Advances in Ophthalmology Practice and Research 2 (2022) 100048

Contents lists available at ScienceDirect

Advances in Ophthalmology Practice and Research

journal homepage: www.journals.elsevier.com/advances-in-ophthalmology-practice-and-research

Full Length Article

Modelling ocular ageing in adults with well-controlled type I diabetes

Jos J. Rozema [a,b,*], Adnan Khan [c,d], David A. Atchison [e]

[a] Visual Optics Lab Antwerp (VOLANTIS), Faculty of Medicine and Health Sciences, Antwerp University, Wilrijk, Belgium
[b] Department of Ophthalmology, Antwerp University Hospital, Edegem, Belgium
[c] Research Division, Weill Cornell Medicine – Qatar, Doha, Qatar
[d] Faculty of Health Sciences, Khyber Medical University, Peshawar, Pakistan
[e] Centre for Vision and Eye Research, Queensland University of Technology, Kelvin Grove, Australia

ARTICLE INFO

Keywords:
Diabetes
Eye model
Refractive error

ABSTRACT

Purpose: To develop a paraxial eye model based on a previously collected cohort of adults with well-controlled type 1 diabetes mellitus (*DM1*) and a limited range of refractive errors.

Methods: The study used the previously published biometric data of *72* participants (Age: *41.5* ± *12.4* years) with *DM1*. Measurements included objective refraction, anterior and posterior corneal radii of curvatures, and internal distances. Moreover, phakometry was used to determine the lens radii of curvature and lens equivalent indices, from which the lens powers were calculated. A multivariate linear regression was performed for each biometric parameter with respect to current age (*Age*), the time since the onset of diabetes (T_{db}), and current levels of glycated hemoglobin (*HbA1c*). The vitreous chamber depth was determined from other distances, and lens equivalent index was chosen to balance the models. These were compared with an existing model for non-diabetic eyes.

Results: Some dependent parameters were not affected by the independent variables (spherical equivalent, anterior corneal radius of curvature, central corneal thickness), some were affected by time since onset (the lens radii of curvatures, anterior chamber depth) and others were affected by both age and time since onset (posterior corneal radius of curvature, lens thickness, axial length). None of the dependent parameters were affected by current levels of *HbA1c*.

Conclusions: The proposed model accurately describes the age-related changes in the eyes of people with *DM1*. In this description the age of diabetes onset plays an important role, especially if the diabetes onset occurred during childhood.

1. Introduction

Diabetes mellitus is a group of metabolic diseases that is characterized by chronic hyperglycemia and comes in two main types. The first type (*DM1*) has an auto-immune destruction of pancreatic beta-cells that leads to loss of insulin secretion, while the second type (*DM2*) is characterized by insulin resistance and impaired insulin secretion.

The condition is well known to cause diabetic retinopathy,[1] but may also alter the ocular shape. For example, authors have reported that people with diabetes have thicker corneas[2–7] (although others have not[8–12]), smaller posterior corneal radii of curvature,[11] shallower anterior chambers, smaller pupil sizes (especially in low light levels),[13–18] and lenses that are thicker,[19] more curved, smaller in diameter and with a lower equivalent refractive index than non-diabetic controls.[8,20–30] Moreover, the normal age-related decrease in short wavelength transmission within the eye is greater in people with diabetes than controls,[31–33] and *DM1* is associated with higher levels of straylight.[31,34] Based on these considerable and consistent biometric differences, it should come as no surprise that diabetes affects refractive error significantly, with *DM1* leading to significantly more myopia,[35,36] and *DM2* leading to significantly more hypermetropia.[8,37] This differences are also reflected in the higher order wavefront aberrations, with some studies,[38,39] but not all,[31] showing significant differences between people with diabetes and non-diabetic controls.

Based on these observations it has been suggested that the eyes of people with diabetes age more rapidly than those of healthy controls of the same age,[8,30,31,40] and which has been associated with having poorly controlled blood sugar levels.[35,41] Moreover, it is conceivable that

* Corresponding author. Building T4, Campus Drie Eiken, University of Antwerp, Universiteitsplein 1, 2610, Wilrijk, Belgium.
E-mail address: Jos.Rozema@uantwerpen.be (J.J. Rozema).

https://doi.org/10.1016/j.aopr.2022.100048
Received 14 December 2021; Received in revised form 3 March 2022; Accepted 22 March 2022
Available online 12 April 2022

individuals diagnosed with *DM1* before the age of *15* years will see even more dramatic differences as disease would disrupt their normal eye growth,[27] complicating matters even further. To this end, the current paper aims to develop a paraxial eye model based on a previously collected cohort of well-controlled *DM1* participants with a limited range of refractive errors,[8,30] This model includes the influence of age, duration of the disease, and the level of glycosylated hemoglobin (*HbA1c*), a well-known blood test used to diagnose and monitor diabetes. These parameters will also account for the influence of diabetes onset on normal eye growth.

2. Materials and methods

2.1. Data

The participants and procedures have been described elsewhere,[8] and only brief descriptions are given here. Some measurements were taken with more than one instrument, but only the ones used for the modelling are mentioned. At least three measurements were taken with each technique and subsequently averaged. The study adhered to the tenets of the declaration of Helsinki. Ethical approval was obtained from the Queensland University of Technology (ethics clearance *1100001182*) before the commencement of the study, and all participants provided written informed consent.

The study had *72* participants (mean ± SD, *41.5* ± *12.4* years, see Table 1) with *DM1*. The majority were recruited from the Longitudinal Assessment of Neuropathy in Diabetes using novel ophthalmic Markers (LANDMark) study[42] at Queensland University of Technology, for which *DM1* participants tended to have low levels of neuropathy, retinopathy and nephropathy, as is common in this population. Duration of diabetes was recorded. Blood was collected and analyzed for *HbA1c* levels in the laboratory, and capillary blood glucose was measured with an Accu-Chek glucometer. The LandMark used study hand dominance to select the opposite eye to be tested, provided it met the inclusion criteria. If it did not, the other eye was tested at a later time and used for analysis if it fulfilled the criteria.[8] For the eight participants recruited outside the LandMark Study the right eye was selected if it met the criteria. A total of *46/72* eyes tested were right eyes. The inclusion and exclusion criteria described fully by Adnan et al. Inclusion criteria included corrected visual acuities $\leq$ *0.1* log minutes of angle resolution (logMAR), Pelli-Robson contrast sensitivity scores $\geq$ *1.65*, spherical equivalent refraction $\leq \pm$*3.5 D*, and normal color vision. Exclusion criteria included signs of more than mild diabetic retinopathy (e.g., soft exudates, venous bleeding and/or severe retinal hemorrhage), other ocular diseases or surgery, epilepsy, other endocrine disorders, hypertension, neurological or psychiatric disorders, anemia, and grades of cataract higher than *1* on the LOCS III scale.[43]

Objective refraction was obtained from the COAS-HD wavefront aberrometer (Wavefront Sciences, Albuquerque, New Mexico, USA) using *2*nd and *4*th order Zernike polynomial coefficients for a *4* mm pupil. Anterior and posterior corneal radii of curvatures were obtained with the Pentacam (Oculus, Wetzlar, Germany), a two-dimensional Scheimpflug camera system. The internal distance measurements of corneal central thickness, anterior chamber depth, lens thickness and axial length were obtained with a partial coherence interferometer, the Lenstar LS 900 (Haag−Streit, Köniz, Switzerland). The 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. The vitreous depth was determined from the other lengths.

Lens radii of curvature and equivalent indices were obtained from a customized phakometer. It determined Purkinje image heights of a semi-circular ring of thirteen 890 nm LEDs positioned 75 mm from the anterior cornea. Using these heights, the distances obtained with the Lenstar, and the corneal radii of curvature obtained with the Pentacam, a raytracing program minimized a merit function of height and vitreous length errors by manipulating the lens radii of curvature and equivalent index. It used corneal, aqueous, and vitreous refractive indices of the Gullstrand *No. 1* eye. As appropriate, conversions were made between refractions and between refractive indices at 890 nm and 555 nm.[44] An estimation of equivalent lens power at 555 nm was made using the think lens equation.

2.2. Modelling and statistics

Using the biometry values of the *72* participants a multivariate linear regression was performed for each parameter P with respect to their current age (*Age*), the time since the onset of diabetes (T_{db}) and current levels of *HbA1c* using the following function:

$$P = a_0 + a_1 \cdot Age + a_2 \cdot T_{db} + a_3 \cdot HbA1c \quad (1)$$

Here coefficients a_0 – a_3 were determined by a stepwise linear procedure, which consisted of first performing a linear regression of the biometry parameter using all three independent variables and determining the fit coefficient with the least significance (i.e., the highest P-value). Next, this procedure was repeated, each time omitting the least significant variable, until all coefficients were significant at the *0.05* level. The remaining terms were included in the model. There may have been significant correlations between *Age*, T_{db}, and *HbA1c* since older patients are more like to have their diabetes for a longer period than younger ones, and this lack of collinearity was verified first using the Variation Inflation Factor (VIF).

This method was used to obtain regressions for spherical equivalent refractive error (*SE*), anterior and posterior radii of curvature of the cornea (R_{ca}, R_{cp}) and the lens (R_{la}, R_{lp}), central corneal thickness (*CCT*), anterior chamber depth from the corneal endothelium until the anterior lens vertex (*ACD*), lens thickness (*LT*) and axial length (*AL*). From these regressions the eye model was subsequently created, assuming a refractive index of *1.376* for the cornea and *1.336* for the aqueous and vitreous humors.

Note that, since it is unlikely that a set of regressions derived from measured data will combine into a perfectly balanced model, two free parameters had to be chosen to balance the model. These were the vitreous chamber depth (*VCD*), calculated as:

$$VCD = AL - CCT - ACD - LT \quad (2)$$

To balance the positions of the ocular surfaces, and the lens equivalent index (n_l) to balance the regression of the refractive error *SE* with the

Table 1
Overview of the study population.

	Men			Women			All		
Age range	N	Age	HbA1c	N	Age	HbA1c	N	Age	HbA1c
20 – 29 years	*9*	*24.0*	*7.50*	*8*	*26.3*	*7.93*	*17*	*25.1*	*7.69*
30 – 39 years	*7*	*36.0*	*7.57*	*5*	*35.2*	*7.37*	*12*	*35.7*	*7.48*
40 – 49 years	*13*	*44.6*	*7.91*	*8*	*45.9*	*8.04*	*21*	*45.1*	*7.96*
50 – 59 years	*10*	*55.6*	*8.07*	*6*	*54.2*	*8.03*	*16*	*55.1*	*8.06*
60 – 69 years	*3*	*62.1*	*7.37*	*0*			*4*	*62.0*	*7.28*
All	*42*	*42.6*	*7.80*	*27*	*41.7*	*7.83*	*70*	*42.2*	*7.82*

calculated refractive error of the model. Given that the regressions of the other lens parameters are functions of *Age* and T_{db}, it is reasonable to assume that n_l has similar dependencies.

All analyses were performed with SPSS 25 (IBM, Armonk, NY, USA) and Excel 365 (Microsoft, Seattle, WA, USA), using the Atchison ageing emmetropic eye model[45] as a normal reference.

3. Results

3.1. Independence of age and diabetes parameters

The Pearson correlation *r* between *Age* and T_{db} was significant (r = 0.440; $P < 0.001$). Since this correlation may lead to collinearity issues between both parameters during the multivariate linear regression, the VIF had to be considered. This factor was found to have a value of *1*, indicating that the correlation between *Age* and T_{db} is of no consequence, and both parameters may be considered as non-collinear and independent.

Hemoglobin level *HbA1c* was neither correlated with *Age* (r = –0.012; $P = 0.922$) nor with T_{db} (r = 0.160, $P = 0.178$). Here too, both VIF values were equal to *1*, meaning that these parameters should also be considered as sufficiently independent to warrant inclusion in the model.

3.2. Regression analysis

Using this procedure, three parameters (*SE*, R_{ca}, *CCT*) were constant, *3* depended only on T_{db} (R_{la}, R_{lp}, *ACD*), *3* parameters depended on both *Age* and T_{db} (R_{cp}, *LT*, and *AL*), and none depended on *HbA1c* (see Table 2). From this, *HbA1c* had relatively little influence on these biometry parameters compared to *Age* or T_{db} and was not considered further.

3.3. Eye model

The model for diabetic eyes was constructed by combining the regressions in Table 1 with equation (3) and the following expression for the equivalent lens index:

$$n_l = 1.4368 - 0.00032 \cdot Age - 0.00002 \cdot T_{db} \quad (3)$$

This function provided the optimal match between the regression of *SE* and the values calculated from the model, keeping the differences within a narrow range of [*–0.12, 0.04*] *D* for an age range of *20–60* years and a T_{db} range of *0 – 40* years (Fig. 1). These differences varied depending on the age of diabetes onset, calculated as *Age* – T_{db}.

The model matched the values and trends of the original data (Fig. 2). Disregarding the age of diabetes onset, the anterior chamber depth *ACD* and lens thickness *LT* showed the same trends as the normal ageing eye model,[45] albeit with considerably higher rates. Other parameters, such as the anterior radius of curvature of the lens R_{La} and the lens equivalent index n_L, followed the same trend and slope as the emmetropic model, but at higher values. However, there were also parameters that followed

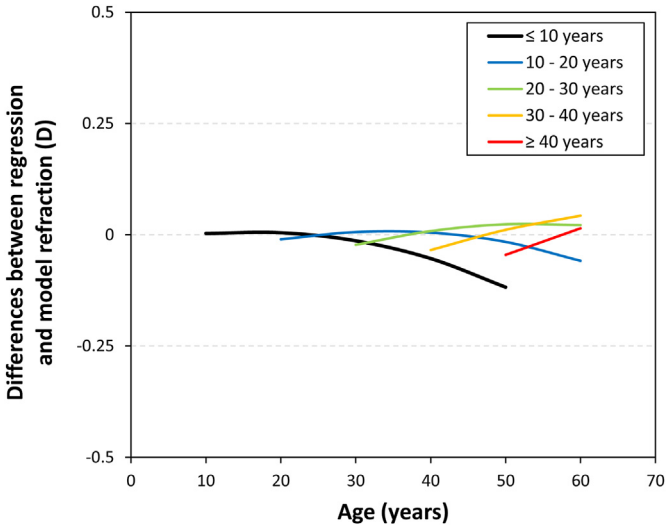

Fig. 1. Differences between the refractive error of the regressions and the eye model for different ages at diabetes onset (colors).

a course different from that of normal ageing, the most important of which was the lens power P_L. While for the normal eye model a gradual decrease of *–0.0425D/yr* was seen, the lens power in the diabetes model showed no significant change. Meanwhile, the vitreous chamber depth *VCD* decreased with age at a rate of *–0.021 mm/yr*, while in the normal ageing model it decreased by *–0.013 mm/yr*. This rate was half the *LT* increase (*+0.043 mm/yr*), while the other half of the lens increase matched the decrease in *ACD* (*–0.022 mm/yr*). Finally, both the normal ageing model and the diabetes model showed a constant axial length *AL*.

The model showed clearly that the age of the diabetes onset and the duration T_{db} affect most non-constant parameters. For *ACD*, *LT*, *VCD*, and R_{la} and R_{lp}) an early onset led to earlier growth changes (Fig. 2). Meanwhile R_{cp}, *AL* and P_L had values that were constant with age but that depended on the age of onset.

4. Discussion

From the literature, it is clear that ocular biometry in individuals with diabetes differs considerably from that of healthy controls. These differences have been described as an accelerated ageing of the eye.[8,30,31,40] To ascertain the validity of this idea, we developed an optical model for the eyes of individuals with Type I diabetes that attempted to integrate all these previous observations.

The observations in Fig. 2 closely match those in earlier reports,[8,11,13–30] but show too many discrepancies with normal growth to support the idea that the influence of diabetes may simply be considered as accelerated ageing. For example, diabetic lenses tend to be thicker and more curved than those of normal eyes,[8,19–30] and their rate of increase for these parameters is higher as well. Although such changes

Table 2
Regression coefficients at *0.05* significance level.

Parameter	Symbol (Unit)	Const. (a_0)	*Age* (yr; a_1)	T_{db} (yr; a_2)	*HbA1c* (%; a_3)	r^2
Spherical equivalent	*SE* (*D*)	*–0.253*	–	–	–	
Corneal RoC (Ant)	R_{ca} (*mm*)	7.751	–	–	–	
Corneal RoC (Post)	R_{cp} (*mm*)	*6.268*	*0.006*	*–0.006*	–	*0.080*
Lens RoC (Ant)	R_{la} (*mm*)	*10.510*	–	*–0.048*	–	*0.217*
Lens RoC (Post)	R_{lp} (*mm*)	*–6.368*	–	*0.024*	–	*0.108*
Central corneal thickness	*CCT* (*mm*)	*0.544*	–	–	–	
Anterior chamber depth	*ACD* (*mm*)	*3.201*	–	*–0.022*	–	*0.391*
Lens thickness	*LT* (*mm*)	*3.052*	*0.019*	*0.024*	–	*0.732*
Axial length	*AL* (*mm*)	*23.52*	*0.024*	*–0.024*	–	*0.094*

RoC: Radius of Curvature; Vars: variables; yr: years.

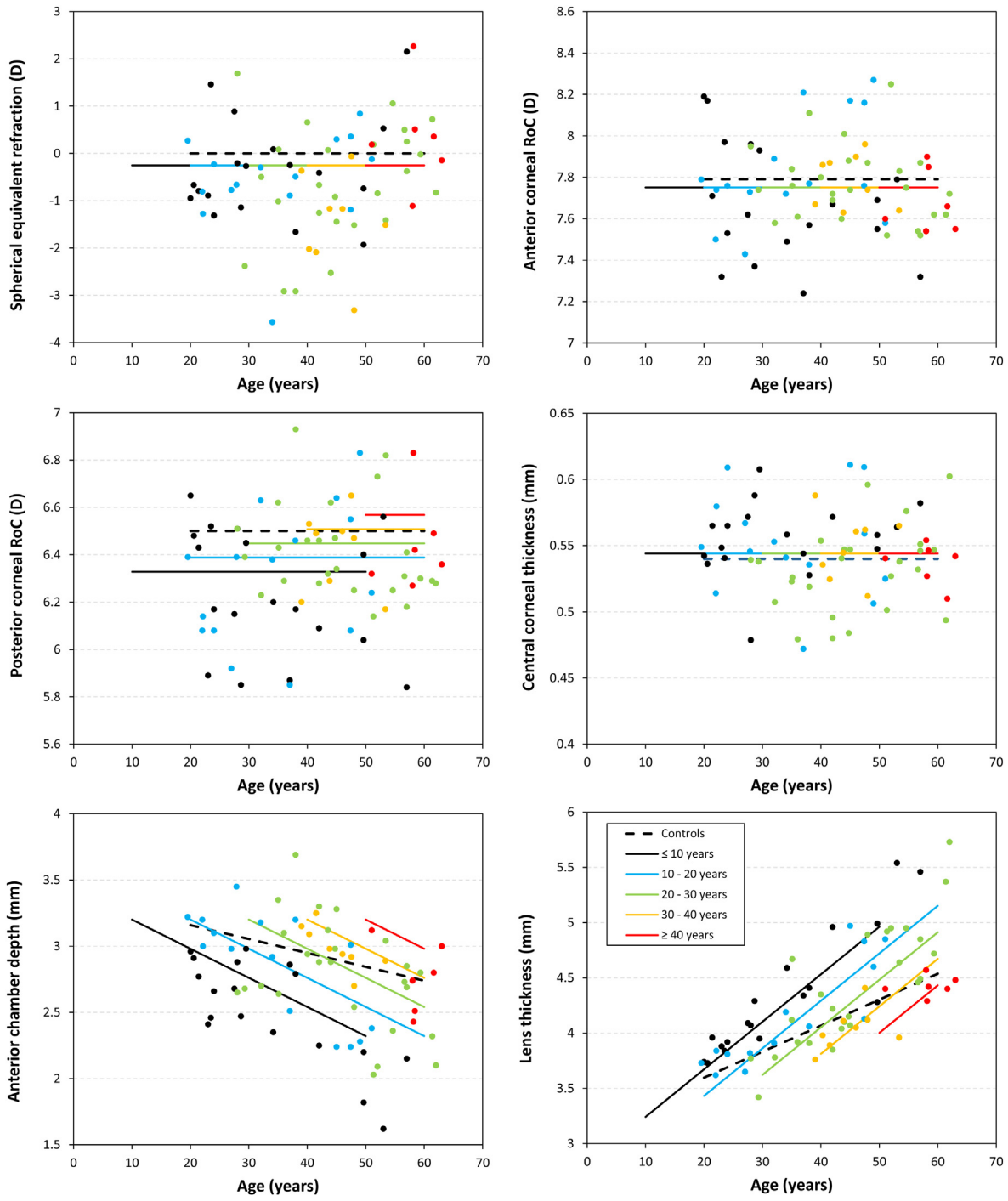

Fig. 2. Overview of agreement between the model (solid lines) and the measured parameters for different ages at diabetes onset (colors). Dashed line corresponds with normal age-appropriate emmetropic values taken from .[45]

are typically associated with increases in lens power, normal eyes would show a gradual decrease instead. Diabetic eyes, on the other hand, show no age-related changes in lens power (Fig. 2).[29] This 'lens paradox'[46] can be resolved by considering the changes in the equivalent lens index, but is obvious that these changes occur differently in diabetes. Consequently, diabetic eyes seem to present their own unique form of refractive development not found in healthy controls of any age.

One new observation is the importance of the age at onset, especially in patients with an onset during childhood. In the first years after birth the eye typically undergoes a period of rapid growth that then slows until it ends around the age of *15–17* years. To ensure good vision, the optical elements of the eye will first fine-tune themselves to provide the best possible unaided vision (*emmetropization*), after which the axial length and the optical elements will coordinate their growth rates to preserve this best unaided vision (*homeostasis*).[47] Sudden disruptions to this homeostasis, such as changes in the child's behavior or environment (e.g., more reading, less exposure to outdoors light) may lead to the development of myopia, with early disruptions being associated with the highest degrees of myopia.[48,49] Slow disruptions like the diabetic changes in the lens found in children,[50–52] on the other hand, allow the eye growth to adapt accordingly, possibly leading to the high lens powers and shorter axial lengths observed in those with an early onset (Fig. 2). This process was confirmed experimentally by Herse,[53] who confirmed that hyperglycemia significantly altered eye growth in young

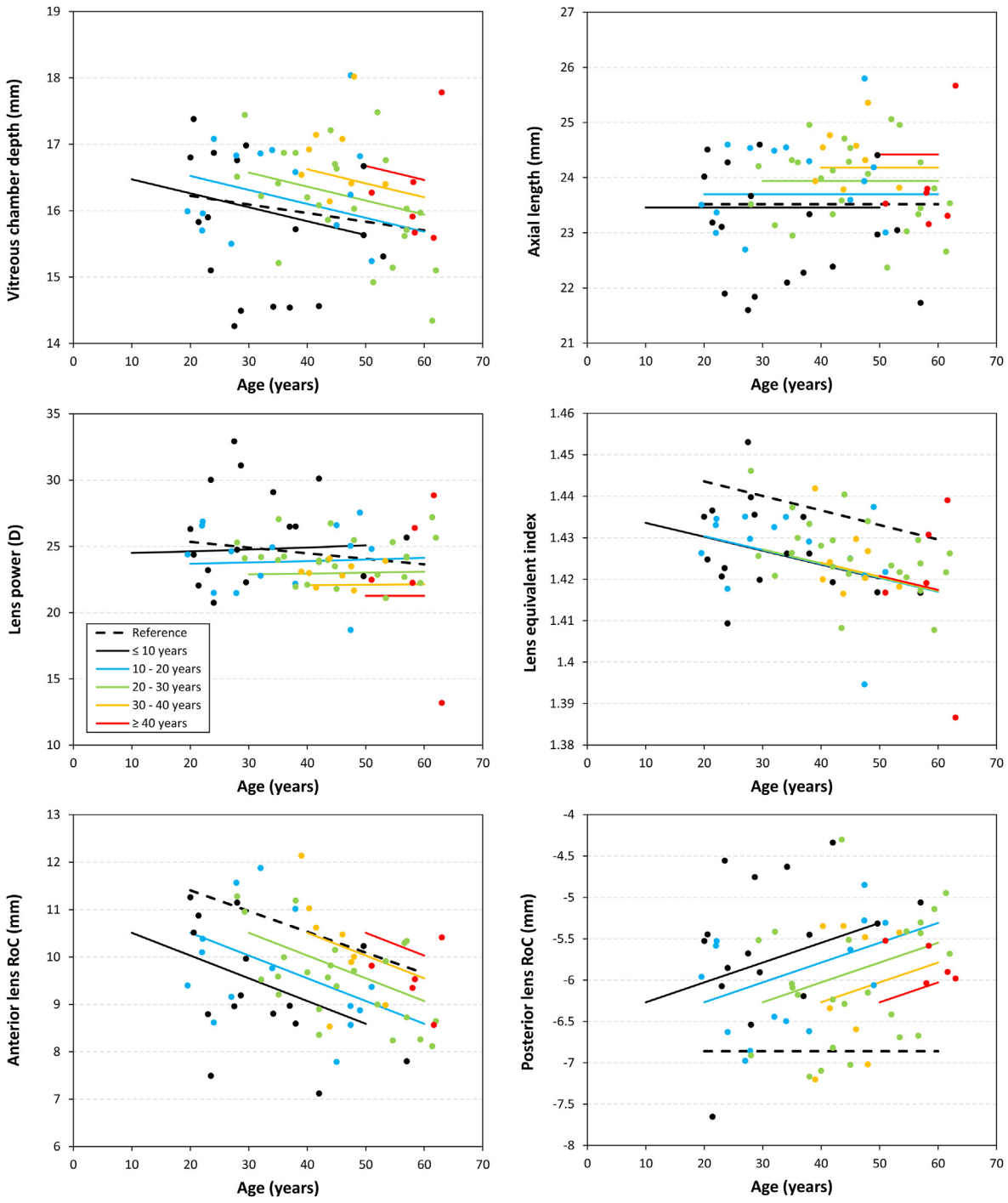

Fig. 2. (*continued*).

rabbits. The effect of hyperglycemia was different in these animals that in humans, as their lenses grew thinner than healthy controls, their anterior chamber depth increased faster, and their axial length stopped increasing too early, leading to excessively short eyes.

A matter of interest is that *DM1* reduces the ability to accommodate.[40,54] Since a diminished accommodative response has been associated with myopia development,[55] this could account for the reports of a higher myopia prevalence in individuals with *DM1*,[22,36] especially in those who are poorly controlled.[35,41] Periods of increased hyperglycemia have been associated with transient hypermetropia[56] due to rapid changes in refractive indices of the eye, especially of the lens,[57] but without noticeable changes in the intraocular curvatures and distances.[58,59] Since periods of hypermetropia are also drivers for myopization,[60] this too may be a factor in the increased myopia prevalence. Even so, no correlations between the ocular biometry and *HbA1c* were found in this (well-controlled) cohort, nor in the pediatric cohorts of Xiao et al.,[50] Uzel et al.[51] and Öztürk et al.[52]

The model produced several minor discrepancies with our earlier work using the same data,[8,30] especially regarding the age-related changes in posterior corneal curvature and lens power. These changes occurred due to an alternative, more holistic modelling approach that no longer includes the influence of axial length. Consequently, the current model is likely more accurate than our earlier results, while also better matching the reports by Wiemer et al.[11,29]

The main limitation of the current work is that the source data consisted of well-controlled individuals with diabetes that had only a

limited range of refractive errors and no ocular pathologies typically associated with diabetes. As such, the model may not be reliable in the presence of the more deleterious effects of hyperglycemia, such as diabetic retinopathy or early cataracts. Even so, the unique combination of biometric parameters found in these patients, along with the importance of the age of diabetes onset, may give important new insights into the robustness of eye growth during refractive development. It would therefore be interesting to develop a longitudinal study that follows the eye growth in children with *DM1* compared to normal controls.

Study Approval

The study adhered to the tenets of the declaration of Helsinki. Ethical approval was obtained from the Queensland University of Technology (ethics clearance 1100001182) before the commencement of the study, and all participants provided written informed consent.

Author Contributions

Conception and design of study: JR, DAA, AK; Data collection: AK; Analysis and interpretation of results: JR; Drafting the manuscript: JR, DAA; All authors reviewed the results and approved the final version of the manuscript.

Acknowledgments

The authors thank the peer reviewers for their opinions and suggestions.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA Ophthalmol*. 2007;298(8):902–916. https://doi.org/10.1001/jama.298.8.902.
2. Busted N, Olsen T, Schmitz O. Clinical observations on the corneal thickness and the corneal endothelium in diabetes mellitus. *Br J Ophthalmol*. 1981;65(10):687–690. https://doi.org/10.1136/bjo.65.10.687.
3. Larsson L-I, Bourne WM, Pach JM, et al. Structure and function of the corneal endothelium in diabetes mellitus type I and type II. *Arch Ophthalmol*. 1996;114(1):9–14. https://doi.org/10.1001/archopht.1996.01100130007001.
4. Lee J, Oum B, Choi H, et al. Differences in corneal thickness and corneal endothelium related to duration in diabetes. *Eye*. 2006;20(3):315–318. https://doi.org/10.1038/sj.eye.6701868.
5. Ozdamar Y, Cankaya B, