surface of the retinal pigment epithelium. Retinal thickness was defined as the distance between these two surfaces. Two OCT scans were made of each subject before, and every 30 minutes during the period of hyperglycemia. In order to quantify the retinal thickness, the foveal map constructed by the software was divided into nine Early Treatment Diabetic Retinopathy Study (ETDRS) areas [6]: the central fovea (central circle with a diameter of 1 mm), and the pericentral area (donut-shaped ring with an inner diameter of 1 mm and an outer diameter of 3 mm) and peripheral area (donut-shaped ring with an inner diameter of 3 mm and an outer diameter of 6 mm), both of which were divided into four quadrants. Retinal thickness was calculated for all separate areas, and for the average pericentral and peripheral regions.

Ocular refractive error was determined with an IRX3 aberrometer (Imagine Eye Optics, Paris, France), which performs wavefront analysis of the eye according to the Hartmann-Shack principle [19] After pupil dilation and paralysis of accommodation with 1.0% cyclopentolate and 5.0% phenylephrine eye-drops, a series of three aberrometry measurements was made before, and every 30 minutes during the hyperglycemic condition. From these measurements, the equivalent refractive error was calculated as: equivalent refractive error (ERE) = sphere + (cylinder / 2).

The measurements at baseline and during maximal hyperglycemia were analyzed, and any change was considered to be meaningful if the difference between the measurements was greater than the threshold of 50 μm for retinal thickness and 0.2 diopters (D) for ERE. The threshold of 50 μm exceeded the 95% confidence interval for the detection of a change in retinal thickness, which has been reported to be approximately 40 μm [4, 20, 28]. A refractive change of more than 0.2 D also surpasses the precision (defined as 95% confidence interval) of the aberrometer for measuring sphere, cylinder, and consequently ERE [3, 31]. In each subject, the significance of a change was obtained from the precision of the measurement instruments and the difference in the ocular parameters at baseline and during hyperglycemia. In the whole group, the significance of a change could be determined by means of Wilcoxon matched pairs signed rank sum tests. P-values $\leq 0.05$ were considered to be statistically significant.

## Results

The changes in blood glucose after the administration of somatostatin and glucose are shown in Figure 1. Mean blood glucose levels rose from 4.0 mmol/l (range 3.4 to 4.5 mmol/l) to 18.4 mmol/l (range 16.1 to 22.0 mmol/l) after the OGTT. Endogenous insulin was suppressed by the subcutaneous injection of somatostatin during the glucose load to a mean value of 2.1 pmol/l (range 0.4 to 4.5 pmol/l), and remained below basal secretion level (< 110.0 pmol/l) for 147 minutes (range 75 to 270 minutes). Subject 01 had a delayed elevation of blood glucose level, compared to the other subjects. This person received a second 75 g oral glucose load after 30 minutes in order to induce a rise in the blood glucose level. In all subjects, the blood glucose and endogenous insulin levels normalized within 6 hours after the OGTT.

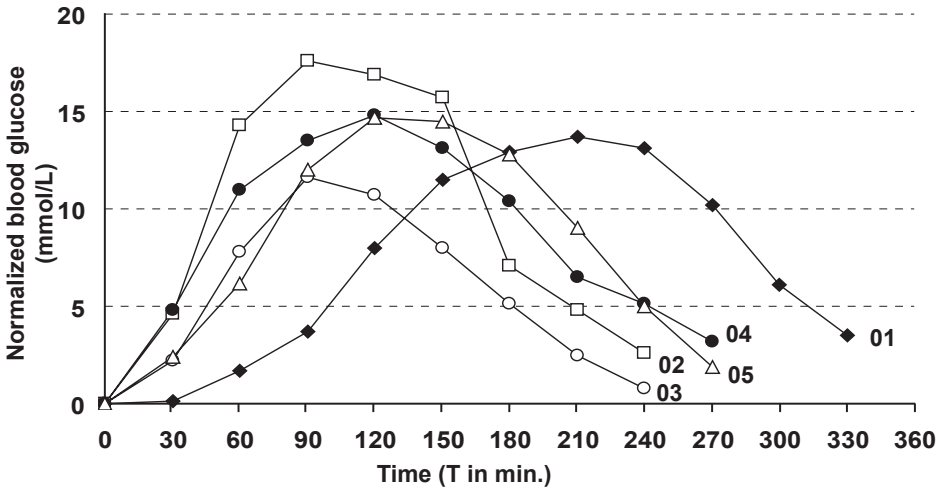


**Figure 1** *Graph of normalized blood glucose levels in the five subjects after the administration of somatostatin and glucose. Data are normalized by subtracting the value at baseline from the measured value in each subject. The oral glucose load (75 g) was administered at T 0. Subject 01 received an extra 75 g oral glucose load at T 30.*

Figure 2 shows the normalized ERE of the five subjects during hyperglycemia. Mean ERE at baseline was 0.6 D (SD 0.6) and 0.7 D (SD 0.6) during maximal hyperglycemia, no significant change was found in the group as a whole. A small, but significant hyperopic shift of 0.4 D (SD 0.2) in ERE was measured in subject

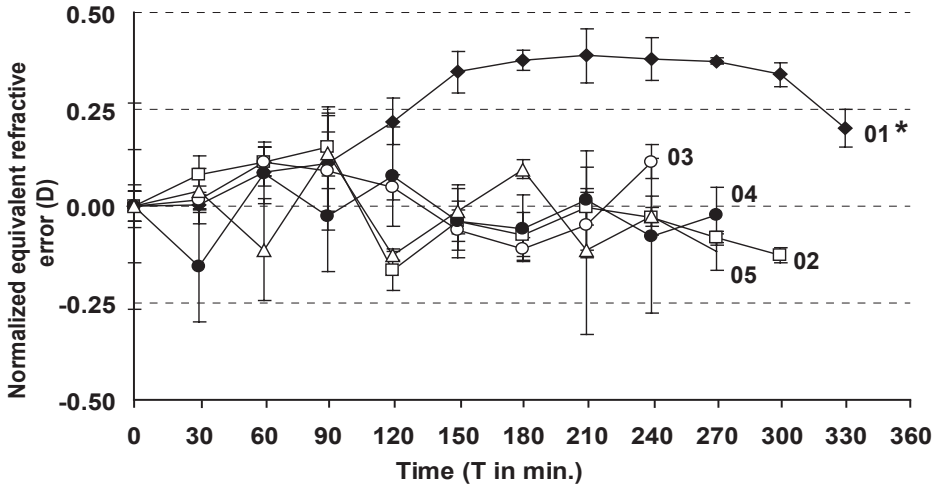


**Figure 2** *Graph of the normalized equivalent refractive error (ERE) in diopters (D) of the five subjects. Data are presented as mean ± standard deviation; three measurements were made of each subject every 30 minutes during the procedure. Data are normalized by subtracting the value at baseline from the measured value in each subject. The oral glucose load was administered at T 0. * Significant difference between ERE at T 0 and T 210 (maximal hyperglycemia), p < 0.001.*

01 during maximal hyperglycemia, compared to the start of the procedure ($p < 0.001$). No significant change in ERE was found in any of the other subjects.

Normalized retinal thickness parameters are shown in Figure 3a (central foveal area), 3b (average pericentral foveal area) and 3c (average peripheral foveal area). Average central foveal thickness, average pericentral foveal thickness, and average peripheral foveal thickness at baseline were 202 μm (SD 8), 277 μm (SD 5), and 243 μm (SD 8). During maximal hyperglycemia average central foveal thickness, average pericentral foveal thickness, and average peripheral foveal thickness were 203 μm (SD 7), 275 μm (SD 3), and 242 μm (SD 9). No significant differences were found in the group as a whole. Furthermore, none of the subjects had any significant changes in the thickness of the central fovea, the pericentral fovea, or the peripheral fovea during maximal hyperglycemia, compared to baseline. The nine separate ETDRS areas were not affected by hyperglycemia. At baseline and during hyperglycemia any change in retinal thickness that occurred in the various areas was less than 15 μm, which was within the previously defined threshold of 50 μm.

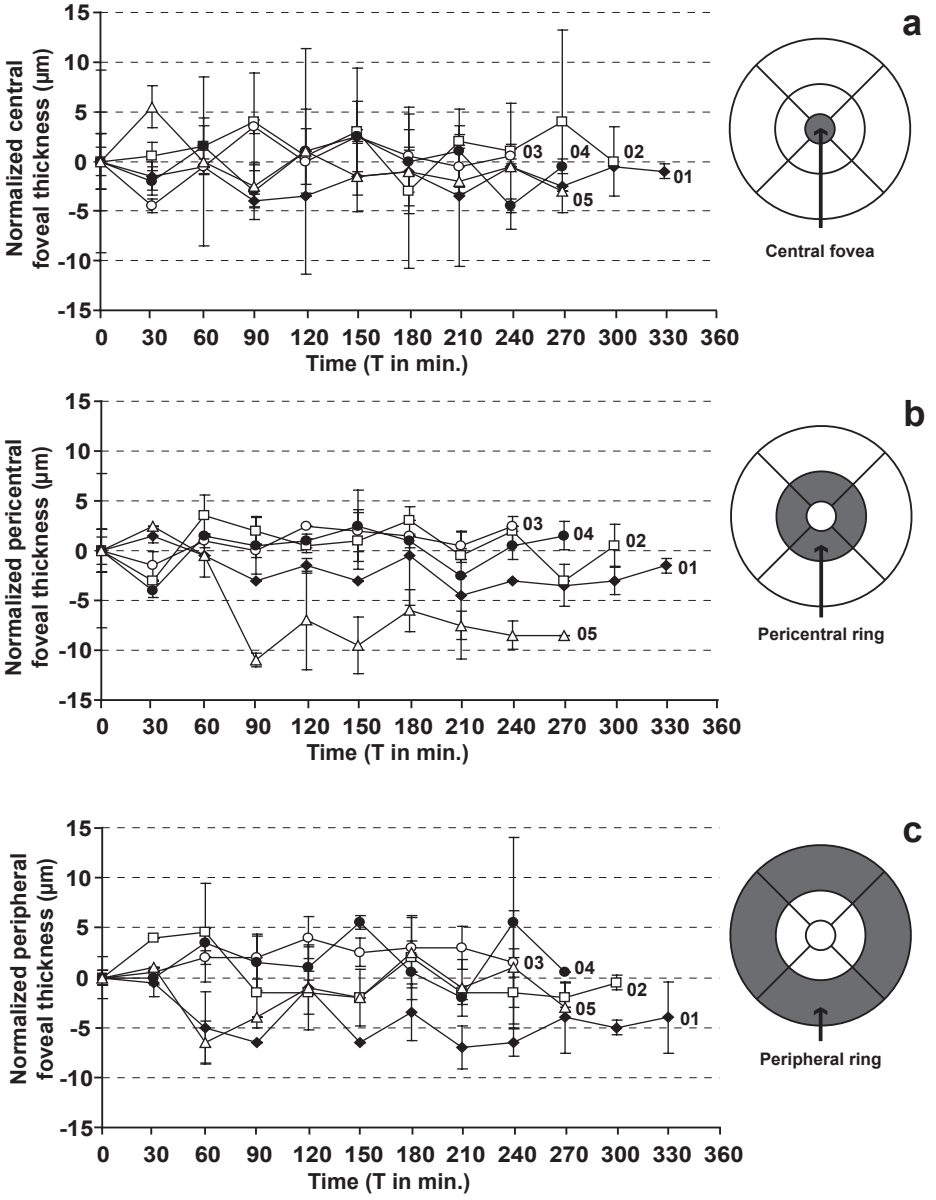


**Figure 3** *Graphs and maps of normalized retinal thickness parameters in the five subjects during hyperglycemia: (a) central fovea, (b) pericentral fovea, (c) peripheral fovea. Data are normalized by subtracting the value at baseline from the measured value in each subject. Each measured area has been indicated by a dark grey area on the retinal maps. No significant changes in retinal parameters were found in any of the subjects. The oral glucose load was administered at T 0.*

## Discussion

Blurred vision is a symptom that occurs frequently in patients with DM and hyperglycemia. The underlying mechanism is still unclear and therefore the present study was carried out in an attempt to identify a possible cause of this symptom. The effect of reproducible hyperglycemia on retinal thickness and refractive error was studied in healthy young subjects who did not suffer from the systemic effects of DM.

No changes in the thickness of the central, pericentral or peripheral foveal areas were found in any of the subjects during hyperglycemia. In addition, no significant change was measured in any of the nine different ETDRS areas of the macula. In their study, Jeppesen et al. [13] also found no significant difference in retinal thickness in healthy subjects during normo-insulinaemic hyperglycemia. Before and 180 minutes after the start of a hyperglycemic clamp they measured the average thickness of the retina, and found that retinal thickness was not affected by hyperglycemia. Although in the present study retinal thickness was measured under different circumstances than in the study of Jeppesen et al. (hypo-insulinaemic hyperglycemia instead of normo-insulinaemic hyperglycemia), the results confirm those of Jeppesen et al..

Retinal thickness has been reported to change in patients with long-term DM and retinopathy. A morphological change in the retina may even occur in the early stages of diabetic retinopathy [2, 7, 8, 18, 21, 23, 26, 32, 33, 35, 38]. These changes in retinal thickness are usually due to abnormal fluid accumulation resulting from a breakdown of the blood-retinal barrier [34]. Goebel et al. [8] measured retinal thickness by means of OCT in 136 patients with different stages of diabetic retinopathy and with a mean DM duration of 16 years. Mean foveal thickness was 307 ± 136 µm in the diabetic subjects, compared to 153 ± 15 µm in healthy subjects. It seems that only long-term hyperglycemia and/or long-term fluctuations in blood glucose levels have any significant influence on the blood-retina barrier and retinal thickness. From the findings of the present study it appears that the blood-retina barrier does not seem to be affected by a single episode of acute hyperglycemia. Nevertheless, the fact that no change in retinal thickness could be determined, does not exclude the possibility that there could be early dysfunction of the blood retina barrier. Other means of examination could evidence such a dysfunction of the blood retina barrier following acute hyperglycemia.

A factor that could have biased the results of this study is the administration of a synthetic somatostatin analogue to the subjects. Somatostatin is a peptide hormone

that inhibits several hormones, including IGF-1 and insulin. IGF-1 is a growth factor that is produced by the hypoxic retina to mediate angiogenesis, resulting in neovascularisation. Somatostatin analogues not only inhibit neovascularisation in patients with advanced diabetic retinopathy, but also stabilize the blood-retinal barrier in patients with diabetic macular edema [16, 17]. It could have been possible that in the present study an increase in retinal thickness during hyperglycemia was prevented by somatostatin. Nevertheless, the efficacy of synthetic somatostatin in the treatment of advanced diabetic retinopathy was investigated by Grant et al. [9]. With maximally tolerated doses of somatostatin (ranging from 200 to 5000 μg/day) after a period of 15 months 1 out of 22 eyes required panretinal photocoagulation, compared to 9 of 24 eyes that were not treated with somatostatin. From the results of the Grant et al. study it seems that only frequent, large doses of somatostatin over a long period of time have any significant effect on the progression of diabetic retinopathy. Although the effect of somatostatin on the healthy retina has not been investigated yet, it seems to be unlikely that the results of the present study were biased by the administration of one single, low dose (100 μg) of somatostatin.

