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Biometry of eyes in type 1 diabetes

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Abstract: This is a comprehensive study of a large range of biometric and optical parameters in people with type 1 diabetes. The parameters of 74 people with type 1 diabetes and an age matched control group were assessed. Most of the people with diabetes had low levels of neuropathy, retinopathy and nephropathy. Marginal or no significant differences were found between groups for corneal shape, corneal thickness, pupil size, and pupil decentrations. Relative to the control group, the diabetes group demonstrated smaller anterior chamber depths, more curved lenses, greater lens thickness and lower lens equivalent refractive index. While the optics of diabetic eyes make them appear as older eyes than those of people of the same age without diabetes, the differences did not increase significantly with age. Age-related changes in the optics of the eyes of people with diabetes need not be accelerated if the diabetes is well controlled.

OCIS codes: (330.4875) Optics of physiological systems; (330.739) Visual optics, pathology.

References and links

1. M. A. Sekeroglu and H. Taylan Sekeroglu, "Refraction paradox in diabetics: An extreme case of transient hyperopia," J. Diabetes **5**(3), 325–326 (2013).
2. N. Busted, T. Olsen, and O. Schmitz, "Clinical observations on the corneal thickness and the corneal endothelium in diabetes mellitus," Br. J. Ophthalmol. **65**(10), 687–690 (1981).
3. L. I. Larsson, W. M. Bourne, J. M. Pach, and R. F. Brubaker, "Structure and function of the corneal endothelium in diabetes mellitus type I and type II," Arch. Ophthalmol. **114**(1), 9–14 (1996).
4. J. Lee, B. Oum, H. Choi, J. Lee, and B. Cho, "Differences in corneal thickness and corneal endothelium related to duration in diabetes," Eye **20**(3), 315–318 (2005).
5. Y. Ozdamar, B. Cankaya, S. Ozalp, G. Acaroglu, J. Karakaya, and S. S. Özkan, "Is there a correlation between diabetes mellitus and central corneal thickness?," J. Glaucoma **19**(9), 613–616 (2010).
6. A. M. Roszkowska, C. G. Tringali, P. Colosi, C. A. Squeri, and G. Ferreri, "Corneal endothelium evaluation in type I and type II diabetes mellitus," Ophthalmologica **213**(4), 258–261 (2000).
7. D. H. W. Su, T. Y. Wong, W. L. Wong, S. M. Saw, D. T. H. Tan, S. Y. Shen, S. C. Loon, P. J. Foster, and T. Aung, "Diabetes, hyperglycemia, and central corneal thickness: The Singapore Malay Eye Study," Ophthalmol. **115**(6), 964–968 (2008).
8. N. G. M. Wiemer, M. Dubbelman, P. J. Kostense, P. J. Ringens, and B. C. P. Polak, "The influence of chronic diabetes mellitus on the thickness and the shape of the anterior and posterior surface of the cornea," Cornea **26**(10), 1165–1170 (2007).
9. K. Inoue, S. Kato, Y. Inoue, S. Amano, and T. Oshika, "The corneal endothelium and thickness in type II diabetes mellitus," Jpn. J. Ophthalmol. **46**(1), 65–69 (2002).
10. G. M. Keoleian, J. M. Pach, D. O. Hodge, S. D. Trocme, and W. M. Bourne, "Structural and functional studies of the corneal endothelium in diabetes mellitus," Am. J. Ophthalmol. **113**(1), 64–70 (1992).

