Abstract
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
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.