In conclusion, the results of this study indicate that in healthy subjects, hyperglycemia does not cause any change in retinal thickness. Furthermore, ocular refraction in general was not affected by hyperglycemia. However, there were interindividual variations, as illustrated by subject 01, who had a hyperopic shift of refraction during hyperglycemia. Therefore, it seems that a refractive change during hyperglycemia can not be explained by a change in retinal thickness. It could well be that other refractive components, such as the lens, are involved in causing blurred vision and refractive alterations during hyperglycemia.

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# Chapter 9

## Therapeutic possibilities for diabetic macular edema

N.G.M. Wiemer, B.C.P. Polak and M.A.H. Veckeneer

*Ned Tijdschr Geneeskd 2006;150(40):2183-7*
*(Translated from Dutch)*

## Abstract

In the coming years there will be a considerable increase in the number of patients with diabetes mellitus, and this implies that there will also be an increase in the prevalence of diabetic macular edema. Diabetic macular edema and diabetic retinopathy are the main causes of legal blindness in adults. Macular edema, or retinal thickening due to abnormal fluid accumulation within the macula, has been reported as a common cause of visual loss and the degree of retinal thickening has been found to be significantly associated with visual acuity. The current therapy for diabetic macular edema consists of the prevention, detection and treatment of risk factors (such as hypertension, hyperglycemia, dyslipidemia, proteinuria and obesity) with additional laser treatment (photocoagulation), if necessary. In many patients, photocoagulation may prevent or reduce vision loss, but it does not usually improve visual acuity. New treatment strategies include intravitreal corticosteroids or vascular-endothelial growth factor (VEGF) inhibitors and oral protein kinase C-inhibitors, angiotensine-converting enzyme (ACE) inhibitors, acetylsalicylic acid or statins. Long-term improvement is not always achieved, and the side-effects can be serious.

## Introduction

Diabetic retinopathy and diabetic macular edema are the main causes of legal blindness (i.e. maximum vision of 0.1) in adults under 65 years of age. At present, the number of patients with diabetes mellitus worldwide is approximately 246 million, and this is expected to increase to 380 million in 2025, mainly due to an increase in the number of patients with diabetes mellitus type 2.[1]

Clinically relevant macular edema (Figure 1), defined as retinal thickening, with or without exsudates within one papil diameter of the centre of the macula, has a prevalence of 10 % in the diabetes population as a whole.[2] Among patients with diabetes mellitus type 1, diabetic macular edema seldom develops during the first 5 years after the diagnosis. On the other hand, patients with diabetes mellitus type 2 have a 3-8 % risk of developing diabetic macular edema within 3 years after the diagnosis.[2]

Diabetic macular edema is a multifactorial disorder, resulting from microvascular changes in the retina, which cause abnormal permeability of the vascular walls.[3] In general, two sub-types can be distinguished: focal and diffuse macular edema. In the focal type, thickening of the retina is caused by leakage from microaneurysmata and dilated capillaries, which is sometimes accompanied by hard exsudates (deposits of protein and fatty substances from the blood). The diffuse type, which can occur with or without cystoid edema, is characterized by generalized leakage from dilated capillaries in the macula region. Subjective symptoms of diabetic macular edema can include: blurred or unclear vision and metamorphopsia (distorted vision). However, it can also occur without complaints.

## Diagnosis

Diabetic macular edema can be assessed with fundus photography, slit-lamp examination (biomicroscopy), fundoscopy, measurement of vision acuity, and examination of the central visual field. Gold standards for the detection of diabetic retinopathy and diabetic macular edema are 7-field stereo-photography, biomicroscopy or fluorescence angiography. Fluorescence angiography is necessary in order to identify diffuse and ischemic edema, especially if no abnormalities are found with fundus-photography (Figure 2) or fundoscopy, and if treatment is indicated. Moreover, increasing use is being made of optical coherence tomography, an objective, non-invasive method in which infra-red

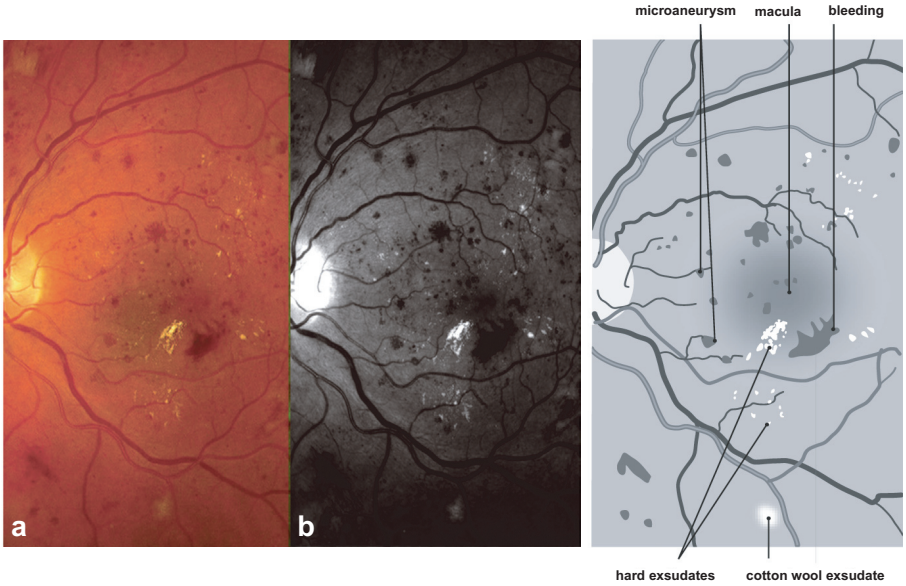


**Figure 1** *Digital fundus photos of the left eye of a patient with clinically relevant diabetic macular edema: (a) color photograph – remarkable are the many hard exsudates, bleedings and micro-aneurysms within one papil diameter of the centre of the macula; soft ("cotton wool") exsudates can also be seen; (b) black and white photos of the same fundus – more details can be seen, due to the greater contrast.*

light produces optical cross-sections of the retina. This makes early detection and follow-up of diabetic macular edema possible, because the thickness and the volume of the retina in the macular region can be determined.[4]

## Risk factors

Successful treatment of diabetic macular edema should focus on prevention of the development and exacerbation of various known risk factors.[5] Risk factors for the development of the macular edema are longer duration of diabetes mellitus, hyperglycemia, hypertension, dyslipidemia, proteinuria, gravidity, ethnicity, and ophthalmological interventions, such as panretinal laser therapy or cataract extraction.[2] Other risk factors include a rapid decline in elevated blood glucose levels, and an elevated body mass index (BMI) and hip-waist measurements (obesity).[6]

The Diabetes Control and Complications Trial and the United Kingdom

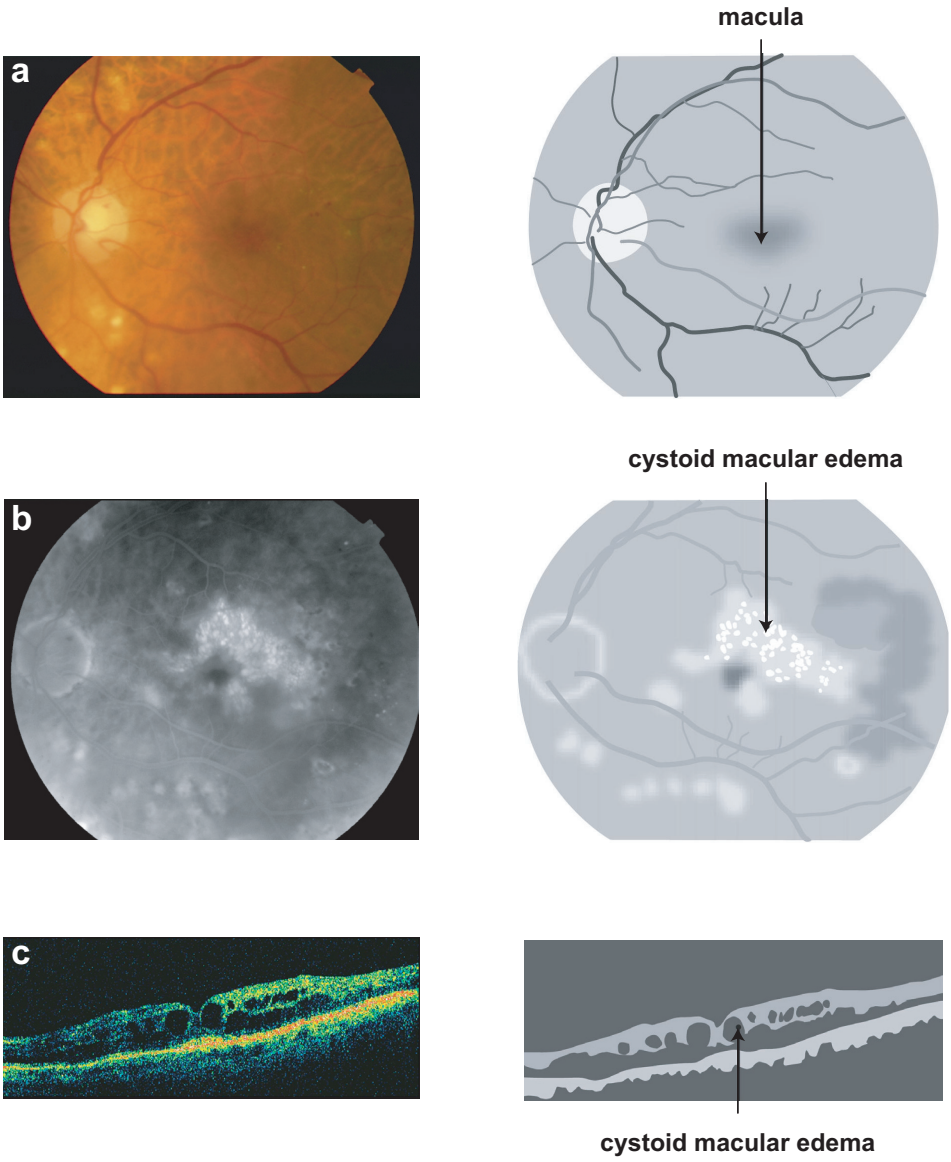


**Figure 2** *Photos of the left eye of a patient with cystoid diabetic macular edema: (a) fundus photo – very few abnormalities can be seen in the macular region; hard and soft ("cotton wool") exsudates can be seen along the vascular curves; (b) fluorescent angiogram: diffuse leakage in the vascular walls with cystoid macular edema; (c) picture obtained with optical coherence tomography: diffusely thickened macula with cystoid structures.*

Prospective Diabetes Study have demonstrated that strict regulation of blood glucose levels in patients with diabetes mellitus type 1 and 2 can offer protection against both the development and progression of diabetic macular edema. In this respect, the aim should be to achieve an average blood glucose level (glycated hemoglobin; HbA1c) of less than 7 %.[7, 8] Careful monitoring of blood pressure also appears to be effective: systolic blood pressure levels of less than 135 mmHg and diastolic levels of less than 85 mmHg are recommended.[9] From the Early Treatment of Diabetic Retinopathy Study it appears that hard exsudates in the retina are associated with increased levels of serum cholesterol.[10] Serious proteinuria is associated with a 95 % higher risk of developing diabetic macular edema in patients with diabetes mellitus type 1.[11] Gravidity can cause serious diabetic macular edema, especially in combination with hypertension and proteinuria. Diabetic macular edema usually disappears spontaneously in the third term of a pregnancy or after the partus, but the edema can also cause a serious, long-term deterioration in vision.[12] In approximately 43 % of patients with proliferative diabetic retinopathy who receive panretinal laser treatment, diabetic macular edema can develop or exacerbate.[13] Among diabetes patients who have undergone cataract extraction, 32-40 % develop macular edema, but in two thirds of these patients the edema disappears spontaneously within 6 months. After lens extraction, diabetic macular edema that was present before the operation can exacerbate, and therefore pre-operative laser coagulation is recommended.[14]

## Treatment

*Current treatment*

Laser treatment should be considered for clinically relevant macular edema, especially if vision is threatened or has deteriorated.[5] In patients with focal diabetic macular edema, laser coagulates are placed at the site of the leakage. For diffuse macular edema, with or without cystoid leakage, grid laser is applied, i.e. with laser coagulation in a lattice pattern. Laser treatment can prevent or slow down deterioration of the visual acuity of many patients, but it does not usually improve. Side-effects of laser therapy include: troublesome paracentral scotomes, spreading of the laser scars and an increase in scotomes, epiretinal fibrosis, and, in exceptional cases, a sudden deterioration in vision due to a central increase in the edema.[15]

*New treatment strategies*

For many patients the visual prognosis after laser treatment is only moderate, so that additional treatment strategies are needed. In patients with diabetic macular edema that is caused by traction of the posterior vitreous membrane on the macula, the posterior vitreous membrane and, if necessary, also the epiretinal fibrosis can be removed in an operation (vitrectomy).[16]

Various different pharmacological interventions are currently being investigated, and sometimes applied with success. An intravitreal injection with the corticosteroid triamcinolonacetonide initially appeared to have a beneficial effect: there was a reduction in retinal thickening and an improvement in visual acuity. However, the effects of this treatment only last for an average of 3 to 6 months, after which the visual acuity reduces again and the retina thickens. The side-effects can be serious: the intravitreal injection can cause bacterial endophthalmitis, and the corticosteroid can cause cataract, an increase in intraocular pressure and glaucoma.[17, 18]

One way in which to prolong the effects of intravitreal corticosteroids is the placement of an intraocular implant, containing flucinolon-acetonide, in the vitreous, which induces a gradual flow of the corticosteroid. Frequent side-effects of this intervention are an increase in intraocular pressure and cataract.[19] Corticosteroids can possibly reduce microvascular leakage by inhibiting the vascular-endothelial growth factor (VEGF), which regulates the proliferation of endothelial cells and plays a role in vascular wall leakage and neovascularisation as a reaction to ischemia of the retina. In a short-term study, treatment with pegaptanib, a VEGF inhibitor, every 6 weeks has been investigated. There was improved visual acuity, the thickness of the macula decreased, and additional laser therapy was needed less rapidly.[20] As yet, no further results of other studies on the effect of pegaptanib have been published.