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11. M. Ziadi, P. Moiroux, P. d'Athis, A. Bron, J. M. Brun, and C. Creuzot-Garcher, "Assessment of induced corneal hypoxia in diabetic patients," Cornea **21**(5), 453–457 (2002).
12. B. Winn, D. Whitaker, D. B. Elliott, and N. J. Phillips, "Factors affecting light-adapted pupil size in normal human subjects," Invest. Ophthalmol. Vis. Sci. **35**(3), 1132–1137 (1994).
13. A. B. Watson and J. I. Yellott, "A unified formula for light-adapted pupil size," J. Vision **12**(10), 1–16 (2012).
14. A. B. Hreidarsson, "Pupil size in insulin-dependent diabetes: relationship to duration, metabolic control, and long-term manifestations," Diabetes **31**(5), 442–448 (1982).
15. A. Zaczek and C. Zetterström, "The effect of phenylephrine and pilocarpine on pupil size and aqueous flare intensity in patients with diabetes mellitus," Acta Ophthalmol. Scand. **76**(4), 413–416 (1998).
16. H.-L. Lei, K.-J. Yang, C.-C. Sun, C.-H. Chen, B.-Y. Huang, S. C. Ng, and L. Yeung, "Obtained mydriasis in long-term type 2 diabetic patients," J. Ocul. Pharmacol. Ther. **27**(6), 599–602 (2011).
17. D. Pittasch, R. Lobmann, W. Behrens-Baumann, and H. Lehnert, "Pupil signs of sympathetic autonomic neuropathy in patients with Type 1 diabetes," Diabetes Care **25**(9), 1545–1550 (2002).
18. Y. Yang, Y. Yu, and K. Yao, "Pupillary dysfunction in Type 2 diabetes mellitus to refine the early diagnosis of diabetic autonomic neuropathy," Neuro-Ophthalmology **30**(1), 17–21 (2006).
19. M. Cahill, P. Eustace, and V. de Jesus, "Pupillary autonomic denervation with increasing duration of diabetes mellitus," Br. J. Ophthalmol. **85**(10), 1225–1230 (2001).
20. D. A. Atchison, E. L. Markwell, S. Kasthurirangan, J. M. Pope, G. Smith, and P. G. Swann, "Age-related changes in optical and biometric characteristics of emmetropic eyes," J. Vision **8**(4), 29, 1–20 (2008).
21. M. Dubbelman and G. Van der Heijde, "The shape of the aging human lens: curvature, equivalent refractive index and the lens paradox," Vision Res. **41**(14), 1867–1877 (2001).
22. N. G. M. Wiemer, M. Dubbelman, P. J. Kostense, P. J. Ringens, and B. C. P. Polak, "The influence of diabetes mellitus type 1 and 2 on the thickness, shape, and equivalent refractive index of the human crystalline lens," Ophthalmology **115**(10), 1679–1686 (2008).
23. N. G. M. Wiemer, M. Dubbelman, E. A. Hermans, P. J. Ringens, and B. C. P. Polak, "Changes in the internal structure of the human crystalline lens with diabetes mellitus type 1 and type 2," Ophthalmology **115**(11), 2017–2023 (2008).
24. J. M. Sparrow, A. J. Bron, N. A. P. Brown, and H. A. W. Neil, "Biometry of the crystalline lens in early-onset diabetes," Br. J. Ophthalmol. **74**(11), 654–660 (1990).
25. N. Løgstrup, A. Sjølie, K. Kyvik, and A. Green, "Lens thickness and insulin dependent diabetes mellitus: a population based twin study," Br. J. Ophthalmol. **80**(5), 405–408 (1996).
26. A. Bron, J. Sparrow, N. Brown, J. Harding, and R. Blakytny, "The lens in diabetes," Eye **7**(2), 260–275 (1993).
27. H. C. Fledelius and K. Miyamoto, "Diabetic myopia - is it lens-induced?," Acta Ophthalmol. **65**(4), 469–473 (1987).
28. S. M. Saw, T. Y. Wong, S. Ting, A. W. P. Foong, and P. J. Foster, "The relationship between anterior chamber depth and the presence of diabetes in the Tanjong Pagar Survey," Am. J. Ophthalmol. **144**(2), 325–326 (2007).
29. L. Pierro, R. Brancato, E. Zaganelli, L. Guarisco, and G. Calori, "Correlation of lens thickness with blood glucose control in diabetes mellitus," Acta Ophthalmol. Scand. **74**(6), 539–541 (1996).
30. N. Løgstrup, A. K. Sjølie, K. O. Kyvik, and A. Green, "Long term influence of insulin dependent diabetes mellitus on refraction and its components: a population based twin study," Br. J. Ophthalmol. **81**(5), 343–349 (1997).
31. N. Brown and J. Hungerford, "The influence of the size of the lens in ocular disease," Trans. Ophthalmol. Soc. U. K. **102**(3), 359–363 (1982).
32. J. Cavallerano, "A review of non-retinal ocular complications of diabetes mellitus," J. Am. Optom. Assoc. **61**(7), 533–543 (1990).
33. S. Moss, R. Klein, and B. Klein, "Accommodative ability in younger-onset diabetes," Arch. Ophthalmol. **105**(4), 508–512 (1987).
34. M. Spafford and J. Lovasik, "Clinical evaluation of ocular and visual functions in insulin-dependent juvenile diabetics," Am. J. Optom. Physiol. Opt. **63**(7), 505–519 (1986).
35. S. Yamamoto, E. Adachi-Usami, and N. Kuroda, "Accommodation power determined with transient pattern visual evoked cortical potentials in diabetes," Doc. Ophthalmol. **72**(1), 31–37 (1989).
36. Adnan, N. Efron, A. Mathur, K. Edwards, N. Pritchard, M. Suheimat, and D. A. Atchison, "Amplitude of accommodation in type 1 diabetes," Invest. Ophthalmol. Vis. Sci. **55**, 7014–7018 (2014).
37. C. I. Braun, W. E. Benson, N. A. Remaley, E. Y. Chew, and F. L. Ferris III, "Accommodative amplitudes in the Early Treatment Diabetic Retinopathy Study: ETDRS Report Number 21," Retina **15**(4), 275–281 (1995).
38. W. Pawelski and H. Gliem, "Studies on the amplitude of accommodation in diabetics [Untersuchungen ber die Akkommodationsbreite bei Diabetikern]," Ophthalmologica **163**(4), 216–226 (1971).
39. M. Lutze and G. H. Bresnick, "Lenses of diabetic patients "yellow" at an accelerated rate similar to older normals," Invest. Ophthalmol. Vis. Sci. **32**(1), 194–199 (1991).
40. N. P. Davies and A. B. Morland, "Color matching in diabetes: optical density of the crystalline lens and macular pigments," Invest. Ophthalmol. Vis. Sci. **43**(1), 281–289 (2002).
41. M. Shahidi, N. P. Blair, M. Mori, and R. Zelkha, "Optical section retinal imaging and wavefront sensing in

#226701 - $15.00 USD Received 13 Nov 2014; revised 9 Dec 2014; accepted 18 Dec 2014; published 4 Feb 2015

diabetes," Optom. Vis. Sci. **81**(10), 778–784 (2004).
42. A. K. Valeshabad, J. Wanek, P. Grant, J. I. Lim, F. Y. Chau, R. Zelkha, N. Camardo, and M. Shahidi, "Wavefront error correction with adaptive optics in diabetic retinopathy," Optom. Vis. Sci. **91**(10), 1238–1243 (2014).
43. N. Pritchard, K. Edwards, C. Dehghani, H. Fadavi, M. Jeziorska, A. Marshall, I. N. Petropoulos, G. Ponirakis, A. W. Russell, G. P. Sampson, A. M. Shahidi, S. Srinivasan, M. Tavakoli, D. Vagenas, R. A. Malik, and N. Efron, "Longitudinal assessment of neuropathy in type 1 diabetes using novel ophthalmic markers (LANDMark): Study design and baseline characteristics," Diabetes Res. Clin. Pract. **104**(2), 248–256 (2014).
44. T. O. Salmon, R. W. West, W. Gasser, and T. Kenmore, "Measurement of refractive errors in young myopes using the COAS Shack-Hartmann aberrometer," Optom. Vis. Sci. **80**(1), 6–14 (2003).
45. J. Tabernero, D. A. Atchison, and E. L. Markwell, "Aberrations and pupil location under corneal topography and Hartmann-Shack illumination conditions," Invest. Ophthalmol. Vis. Sci. **50**(4), 1964–1970 (2009).
46. A. Mathur, D. A. Atchison, and J. Tabernero, "Effect of age on components of peripheral ocular aberrations," Optom. Vis. Sci. **89**(7), 967–976 (2012).
47. J. Tabernero, A. Benito, V. Nourrit, and P. Artal, "Instrument for measuring the misalignments of ocular surfaces," Opt. Express **14**(22), 10945–10956 (2006).
48. D. A. Atchison and G. Smith, "Chromatic dispersions of the ocular media of human eyes," J. Opt. Soc. Am. A **22**(1), 29–37 (2005).
49. H. Saunders, "Age-dependence of human refractive errors," Ophthalmic. Physiol. Opt. **1**(3), 159–174 (1981).
50. H. Saunders, "A longitudinal study of the age-dependence of human ocular refraction," Ophthalmic. Physiol. Opt. **6**(1), 39–46 (1986).

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia. It has multiple complications and premature morbidity and mortality. It is reaching epidemic levels throughout the world, producing cardiovascular complications, eye and kidney diseases and limb amputations. Reducing morbidity and mortality, and improving quality of life are major public health goals. Diabetes affects the optics and biometry of the eye and blurriness of vision is often the first sign of its presence [1]. This introduction highlights differences known about the biometry of diabetic and non-diabetic eyes.

Several studies have reported greater central corneal thickness in adults and children with diabetes than in non-diabetic individuals [2–7], but some have not [8–11]. Wiemer *et al.* [8] found smaller posterior radii of curvature in people with diabetes than in controls without differences in anterior radius of curvature, and without effect on overall corneal power.

The natural pupil becomes smaller with increase in age [12, 13] and is smaller in people with diabetes than in those without diabetes, particularly at low light levels [14–19].

With increasing age, anterior chamber depth decreases and the lens becomes thicker, more curved, and its equivalent refractive index decreases [20, 21]. These changes are more pronounced in people with diabetes than in controls [22–31], and are dependent on diabetes duration [24, 25]. Wiemer *et al.* [22] found the greater surface curvatures in diabetes were restricted to people with type 1 diabetes (DM1). For DM1, Wiemer *et al.* [22] found the age-related change in equivalent refractive index was nearly twice that of controls at -0.0007/year, but this was balanced by steeper surface curvatures so that there was no significant change in lens power. The decrease in equivalent refractive index in diabetic lens might be the result of the change in refractive index distribution such as occurs in aging or to an overall decrease in refractive index throughout the lens.

There are other changes in optics in diabetes that are probably related to the lens changes. People with diabetes have lower amplitude of accommodation than age matched controls [32–36], with estimates that diabetes duration is between 40% and 100% as important as age in reducing amplitude [33, 36–38]. The age-related decrease in ocular transmission at short wavelengths (or lens yellowing) is greater in people with diabetes than controls [39, 40]. It has been reported that people with diabetes have greater higher-order aberrations than controls at fixed pupil sizes [41, 42], although differences will be reduced under natural conditions because of the smaller pupil sizes with diabetes.

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Previous studies of the biometry and optics of the eye in diabetes lead to the hypothesis that eyes of people with diabetes act as older eyes than those of people of the same age without diabetes. These studies were conducted on people with different types of diabetes, large variations of glucose level, and large ranges of refractions. An accurate characterization of the influence of long-term diabetes mellitus on the refractive components of the eye will assist in modeling changes in visual performance and refractive status of diabetic patients. We have therefore conducted a study on a cohort of type 1 diabetes participants with a limited range of refractive errors. While there have been studies with larger numbers of people, this is the most comprehensive study of a large range of biometric and optical parameters.

2. Methods

2.1. Participants

The study adhered to the tenets of the declaration of Helsinki. Ethical approval was obtained from the Queensland University of Technology before the commencement of the study. All participants provided written informed consent. The study had 74 participants (mean $\pm$ SD, 40 $\pm$ 12 years) with DM1 and 64 age-matched control participants (mean $\pm$ SD, 43 $\pm$ 12 years). Participants had case history, slit lamp biomicroscopy, intraocular pressure (I-Care) and color vision assessment (Lanthony desaturated 15) as part of visual functions testing and ocular health assessment. Blood was collected and analyzed for HbA_{1c} levels in the laboratory, and capillary blood glucose was measured with an Accu-Chek glucometer.

The majority of participants were recruited from the Longitudinal Assessment of Neuropathy in Diabetes using novel ophthalmic Markers (LANDMark) study [43] at the Institute of Health and Biomedical Innovation, for which DM1 participants tended to have low levels of the classic triad of diabetic complications – neuropathy, retinopathy and nephropathy. In the LANDMark study, people were examined for the eye on the side of hand dominance; as this testing involved contact with the cornea, we examined the fellow eye on the same day where possible. If this eye did not fulfil the criteria and the participant was able to return on another day, we tested the better eye. For participants recruited outside the LANDMark study, the right eye was selected where it fulfilled the criteria; otherwise the left eye was selected.

Criteria for inclusion were corrected visual acuities $\leq$ 0.1 log minimum angle resolution (logMAR), Pelli-Robson contrast sensitivity scores $\geq$ 1.65, equivalent spherical refraction $\leq \pm$3.5 D, and normal color vision. Exclusion criteria were more than mild diabetic retinopathy (e.g. soft exudates, venous bleeding and/or severe retinal hemorrhage), retinal diseases, glaucoma, uveitis, ocular trauma or surgery, epilepsy, endocrine disorders (except diabetes), hypertension, neurological or psychiatric disorders, anemia, contact lens wear and cataract (posterior subcapsular, cortical and nuclear of grades higher than 1). Slit lamp photographs and C-Quant values (straylight $>$ 1.60 log(s) was excluded) were used to classify participants with and without cataract on the basis of the lens opacity classification system III.

2.2. Data analysis

Analyses were performed with IBM SPSS Statistics version 21. Statistical significance was set at $p < 0.05$ for all tests. Normality of data was determined by Kolmogorov-Smirnov and Shapiro-Wilk tests. The Student unpaired t-test and the chi-square test determined significance of differences between the two groups for non-categorical data and categorical data, respectively. Results for these tests in Table 1 are the group means and 95% confidence intervals, and the results in the text are the mean differences (control group subtracted from the diabetes group) together with 95% confidence intervals. Multiple regression analysis was used to determine the combined effects of age and diabetes duration on ocular parameters but with gender

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and/or axial length as additional factors where these were significant according to simple linear regression. This analysis was done for the whole group, with duration for the participants without diabetes given as zero, and for only the participants with diabetes. For linear fits of a parameter as a function of age in figures, errors given are the standard errors. ANCOVA analysis was performed to determine the difference in age-related slopes for each ocular parameter between diabetes and control groups.

2.3. Techniques

Objective refraction was obtained from the COAS-HD wavefront aberrometer (Wavefront Sciences, Albuquerque, New Mexico, USA) using 2nd and 4th order Zernike polynomial coefficients for a 4 mm pupil. This has been found to be a reliable, accurate instrument for determining refraction [44]. It has an internal target which is kept optically beyond the refraction point in order to relax accommodation. At least three sets of results were averaged to give the spherical equivalent refraction. At least three eye images were taken with the aberrometer under unaccommodated conditions. Pupil diameter and pupil decentration relative to the corneal limbal centre, were determined [45, 46]. Nasal and superior decentrations were given a positive sign. Results were averaged.

The Medmont E-300 anterior corneal topographer was used for corneal topography. The corneal height data corresponding to at least two images, having alignment quality specification of $\geq 95\%$, were re-referenced from the keratometric axis to the pupil center of the aberrometer images to determine conicoids

$$X^2 + (1+Q)Z^2 - 2ZR = 0 \tag{1}$$

where X and Y are axes perpendicular to the Z-axis passing through the line of sight, R is the vertex radius of curvature and Q is the asphericity across a 6 mm diameter [20]. Results were averaged. In addition, three good "quality value" images were taken with the Oculus Pentacam, a two dimensional Scheimpflug camera system. As well as anterior corneal topography, these images provided anterior and posterior corneal radii of curvatures, corneal central thickness, and anterior chamber depth. Results were averaged.

Three distance measurements were taken for each participant with a partial coherence interferometer, the Lenstar LS 900 (Haag−Streit, Köniz, Switzerland). This gave corneal central thickness, anterior chamber depth, lens thickness and axial length. Results were averaged. The Pentacam also gave the corneal central thickness and anterior chamber depth.

Phakometry gave lens radii of curvature, equivalent refractive index and equivalent power. The phakometer was based on the system developed by Tabernero *et al.* [47]. It moved on a moveable breadboard relative to the participants who were supported by a forehead/chin rest. The source was a semicircular ring of thirteen 890 nm LEDs 75 mm from the anterior cornea (Fig. 1). Purkinje images were captured by a CCD camera with a telecentric lens. An organic LED presented the fixation target through a Badal lens and beam splitter, and spherical equivalent refraction (−8 to +3 D) of the participant was corrected by moving the OLED with respect to the Badal lens. Image analysis was performed using custom built software to determine heights of the Purkinje images PI (anterior cornea), PIII (anterior lens), and PIV (posterior lens).

Lens radii of curvature and equivalent refractive index were estimated by a merit function

$$MF = MF_1 + MF_2 + MF_3 = (V_{the} - V_{exp})^2 + (h_{3the} - h_{3exp})^2 + (h_{4the} - h_{4exp})^2 \tag{2}$$

MF is the combination of components MF_1, MF_2 and MF_3. MF_1 is the square of the difference between experimental V_{exp} and theoretical vitreous length V_{the} obtained from ray tracing into the eye to the retina. MF_2 is the squares of the difference between experimental PIII height

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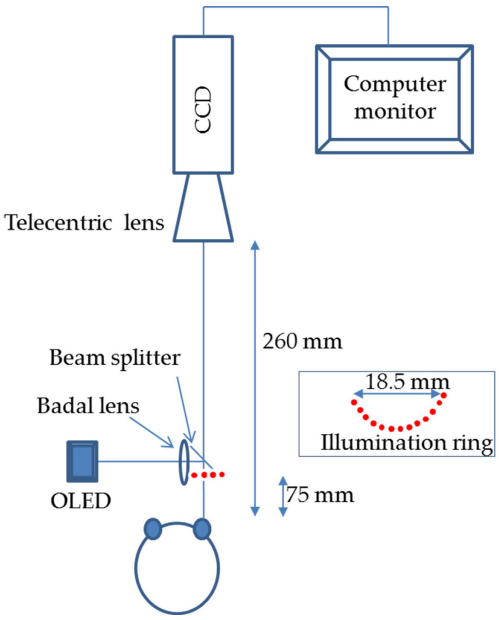

Fig. 1. Phakometer

h_{3exp} and theoretical PIII height h_{3the} obtained from ray tracing into- and then out-of-the-eye after reflection from the anterior lens surface. MF_3 is the squares of the difference between experimental PIV height h_{4exp} and theoretical PIII height h_{4the} obtained from ray tracing into- and then out-of-the-eye after reflection from the posterior lens surface.

A program was written to minimize the merit function by manipulating lens radii of curvature and equivalent refractive index. The merit function stopped after 2000 cycles or when the difference between successive estimates was less than 0.01%, depending on which came first (nearly always the latter). The program used a four refracting-surface model eye. Refractive indices at 555 nm were those of the Gullstrand number 1 eye: 1.376, 1.336 and 1.336 for cornea, anterior chamber and vitreous chamber, respectively. Refractive indices for wavelength 890 nm were determined from dispersion equations provided by Atchison & Smith [48]: 1.36822, 1.32829 and 1.32855, respectively. Atchison & Smith also provided a correction to the refraction:

$$Rx_{890} = Rx_{550} + 0.839 \tag{3}$$

The Lenstar instrument gives a default axial length by subtracting 200 μm from the length measured to the retinal pigment epithelium; this 200 μm was reinstated because the photoreceptor position rather than the internal limiting membrane is relevant for refraction. Corneal thickness, anterior chamber depth and lens thickness for the model were obtained from the Lenstar, and the vitreous depth was determined from these and the modified axial length. Anterior and posterior corneal radii of curvature were obtained from the Oculus Pentacam.

After the lens radii of curvature and lens equivalent index were determined, an estimate of lens refractive index at 555 nm was made. From equations for the different media [48], a linear relationship between the lens indices at the two wavelengths was

$$n_{L555} = 1.0262 n_{L890} - 0.0273 \tag{4}$$

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Lens equivalent power F_e at 555 nm was calculated from

$$F_e = F_{L1} + F_{L2} - \frac{t_L}{n_L} F_{L1} F_{L2} \tag{5}$$

where n_L is lens refractive index at 555 nm, t_L is lens thickness, and F_{L1} and F_{L2} are front and back surface powers

$$F_{L1} = (n_L - n_a)/r_{L1} \ , \ F_{L2} = (n_v - n_L)/r_{L2} \tag{6}$$

where n_a and n_v are refractive indices of aqueous and vitreous at 555 nm, and r_{L1}, and r_{L2} are radii of curvature of the lens front and back surfaces.

3. Results

3.1. Characteristics of groups and summary of results

Table 1 shows characteristics of the groups. Five participants from the diabetes group had poor phakometry images and were excluded from corresponding analyses. Due to limited time availability, the Medmont corneal topographer was not used with 39 participants, and a further five participants had poor images and were excluded from corresponding analyses. There is no significant difference in spherical equivalent refraction and corrected visual acuity between groups, but log contrast sensitivity is slightly higher in the control group than in the diabetes group.

Figure 2 shows the association between diabetes duration and age. There is a significant linear relationship (slope +0.38, $p < 0.001$), but correlation is low (R^2 0.18). Some older participants have had diabetes for only a short time e.g. the cluster of 3 people with ages 58 - 62 years and durations less than 5 years.

3.2. Ocular biometry

Table 2 shows multiple regression fits for biometric and other parameters, both for the whole group and for the diabetes group alone. The emphasis was on diabetes duration and age as factors, but axial length and gender were included where they had significant effects in regression fits that includes diabetes duration and/or age; otherwise no factors are shown.

Figure 3 shows biometric parameters as a function of age for the diabetes and control groups. Fits from the Wiemer study [22] are shown in Figs. 3(f), (h) and (i), and will be mentioned in the Discussion.

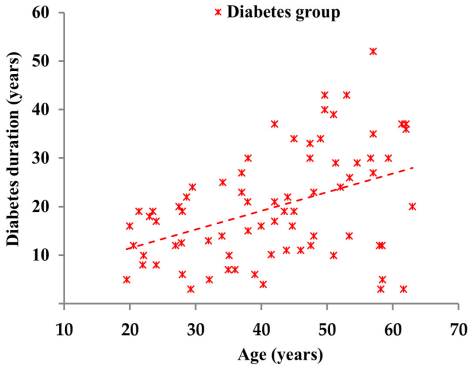

Fig. 2. Diabetes duration as a function of age.

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Table 1. Parameters of participant groups. P-values are bolded where there are significantly differences between groups. Errors are 95% confidence intervals.

Parameters and numbers in groups (diabetes/control)	Diabetes group	Control group	P-values
Number of eyes (R/L), (74/64)	48/26	54/10	
Gender (F/M) (74/64)	30/44	44/20	**0.001**
Age (mean $\pm$ SD, age range in years), (74/64)	40 ± 12, $19-63$	43 ± 12, $20-62$	0.77
Visual acuity (LogMAR), (74/64)	-0.02 ± 0.05	-0.04 ± 0.05	0.55
Log contrast sensitivity, (74/64)	1.81 ± 0.03	1.89 ± 0.03	$<$ **0.001**
Spherical equivalent refraction (D), aberrometer (74/64)	-0.58 ± 0.26	-0.44 ± 0.24	0.44
Anterior corneal radius of curvature (mm), Pentacam (74/64)	$+7.76 \pm 0.05$	$+7.82 \pm 0.07$	0.15
Anterior corneal radius of curvature (mm), Medmont (47/47)	$+7.73 \pm 0.06$	$+7.78 \pm 0.07$	0.24
Anterior corneal asphericity Q, (47/47)	-0.06 ± 0.04	-0.07 ± 0.04	0.86
Corneal centre thickness (mm), Pentacam (74/64)	0.545 ± 0.007	0.537 ± 0.011	0.26
Corneal centre thickness (mm), Lenstar (74/64)	0.542 ± 0.007	0.537 ± 0.009	0.37
Posterior corneal radius of curvature (mm), (74/64)	$+6.36 \pm 0.06$	$+6.43 \pm 0.07$	0.07
Anterior chamber depth (mm), Pentacam (74/64)	2.75 ± 0.09	2.86 ± 0.09	0.09
Anterior chamber depth (mm), Lenstar (74/64)	2.74 ± 0.09	2.89 ± 0.09	**0.03**
Pupil diameter (mm), (74/64)	5.96 ± 0.21	6.22 ± 0.21	0.08
Pupil decentration along x-axis (mm), (47/47)	$+0.17 \pm 0.15$	$+0.30 \pm 0.12$	0.19
Pupil decentration along y-axis (mm), (47/47)	$+0.11 \pm 0.10$	$+0.16 \pm 0.09$	0.43
Anterior lens radius of curvature (mm), (67/62)	$+9.53 \pm 0.26$	$+10.62 \pm 0.29$	$<$ **0.001**
Posterior lens radius of curvature (mm), (67/62)	-5.89 ± 0.18	-6.32 ± 0.19	$<$**0.01**
Lens equivalent refractive index, 555nm, (67/62)	1.426 ± 0.003	1.431 ± 0.003	$<$ **0.01**
Lens central thickness (mm), Lenstar (74/64)	4.31 ± 0.11	4.01 ± 0.09	$<$ **0.001**
Lens equivalent power (D), 555 nm (67/62)	25.06 ± 0.80	24.28 ± 0.59	0.13
HbA_{1c} (m mol), (74/64)	7.80 ± 0.26	5.03 ± 0.08	$<$ **0.001**
Blood glucose level (m mol), (74/64)	9.30 ± 0.78	$-$	$-$
Diabetes duration (years)	19 ± 9	$-$	$-$

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Table 2. Multiple regression fits for the whole group and for the diabetes group alone. No coefficients appear where both diabetes duration and age are not significant factors.

Parameter	Group	Duration (years)	Age (years)	Axial length (mm)	Constant (D, mm, -)	R^2
Spherical equivalent	whole group		+0.020	−0.538	+11.45	0.24
refraction (D)	diabetes group		+0.025	−0.660	+14.11	0.29
Anterior corneal radius of curvature(mm), Pentacam	whole group diabetes group					
Anterior corneal radius of curvature (mm), Medmont	whole group diabetes group					
Anterior corneal asphericity *Q*	whole group diabetes group		+0.004		−0.68	0.15
Corneal centre thickness	whole group	+0.0005			+0.552	0.04
(mm), Pentacam	diabetes group					
Corneal centre thickness (mm), Lenstar	whole group diabetes group					
Posterior corneal radius of curvature (mm)	whole group diabetes group					
Anterior chamber depth	whole group	−0.009	−0.010	+0.147	−0.21	0.43
(mm), Pentacam	diabetes group	−0.016	−0.007	+0.146	−0.12	0.54
Anterior chamber depth	whole group	−0.009	−0.010	+0.147	−0.21	0.43
(mm), Pentacam	diabetes group	−0.016	−0.007	+0.146	−0.12	0.54
Anterior chamber depth	whole group	−0.008	−0.011	+0.179	−0.87	0.46
(mm), Lenstar	diabetes group	−0.013	−0.010	+0.187	−1.00	0.56
Pupil diameter (mm)	whole group		−0.029	+0.280	+0.76	0.29
	diabetes group		−0.025	+0.305	−0.07	0.24
Pupil decentration along	whole group					
x-axis/y-axis (mm)	diabetes group					
Anterior lens radius of	whole group	−0.045	−0.026	+0.460	+0.72	0.47
curvature (mm)	diabetes group	−0.040		+0.418	+0.98	0.40
Posterior lens radius of curvature (mm)	whole group diabetes group	+0.017	+0.012	−0.270	−0.35	0.25
Lens central thickness,	whole group	+0.016	+0.021	−0.091	+5.35	0.73
Lenstar (mm)	diabetes group	+0.020	+0.021	−0.113	+5.69	0.77
Lens equivalent refractive	whole group	−0.0003	−0.0004	−0.0033	+1.525	0.35
index	diabetes group	−0.0003		−0.0041	+1.537	0.28
Lens equivalent power (D)	whole group diabetes group		−0.046	−1.997	+73.70	0.59

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Figure 3(a) shows spherical equivalent refraction. There is no significant age-related slope for either group, and the slope difference between groups is also not significant. However age and axial length, although not diabetes duration, contribute significantly to the multiple regression fits. The mean difference in refraction between groups is not significant.

Results for anterior corneal radius of curvature are similar for the Medmont topographer and Oculus Pentacam (Tables 1 and 2). The relationship between radius of curvature and age is not significant for either group and slope differences between the groups are not significant. Neither age nor diabetes duration contribute significantly to the multiple regression fits. The mean differences in radius of curvature between groups are not significant.

Figure 3(b) shows Medmont-determined anterior corneal asphericity. There is a significant positive age-related slope for the diabetes group (+0.004/year, R^2 0.14, p 0.01), but the slope difference between groups is not quite significant (p 0.08). Age contributes significantly to the multiple regression fit for the diabetes group alone, and diabetes duration does not contribute significantly to either multiple regression fit. The mean difference in asphericity between groups is not significant.

Results for corneal central thickness are presented here mainly for the Lenstar (Fig. 3(c)), but results for the Oculus Pentacam are similar (Table 1). There is no significant age-related slope for either group, and the slope difference between groups is not quite significant (p 0.07). Neither age nor diabetes duration contributes significantly to the multiple regression fits. The mean difference in thickness between the groups is not significant.

The relationship between posterior corneal radius of curvature and age is not significant for either group and the slope difference between groups is not significant. Neither age nor diabetes duration contributes significantly to the multiple regression fits. The mean difference in radius of curvature between the groups approaches significance (-0.08 ± 0.08 mm, p 0.07).

Results for anterior chamber depth are presented here mainly for the Lenstar (Fig. 3(d)), but results for the Pentacam are similar (Tables 1 and 2). For each group there is a significant age-negative related slope (-0.013 and -0.010 mm/year for diabetes and control groups, respectively), but the slope difference between groups is not significant. Diabetes duration, age and axial length contribute significantly to the multiple regression fits. The diabetes group has significantly shallower anterior chamber depths than the control group (mean difference -0.14 ± 0.13 mm, p 0.03).

Figure 3(e) shows pupil diameter. For each group there is a significant negative age-related slope (-0.024 and -0.029 mm/year for diabetes and control groups, respectively), but the slope difference between groups is not significant. Age, but not diabetes duration, contributes significantly to the multiple regression fits. The mean difference in pupil diameter between the groups (-0.26 ± 0.30 mm) is not quite significant (p 0.08).

The relationships between pupil decentration components and age are not significant for either group and slope differences between groups are not significant. Neither age nor diabetes duration contributes significantly to the multiple regression fits. The mean differences in decentration components between groups are not significant.

Figure 3(f) shows anterior lens radius of curvature. For each group there is a significant negative age-related slope, i.e. radius of curvature is smaller with increase in age (-0.024 and -0.043 mm/year for diabetes and control groups, respectively), but the slope difference between groups is not significant. Diabetes duration, age and axial length contribute significantly to the multiple regression fit for the whole group, but age is omitted for the diabetes group. The diabetes group has significantly smaller radii of curvature than the control group (mean difference -1.09 ± 0.40 mm, $p < 0.001$).

Figure 3(g) shows posterior lens radius of curvature. For the control group only, there is a significant positive age-related slope, i.e. radius of curvature is smaller with increase in age

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(+0.023 mm/year), but the slope difference between groups is not quite significant ($F_{1,125}$ = 3.36, p 0.07). Diabetes duration, age and axial length contribute significantly to the multiple regression fit for the whole group, but neither contributes for the diabetes group alone. The diabetes group has smaller radii of curvature than the control group (mean difference +0.43 $\pm$ 0.26 mm, $p < 0.01$).

Figure 3(h) shows lens central thickness. For each group there is a significant positive age-related slope (+0.027 and +0.021 mm/year for diabetes and control groups, respectively), but the slope difference between groups is not quite significant (p 0.11). Diabetes duration, age and axial length contribute significantly to the multiple regression fits. The diabetes group has greater lens thickness than the control group (mean difference +0.29 $\pm$ 0.15 mm, $p < 0.001$).

Figure 3(i) shows lens equivalent refractive index. For each group there is a significant negative age-related slope (-0.00033 and -0.00056/year for diabetes and control groups, respectively), but the slope difference between groups is not quite significant (p 0.08). Diabetes duration, age and axial length contribute significantly to the multiple regression fit for the whole group, but age is omitted for the diabetes group. The diabetes group has lower equivalent index than the control group (mean difference -0.006 ± 0.004, $p < 0.01$).

Figure 3(j) shows lens equivalent power. For each group there is a negative age-related slope, which is significant for the control group (-0.052 D/year, p 0.02) but is not quite significant for the diabetes group (-0.056 D/year, p 0.06), and the slope difference between groups is not significant. Age and axial length contribute significantly to the multiple regression fit for the whole group, but neither age nor diabetes contributes for the diabetes group. The mean difference in power between groups is not significant.

4. Discussion

Considering the results shown in Tables 1 and 2, in Fig. 3 and across the different statistical tests, the biometric parameters can be classified into four categories: A) parameters that are not influenced by age nor by diabetes, B) parameters that are influenced by age but not by diabetes, C) parameters that are influenced by both age and diabetes, but diabetes does not affect the rate of change with age, and D) parameters that are influenced by both age and diabetes, with diabetes increasing the rate of change with age. Parameters in category A are the corneal parameters of anterior and posterior surface radii of cornea, anterior surface asphericity and central thickness, and the pupil decentrations. Parameters in category B are the spherical equivalent refraction, pupil diameter and lens equivalent power. Parameters in category C are anterior chamber depth, anterior and posterior lens radii of curvature, lens thickness and lens equivalent refractive index. There are no parameters in category D. It appears likely that in some cases one parameter might have moved to another category concerning the influence of diabetes if there had been more participants.

For category A parameters, the results agree with Wiemer *et al.* [8] concerning anterior radius of curvature and with the studies that have found central corneal thickness does not change with diabetes [8–11]. The results do not agree with Wiemer *et al.* [8] concerning posterior radius of curvature. They found a significant difference between groups of -0.14 ± 0.08 mm compared with -0.08 ± 0.08 mm here (p = 0.07). A power analysis of our results using α 0.05 and power 0.8 indicates that 159 participants per group are needed to show significance. While we have put anterior corneal asphericity in category A, we note that it changes significantly with age for the diabetes group.

For category B parameters, the spherical equivalent is representative of the hypermetropic shift that occurs during adulthood [49, 50] (Fig. 3(a)). We have put pupil diameter in this category, although the influence of diabetes is marginally significant (p = 0.08) and the literature indicates that pupil size is smaller in the presence of diabetes [14–19]. A power analysis indi-

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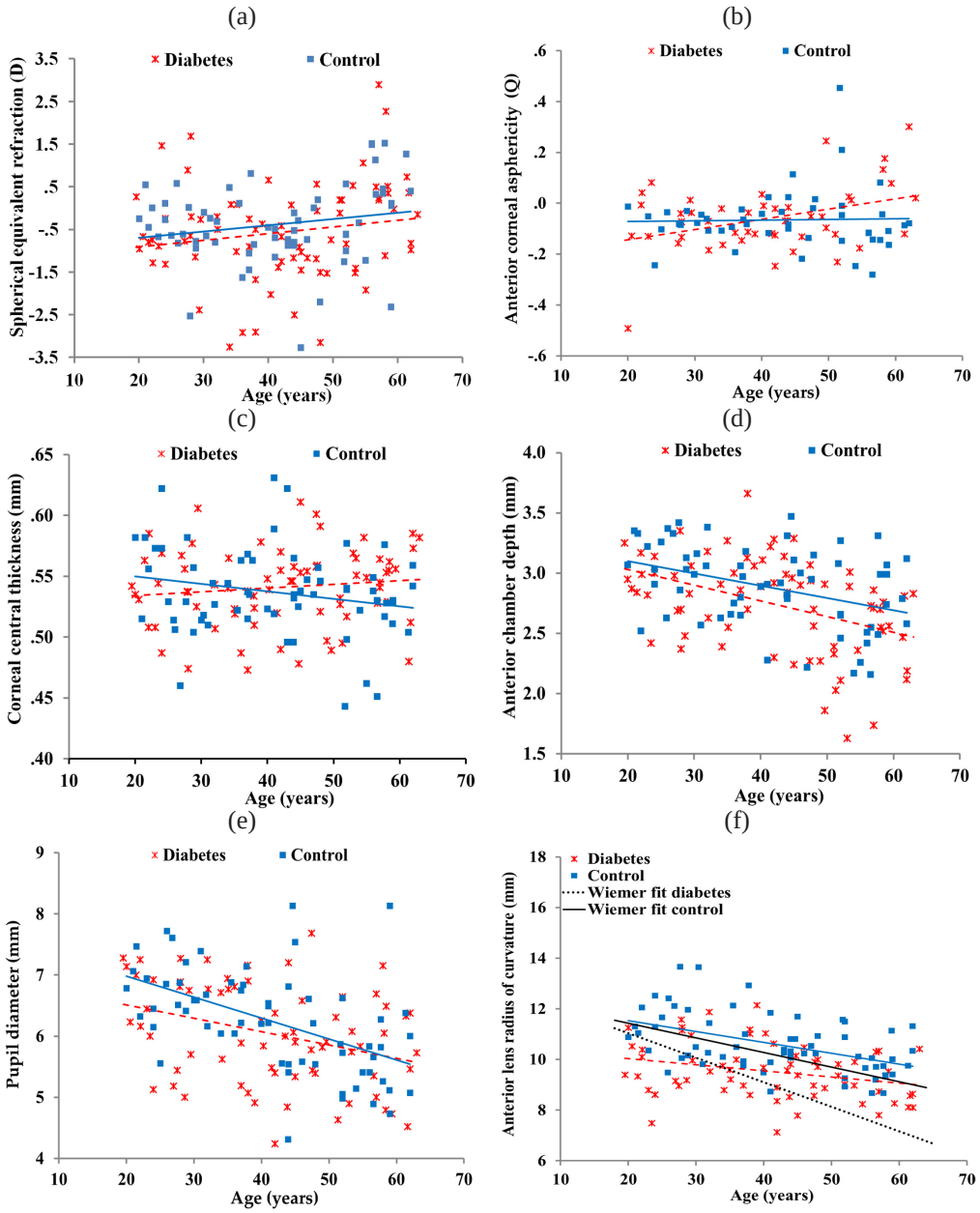

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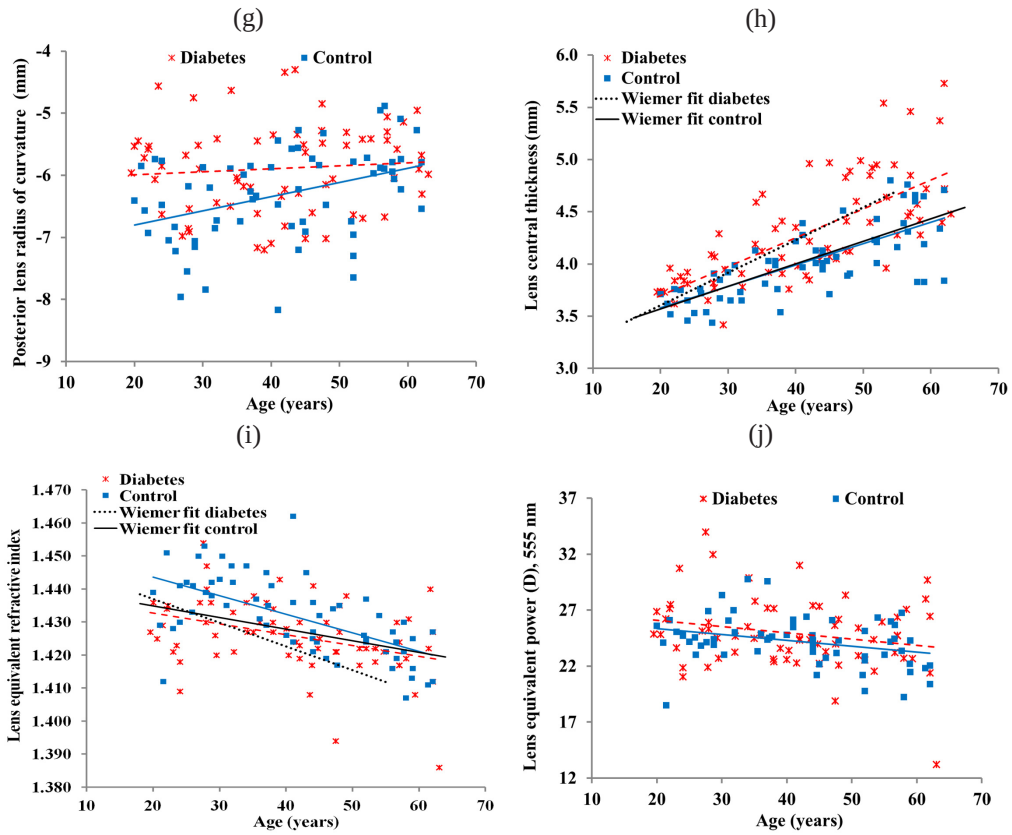

Fig. 3. Relationships between parameters and age for diabetes and control groups. (a) spherical equivalent refraction, (b) anterior corneal asphericity; (c) corneal central thickness, (d) pupil diameter, (e) anterior chamber depth, (f) anterior lens radius of curvature, (g) posterior lens radius of curvature, (h) lens central thickness, (i) lens equivalent refractive index, and (j) lens equivalent power. Fits for diabetes type 1 participants are included from the Wiemer *et al.* study [22] in (f), (h) and (i).

cates that 100 participants per group are needed to show significance. For lens power, we find a reduction with age (−0.05 D/ year) (Fig. 3(j)). This is consistent with the study of Atchison *et al.* [20] (−0.03 D/year) using similar instrumentation with a non-diabetic group, but Wiemer *et al.* [22] did not find a trend.

For category C parameters, we find the effects of diabetes as follows: anterior chamber depth is smaller (Fig. 3(d)), the lens surface radii of curvature are smaller (Fig. 3(f) and (g)), the lens is thicker (Fig. 3(h)), and the equivalent refractive index is lower (Fig. 3(i)). These effects correspond to the directions occurring with increasing age, and have been found in previous studies with diabetes type I participants [22, 24]. However, the previous studies found accelerated aging trends in the presence of diabetes for anterior chamber depth, anterior lens surface radius of curvature and lens thickness, and, in the study of Wiemer *et al.* for the posterior lens surface radius of curvature and equivalent refractive index. For these studies, these parameters would be in our category D.

As one example of comparison between our study and that of Wiemer *et al.*, our non-significant difference in age-related rate of change between diabetes and control groups for

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anterior chamber depth was -0.003/year, compared with -0.009 ± 0.008 mm/year for the Wiemer *et al.* study. Other comparisons between the respective studies are: anterior lens radius of curvature +0.019 mm/year (not significant, ns) and -0.037 ± 0.027 mm/year (Fig. 3(f)); posterior lens radius of curvature -0.018 mm/year (ns) and $+0.023 \pm 0.021$ mm/year; lens thickness +0.006 mm/year (ns) and $+0.020 \pm 0.008$ mm/year (Fig. 3(h)); equivalent refractive index +0.00023/year (ns) and -0.0003 ± 0.0002/year (Fig. 3(i)).

There are several differences between methods and the participants between this and the studies by Wiemer *et al.* [8, 22] and Sparrow *et al.* [24] which may account in large part for differences in results. The previous studies used Scheimpflug imaging for all of their lenticular-related parameters, while we used phakometry. Wiemer *et al.* included participants with advanced stage retinopathy, and it is likely that this was the case for Sparrow *et al.* who did not exclude on the basis of retinopathy. Wiemer *et al.* had a large range of refractions for both diabetes and control groups (-10 to +6 D), while Sparrow *et al.* did not indicate any limitation in refraction. This study included participants with no more than minimal diabetic retinopathy and had a restricted range of refraction for both diabetes and control groups (-3 to +2 D).

This investigation indicates that people with well-controlled diabetes relative to neuropathy and who are striving to remain compliant with health/lifestyle/medications, given that they were monitored annually in the LANDMark study, need not have accelerated changes in the optics of the eye with aging, and presumably the serious consequences of diabetes can be slowed.

The results reported here form part of a study into the ocular optics of people with type 1 diabetes. We found lower amplitude of accommodation in people with diabetes than in age-matched controls, with the estimate that people with diabetes will experience presbyopia a few years earlier in life than people without diabetes [36]. Results for parameters of straylight, lens yellowing, ocular aberrations and lens shape and refractive index distribution will be reported later.

The study has limitations. The diabetes group may be considered to be "well controlled". While this might be considered to be a strength in that we were dealing with a relatively homogenous group, it is a weakness in that differences between people with and without diabetes were not as marked as would have been otherwise expected, especially concerning the influence of diabetes on rates of change of parameters with age as discussed above. As discussed earlier, sample sizes were insufficient for some tests. As cycloplegia was not used in the study, it is possible that some younger participants exerted some accommodation during tests which would affect results; the age balance between the groups moderates this influence when comparing the groups for parameters.

5. Conclusions

These findings support the hypothesis that eyes of people with diabetes act as older eyes than those of people of the same age without diabetes. However, the differences have not increased significantly with age in this study. Relative to a control group, a type 1 diabetes group has demonstrated smaller anterior chamber depths, more curved lenses, greater lens thickness and lower lens equivalent refractive index. Marginal or no significant differences have been found for corneal shape, corneal thickness, pupil size, and pupil decentrations. As nearly all of the diabetes participants have low levels of neuropathy, retinopathy and nephropathy, it is concluded that age-related changes in the optics of the eyes of people with diabetes need not be accelerated if the diabetes is well controlled.

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