Another type of pharmacological treatment is selective inhibition of protein-kinase C (PKC), an enzyme that can possibly increase the expression of VEGF in hyperglycemia. Oral PKC inhibitors are well accepted, and they improve the retinal circulation time in patients with diabetes mellitus.[21] The effect of ruboxistaurin, a PKC inhibitor, has been investigated in two double-blind studies. In one of these studies the primary aims, i.e. a decline in diabetic macular edema and an improvement in visual acuity, were not achieved, but it did result in slowing down a reduction in visual acuity in certain patient groups.[22] The results of the other study are similar. However, before any definite conclusions can be drawn about the benefits of treatment with a PKC inhibitor, we must await the results of clinical trials that are currently being carried out (http://eyephoto.ophth.wisc.edu/PresentationsPublications/PKCInhibitorTrials.pdf). Angiotensine-converting

enzyme (ACE) inhibitors and acetylsalicylic acid have no direct beneficial effect, and research results must demonstrate whether statins can slow down the development or progression of diabetic macular edema.[9, 10, 23]

## Conclusion

At the present, the most important aspect in the treatment of diabetic macular edema is an adequate and targeted identification and treatment of risk factors. Further research in the coming years will have to indicate which additional therapy is the most beneficial.

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# Chapter 10

## General discussion and summary

Diabetes mellitus affects hundreds of millions of people worldwide, resulting in considerable morbidity and mortality. Well-known ocular complications of diabetes are diabetic retinopathy and cataract (Ch 1.3). Diabetes mellitus also has a significant effect on the refractive properties of the human eye. In patients with diabetes the lens becomes thicker and the shape of its anterior and posterior surface becomes more convex (Ch 1.3.4). Furthermore, subjective symptoms of blurred vision and refractive changes are frequently reported features of dysregulated blood glucose levels (Ch 1.4.1).

The exact influence of chronic and acute diabetes mellitus on the refractive properties of the eye is still a matter of discussion, mainly because appropriate tools to accurately measure the refractive components of the eye have only recently become available. Ocular refraction depends on the shape of the cornea and lens, the refractive indices of these ocular media, and the axial length of the eye. Therefore, accurate measurements of the refractive elements of the diabetic eye are a prerequisite for finding anomalies of the refractive system of diabetic patients and for investigating the underlying mechanism of blurred vision and refractive changes during sustained and acute hyperglycemia. The studies described in this thesis focused on the mechanisms underlying blurred vision and refractive changes in patients with diabetes mellitus by investigating sustained and transient changes in the refractive elements of the diabetic eye. Accurate measurements of the geometry of the anterior eye segment and the refractive error of the diabetic and healthy eye were obtained by means of corrected Scheimpflug imaging (Ch 1.5.1) and Hartmann-Shack aberrometry (Ch 1.5.2). The aims of the present study were:

- To accurately measure the thickness and the shape of the cornea, and the thickness, shape and internal structure of the lens in patients with diabetes mellitus type 1 and type 2 (Chapters 2, 3, and 4).

- To investigate the mechanisms underlying blurred vision and refractive changes by measuring the geometry of the cornea and the lens, the ocular refractive error, and the retinal thickness of the eye during an episode of acute hyperglycemia Chapters 5, 6, 7 and 8).

*Sustained influence of diabetes mellitus on the geometry of the cornea and the lens of the human eye*

The main refractive components of the eye are the cornea and the lens. The anterior surface of the cornea contributes to approximately two-third of the total refractive power of the eye, and the remaining power is provided by the posterior corneal surface and the anterior and posterior surfaces of the lens. Changes in the radius of curvature of either the anterior or the posterior surface, or changes in the thickness of the cornea or the lens can alter the refractive power of the eye. In the present study diabetes mellitus type 1 and type 2 both appeared to have a small but significant effect on the posterior radius of curvature of the cornea; people with diabetes appeared to have a slight decrease in the radius of the posterior corneal surface, resulting in a small change in the refractive power of the posterior corneal surface. However, because of the small change in posterior corneal radius, and because the radius (and thus the power) of the anterior corneal surface was not affected by diabetes mellitus type 1 or type 2, it can be concluded that the cornea does not play a major role in sustained diabetic refractive alterations (Chapter 2).

The normal healthy lens constantly grows during life and is characterized by an increase in thickness and a decrease in the anterior and posterior radius of curvature (i.e. an increase in convexity). From the observations in Chapter 3 it can be concluded that in patients with diabetes mellitus type 1 the most prominent changes in the anterior eye segment occur within the lens. The lenses of patients with diabetes type 1 were significantly thicker and more convex than those of healthy subjects. The duration of the disease was an important determinant of changes in lens biometry; the increase in lens thickness with each year of diabetes was approximately twice the annual age-related increase. The decrease in the anterior and posterior radius of curvature of the lens with each year of diabetes was approximately two and three times the annual age-related decrease, respectively. This effect of diabetes type 1 on lens biometry was even more pronounced than has been reported in earlier Scheimpflug studies (for references see Ch 1.3.4), in which no correction had been made for the distortion inherent to Scheimpflug imaging (Ch 1.5.1). The increase in convexity of the lens with diabetes type 1 is expected to result in an increase in the refractive power of the lens, and consequently in a myopic shift of ocular refraction. Surprisingly, however, the refractive power of the lens remained unaffected by diabetes mellitus. This can be explained by the fact that the equivalent refractive index of the lens decreases with diabetes, and that this decrease compensates for the more convex shape of the diabetic lens. As a result, the diabetic eye does not become more myopic with increasing duration of the disease. Finally, an essential difference was found in the

effect of diabetes type 1 and type 2 on lens biometry; the geometry of the lenses of patients with diabetes mellitus type 2 did not differ from that of healthy lenses. This may indicate a fundamental difference in pathogenesis between diabetes mellitus type 1 and type 2 (Chapter 3).

In Chapter 4 the origin of the increased dimensions of the lens in patients with diabetes mellitus was further investigated. It was hypothesized that the increased size of the diabetic lens could be due to a more rapid growth of the lens, or to an overall swelling of the lens. A more rapid growth of the diabetic lens would lead to an increase in the thickness of one specific layer of the cortex of the lens, since the growth of the healthy lens has been reported to be entirely due to an increase in that particular cortical layer. However, when an overall swelling of the lens fibers would occur, one would expect an increase in the thickness of all the different zones of the lens. In the study summarized in Chapter 4 it appeared that all layers in the lens were enlarged in patients with diabetes mellitus type 1. Therefore, it was concluded that the profound increase in the size of the lens of patients with diabetes mellitus type 1 is most likely the result of an overall swelling, affecting all parts of the lens due to an influx of water (Chapter 4). Evidence in favor of an influx of water in the lens is the observation that the equivalent refractive index of the lens decreases with diabetes (Chapter 3). Finally, consistent with the results described in Chapter 3, diabetes mellitus type 2 appeared to have no or very little effect on the thickness of the various layers of the lens (Chapter 4).

*Transient influence of diabetes mellitus on the refractive properties and retinal thickness of the human eye*

Blurred vision is a common ocular symptom of diabetes mellitus. Normal visual acuity requires a sharp image projected by the refractive system of the eye onto the retina, accurate translation of the image to action potentials by the retina, and processing of that information by the visual cortex of the brain. Errors in any part of the system could result in blurred vision. Therefore, the causes of blurred vision can be numerous, but are best considered by two determinants: the image formation system of the eye (i.e. the refractive system and the retina), and the image-processing system (e.g. the visual cortex and related areas in the brain). Changes in the image formation system include refractive errors and/or optical aberrations due to changes in the geometry of the cornea and the lens, and retinal disease such as for instance diabetic macular edema. The present study focused on changes in the image formation system as a possible cause of blurred vision in patients with diabetes mellitus.

First, the ocular refractive properties (geometry of the cornea and lens, refractive power and optical aberrations) of patients with diabetes mellitus type

1 and type 2 were measured during the presence and absence of symptoms of blurred vision and hyperglycemia. The optical properties of the cornea and lens were measured as described above by means of corrected Scheimpflug imaging, Hartmann-Shack aberrometry, and optical coherence tomography. From a group of 229 patients with diabetes mellitus, we studied those subjects (n = 25) who had subjective symptoms of blurred vision and hyperglycemia at the first visit. After the first visit they were asked to return for a second visit when the symptoms of hyperglycemia and blurred vision had disappeared. A comparison of the results at the two visits revealed that no significant changes had occurred in the thickness or shape of the cornea, nor in the thickness, shape and equivalent refractive index of the lens. Furthermore, only very small changes were observed in the refractive error and optical aberrations during hyperglycemia, which could not explain the symptoms of blurred vision. This indicated that the symptoms of blurred vision in patients with diabetes and moderate hyperglycemia do not seem to be caused by a change in the refractive components of the eye, and that a more severe and prolonged elevation of the blood glucose levels is needed to induce significant changes in the refractive system of the eye (Chapter 5). This is demonstrated in Chapter 6, which provides a description of a case-report, from which it can be seen that severe prolonged hyperglycemia can cause changes in the refractive properties of the eye. In both eyes of a 27-year old man with newly diagnosed diabetes mellitus, severe hyperglycemia and symptoms of blurred vision, hyperopic shifts in refraction due to changes in the geometry of the lens were found. The thickness of the lens had increased, its anterior surface had become more convex, and the equivalent refractive index had decreased. After three weeks the blood glucose was at normal levels and the symptoms of blurred vision and ocular changes had disappeared.

In order to further investigate the mechanisms underlying blurred vision and refractive changes, two experimental studies were performed. These studies were also meant to verify the controversial results of an earlier study, in which dramatic changes in lens thickness (1 mm) and ocular refractive error (-2 D) were reported in healthy subjects during induced acute hyperglycemia. In contrast to this earlier study, in which autorefractometry and ultrasound biometry was used, we used corrected Scheimpflug imaging, Hartmann-Shack aberrometry, and optical coherence tomography to measure the image formation system (i.e. refractive system and the retina) of healthy subjects during induced acute hyperglycemia. Surprisingly, in 4 out of 5 subjects no changes were found in the cornea and the lens, nor in the refractive error and ocular aberrations of the eye (Chapter 7). However, one subject had a hyperopic shift (+0.4 D) of ocular refraction, accompanied by a change in shape and refractive index of the lens

during hyperglycemia.

The results of Chapters 6 and 7 may provide an explanation for the controversy in the literature with regard to refractive changes during acute hyperglycemia. It could be that if the change in the shape of the lens is small, hyperopia will predominate during hyperglycemia, due to a decrease in the refractive index of the lens. Alternatively, if the change in the shape of the lens is large in comparison to the decrease in the refractive index of the lens, the overall refractive error will result in myopia. In summary, there seems to be a delicate balance between changes in the shape and the refractive index of the lens, which eventually determine the overall refractive outcome.

Finally, retinal thickness was measured during acute induced hyperglycemia (Chapter 8). Macular edema, or retinal thickening due to abnormal fluid accumulation within the macula, has been reported as a common cause of visual loss and the degree of retinal thickening has been found to be significantly associated with visual acuity (Chapter 9). However, in the present study, retinal thickness did not change during acute induced hyperglycemia, and so does not seem to be an explanation for blurred vision (Chapter 8).

*Conclusions*

In this thesis we have shown that long-term diabetes mellitus type 1 has a major influence on the geometry of the lens. With increasing duration of the disease the diabetic lens becomes thicker and more convex as compared to a non-diabetic lens, as a result of overall swelling affecting all parts of the lens. These changes do not affect the refractive power of the lens due to a decrease in the equivalent refractive index of the lens. Furthermore, diabetes mellitus type 2 had very little effect on the refractive properties of the eye, which suggests a difference in the pathophysiological mechanisms underlying diabetes mellitus type 1 and type 2.

Severe acute hyperglycemia can cause changes in the refractive properties of the eye: a hyperopic shift in refraction is the result of a change in both the shape and the equivalent refractive index of the lens. Myopic and hyperopic shifts reported in the literature may be explained by the fact that both the shape and the equivalent refractive index of the lens change during hyperglycemia. Therefore, we hypothesize that a subtle balance exists between changes in the shape and the refractive index of the lens, which will eventually determine the overall refractive outcome. Subjective symptoms of blurred vision are not necessarily caused by a change in the image formation system of the eye, but they could also be the result of alterations in the image-processing system in the brain. Further research could possibly provide more insight into the role of image-processing in the brain during acute metabolic dysregulation.

# Nederlandse samenvatting

Wereldwijd zijn er miljoenen mensen met diabetes mellitus, hetgeen resulteert in aanzienlijke morbiditeit en mortaliteit. Bekende oogheelkundige complicaties van diabetes mellitus zijn diabetische retinopathie en cataract (Hoofdstuk 1.3). Diabetes mellitus heeft ook een significant effect op de refractieve eigenschappen van het menselijk oog. Bij patiënten met diabetes mellitus wordt de lens dikker en de vorm van het voorste en achterste lens oppervlak wordt boller (Hoofdstuk 1.3.4). Daarnaast komen subjectieve symptomen van wazig zien en veranderingen van de refractie regelmatig voor bij acute ontregelde bloedglucosewaarden (Hoofdstuk 1.4.1).

Zowel de exacte invloed van het langdurig hebben van diabetes mellitus, alsmede het effect van acute ontregelde diabetes mellitus op de refractieve eigenschappen van het oog is nog een punt van discussie, voornamelijk vanwege het feit dat er pas recentelijk een methode beschikbaar is gekomen om alle optische elementen van het oog nauwkeurig te meten. De refractie van het oog is afhankelijk van de vorm van het hoornvlies en de lens, de brekingsindices van de oculaire media en de oogaslengte. Daarom zijn nauwkeurige metingen van de refractieve elementen van het diabetische oog belangrijk om afwijkingen te vinden in het refractieve systeem van patiënten met diabetes mellitus en daarnaast om het onderliggende mechanisme van wazig zien en refractieveranderingen tijdens acute ontregelde diabetes te onderzoeken. Het onderzoek dat beschreven is in dit proefschrift richtte zich op het onderliggende mechanisme van wazig zien en refractieveranderingen bij patiënten met diabetes mellitus door middel van het onderzoeken van langdurige en voorbijgaande (reversibele) veranderingen in de refractieve componenten van het diabetische oog. Nauwkeurige metingen van de geometrie van het voorste oogsegment en de refractie van het diabetische en gezonde oog werden verkregen met behulp van gecorrigeerde Scheimpflug fotografie (Hoofdstuk 1.5.1) en Hartmann-Shack aberrometrie (Hoofdstuk 1.5.2). De doelstellingen van deze studie waren:

- Het nauwkeurig meten van de dikte en de vorm van het hoornvlies, en de dikte, de vorm en de inwendige structuur van de lens bij patiënten met diabetes mellitus type 1 en type 2 (Hoofdstukken 2, 3, en 4).

- Het onderzoeken van het onderliggende mechanisme van wazig zien en refractie veranderingen tijdens acute hyperglykemie (hoge bloedglucose waarden) door middel van metingen van de geometrie van het hoornvlies en de lens, de refractie afwijking en de dikte van het netvlies van het oog (Hoofdstukken 5, 6, 7 en 8).

*Langdurige invloed van diabetes mellitus op de geometrie van het hoornvlies en de lens van het menselijk oog*

De belangrijkste refractieve componenten van het oog zijn het hoornvlies en de lens. De voorzijde van het hoornvlies draagt ongeveer twee-derde bij aan het totale refractieve vermogen van het oog, de achterzijde van het hoornvlies en de voor- en achterzijde van de lens zorgen voor het overige deel. Het refractieve vermogen van het oog kan veranderen door veranderingen in de dikte of de kromming van het oppervlak van de voor- of achterzijde van het hoornvlies en de lens. In de huidige studie bleken zowel diabetes mellitus type 1 als ook type 2 een klein maar significant effect te hebben op de kromming van het oppervlak van de achterzijde van het hoornvlies; mensen met diabetes blijken een enigszins boller oppervlak van de achterzijde van het hoornvlies te hebben dan gezonde mensen, hetgeen resulteert in een kleine verandering in het refractieve vermogen van de achterzijde van het hoornvlies. Echter, omdat deze verandering zeer klein was en diabetes mellitus verder geen invloed had op de vorm (en tevens het refractieve vermogen) van de voorzijde van het hoornvlies, concluderen wij dat het hoornvlies geen grote rol speelt bij langdurige refractieveranderingen ten gevolge van diabetes mellitus (Hoofdstuk 2).

De gezonde lens blijft groeien gedurende het leven, hetgeen betekent dat de dikte toeneemt en de voor- en achterzijde van de lens boller worden. Uit de observaties beschreven in Hoofdstuk 3 wordt duidelijk dat de meest prominente veranderingen in de geometrie van het voorste oogsegment ten gevolge van diabetes mellitus plaatsvinden in de lens. De lenzen van patiënten met diabetes type 1 waren significant dikker en boller dan de lenzen van gezonde mensen. De duur van de ziekte was een belangrijke determinant van de veranderingen in de biometrie van de lens; de toename van de lensdikte met elk jaar van het hebben van diabetes was ongeveer twee keer het normale effect van veroudering op de lens. Het boller worden van de voor- en achterzijde van de lens met elk jaar diabetes was respectievelijk twee en drie keer het normale verouderingseffect op de lens. Dit effect van diabetes mellitus type 1 op de biometrie van de lens was zelfs nog groter dan eerdere Scheimpflug studies hebben gerapporteerd (Hoofdstuk 1.3.4). In deze eerdere studies werd echter geen rekening gehouden met een zekere mate van beeldvervorming die inherent is aan Scheimpflug fotografie (Hoofdstuk 1.5.1). Logischerwijs zou het boller worden van de lens ten gevolge van diabetes een toename in het refractieve vermogen van de lens bewerkstelligen, met een daarbij gepaard gaande myopisering van de refractie van het oog. Echter, verbazingwekkend genoeg veranderde het refractieve vermogen van de lens niet door diabetes mellitus. Dit kan verklaard worden door het feit dat de equivalente brekingsindex van de lens afneemt door diabetes en dat deze

afname in brekingsindex compenseert voor het boller worden van de diabetische lens. Dit mechanisme heeft tot gevolg dat het diabetische oog niet meer myoop wordt met toenemende duur van de ziekte. Tot slot werd er een essentieel verschil in het effect van diabetes mellitus type 1 en type 2 op de biometrie van de lens gevonden; de geometrie van de lens van patiënten met diabetes mellitus type 2 verschilde niet van die van gezonde mensen. Dit duidt aan dat er mogelijk een fundamenteel verschil in pathogenese bestaat tussen diabetes mellitus type 1 en type 2 (Hoofdstuk 3).

In hoofdstuk 4 werd de oorsprong van de toegenomen lensomvang bij patiënten met diabetes mellitus onderzocht. De hypothese was dat de toegenomen omvang van de diabetische lens veroorzaakt wordt door ofwel een versnelde groei van de lens, ofwel door een gegeneraliseerde zwelling van de lens. Een versnelde groei van de lens zou gekarakteriseerd worden door een toename van de dikte van één specifieke laag in de cortex van de lens, omdat het aangetoond is dat de groei van de gezonde lens het gevolg is van een toename van die specifieke corticale lenslaag. Echter, indien er sprake zou zijn van een zwelling van de lens of van de individuele lensvezels, dan zou men een een toename van de dikte van alle verschillende lenslagen kunnen verwachten. Uit het onderzoek beschreven in Hoofdstuk 4 bleek dat alle verschillende lagen van de lens van patiënten met diabetes mellitus type 1 in dikte toenamen. Daarom werd geconcludeerd dat de toegenomen omvang van de lens door diabetes mellitus type 1 hoogstwaarschijnlijk veroorzaakt werd door een gegeneraliseerde zwelling van alle delen van de lens door een influx van water (Hoofdstuk 4). Bewijs voor een influx van water in de lens is de observatie dat de equivalente brekingsindex van de lens afneemt door diabetes mellitus (Hoofdstuk 3). Tot slot, overeenkomstig met de resultaten die beschreven zijn in Hoofstuk 3, blijkt diabetes mellitus type 2 slechts een minimaal effect te hebben op de verschillende lagen van de lens (Hoofdstuk 4).

*Kortdurende invloed van diabetes mellitus op de refractieve eigenschappen en de dikte van het netvlies van het menselijk oog*

Wazig zien is een veelvoorkomend oogheelkundig symptoom van diabetes mellitus. Voor een normale gezichtsscherpte zijn de volgende factoren noodzakelijk: een beeld dat scherp op de retina geprojecteerd wordt door het refractieve systeem van het oog, een nauwkeurige vertaling van lichtstralen naar actiepotentialen door de retina en het verwerken van die informatie door de visuele cortex van de hersenen. Het falen van een of meerdere onderdelen binnen dit systeem kan resulteren in wazig zien. Dit betekent dat de oorzaken van wazig zien veelvuldig kunnen zijn en dat zij het beste onderverdeeld kunnen worden in twee determinanten: het beeldvormende systeem van het oog (het refractieve systeem

en het netvlies) en het beeldverwerkende systeem (de hersenen). Veranderingen in het beeldvormende systeem houden in: refractie afwijkingen en/of optische aberraties door veranderingen in de geometrie van het hoornvlies en de lens, en netvlies afwijkingen zoals diabetisch macula oedeem. Deze studie richtte zich op veranderingen in het beeldvormende systeem als mogelijke oorzaak van wazig zien bij patiënten met diabetes mellitus.

In eerste instantie werd het oculaire refractieve systeem (geometrie van het hoornvlies en de lens, refractie en optische aberraties) gemeten bij patiënten met diabetes mellitus type 1 of type 2 tijdens het aan- of afwezig zijn van de symptomen van wazig zien en hyperglykemie. De optische eigenschappen van het hoornvlies en de lens werden gemeten zoals boven beschreven door middel van gecorrigeerde Scheimpflug fotografie, Hartmann-Shack aberrometrie en optische coherentie tomografie. Uit een groep van 229 patiënten met diabetes mellitus includeerden wij diegenen (n = 25) die subjectieve klachten van wazig zien en hyperglykemie hadden. Na een eerste serie metingen werden zij gevraagd om terug te komen voor een tweede serie metingen, wanneer de symptomen van wazig zien en hyperglykemie verdwenen waren. Een vergelijking tussen de resultaten van beide metingen maakte duidelijk dat er geen significante veranderingen konden worden aangetoond in de dikte of de vorm van het hoornvlies, of in de dikte, vorm en equivalente brekingsindex van de lens. Verder waren er slechts minimale veranderingen in de refractie en de optische aberraties van het oog tijdens hyperglykemie, die niet de symptomen van wazig zien konden verklaren. Dit betekende dat de symptomen van wazig zien bij patiënten met diabetes en matige hyperglykemie niet veroorzaakt lijken te worden door een verandering in de refractieve componenten van het oog en dat een ernstigere en langere verhoging van de bloedglucose spiegels waarschijnlijk nodig is om significante veranderingen in het refractieve systeem van het oog te bewerkstelligen (Hoofdstuk 5). Dit wordt als zodanig aangetoond in Hoofdstuk 6, waarin een case-report beschreven wordt, waaruit blijkt dat langdurige ernstige hyperglykemie veranderingen in de refractieve eigenschappen van het oog kan veroorzaken. In beide ogen van een 27-jarige man met recent gediagnostiseerde diabetes mellitus, ernstige hyperglykemie en symptomen van wazig zien, werden hypermetrope veranderingen ten gevolge van veranderingen in de geometrie van de lens gevonden. De dikte van de lens was toegenomen, het oppervlak van de voorzijde van de lens was boller geworden en de equivalente brekingsindex was afgenomen door de hoge bloedglucose waarden. Na drie weken was de bloedglucose genormaliseerd en waren de symptomen van wazig zien en de veranderingen in de lens verdwenen.

Met het doel om het onderliggende mechanisme van wazig zien en refractie

veranderingen te onderzoeken werden nog twee experimentele studies uitgevoerd. Deze studies werden ook verricht om de opvallende resultaten te verifiëren van een eerdere studie, waarin grote veranderingen in lensdikte (1 mm) en refractie van het oog (-2.0 D) gemeten werden in gezonde proefpersonen gedurende acuut geïnduceerde hyperglykemie. In tegenstelling tot deze eerdere studie, waarin de metingen verricht werden met autorefractometrie en echografie, gebruikten wij gecorrigeerde Scheimpflug fotografie, Hartmann-Shack aberrometrie en optische coherentie tomografie om het beeldvormende systeem (het refractieve systeem en het netvlies) van gezonde proefpersonen gedurende acute geïnduceerde hyperglykemie te meten. Tot onze verbazing vonden wij bij 4 van de 5 proefpersonen geen veranderingen in het hoornvlies of de lens en ook niet in de refractie of de aberraties van het oog (Hoofdstuk 7). Echter, één van de proefpersonen had een hypermetrope verandering (+0.4 D) van de refractie, gepaard gaande met een verandering in de vorm en de equivalente brekingsindex van de lens tijdens hyperglykemie.

De resultaten van Hoofdstukken 6 en 7 zouden een verklaring kunnen vormen voor de controverse in de literatuur met betrekking tot refractie veranderingen gedurende hyperglykemie. Het zou zo kunnen zijn dat indien de verandering van de vorm van de lens klein is, hypermetropie zal predomineren door een afname in de brekingsindex van de lens. Andersom, indien de verandering van de vorm van de lens relatief groot is in vergelijking met de afname in de brekingsindex van de lens, zal de totale refractie resulteren in myopie. Samengevat lijkt er een delicaat evenwicht te bestaan tussen veranderingen in de vorm en de brekingsindex van de lens, welke uiteindelijk de uitkomst van de refractie bepaalt.

Tot slot werd de dikte van het netvlies tijdens acute geïnduceerde hyperglykemie ook onderzocht (Hoofdstuk 8). Het is beschreven dat macula oedeem, ofwel een verdikking van het netvlies door abnormale vloeistof accumulatie in de gele vlek, een veelvoorkomende oorzaak is van het verlies van de gezichtsscherpte. Daarnaast is de mate van de verdikking van het netvlies significant geassocieerd met de gezichtsscherpte (Hoofdstuk 9). Echter, in deze studie veranderde de dikte van het netvlies niet tijdens acute geïnduceerde hyperglykemie en leek het de symptomen van wazig zien niet te kunnen verklaren (Hoofdstuk 8).

*Conclusie*

In dit proefschrift hebben wij aangetoond dat diabetes mellitus type 1 op de lange termijn een grote invloed heeft op de geometrie van de lens. Met een toename van de duur van de diabetes wordt de lens dikker en boller dan de gezonde lens, door een gegeneraliseerde zwelling van alle verschillende lagen van de lens. Deze veranderingen hebben geen invloed op het refractieve vermogen van de lens door

een daling van de equivalente brekingsindex van de lens. Verder had diabetes mellitus type 2 slechts een minimaal effect op de refractieve eigenschappen van het oog, hetgeen een verschil in de onderliggende pathofysiologische mechanismen van diabetes mellitus type 1 en type 2 suggereert.

Ernstige acute hyperglykemie kan veranderingen in de refractieve eigenschappen van het oog bewerkstelligen: een hypermetrope verschuiving van de refractie is het resultaat van een verandering in de vorm en de equivalente brekingsindex van de lens. Myope en hypermetrope veranderingen in de refractie, zoals gerapporteerd in de literatuur, zouden verklaard kunnen worden door een verandering in zowel de vorm alsook de equivalente brekingsindex van de lens tijdens hyperglykemie. Derhalve veronderstellen wij dat er een subtiele balans bestaat tussen veranderingen in de vorm en de brekingsindex van de lens, die uiteindelijk de uitkomst van de refractie zal bepalen. Subjectieve symptomen van wazig zien worden niet noodzakelijk veroorzaakt door een verandering in het beeldvormende systeem van het oog, maar deze zouden ook het gevolg kunnen zijn van veranderingen in het beeldverwerkende systeem in de hersenen. Verder onderzoek zou eventueel meer inzicht kunnen verlenen in de rol van het beeldverwerkende systeem gedurende acute metabole ontregeling.

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# Curriculum Vitae

Nanouk G.M. Wiemer werd op 10 maart 1980 geboren te Rotterdam. Na het behalen van haar Gymnasium diploma aan het Stedelijk Gymnasium te Breda in 1998, startte zij met haar studie Geneeskunde aan de Universiteit Leiden. In mei 2003 behaalde zij het doctoraalexamen, na het uitvoeren van een wetenschappelijke stage bij de afdeling Gynaecologie en Verloskunde in het Royal Adelaide Hospital in Adelaide, Australië. Haar artsexamen voltooide zij in april 2005 na onder andere een keuze co-schap in het Oogziekenhuis te Rotterdam. Aansluitend begon zij met haar promotieonderzoek bij de afdeling Oogheelkunde (in samenwerking met Oogheelkundige Fysica) en het Instituut voor Extramuraal Geneeskundig Onderzoek (EMGO) van het VU medisch centrum te Amsterdam. Gedurende dit onderzoek nam zij deel aan diverse cursussen als onderdeel van het postinitiële masteronderwijs Epidemiologie. Sinds oktober 2007 is zij bij de afdeling Oogheelkunde van het VU medisch centrum werkzaam als arts-assistent in opleiding tot oogarts.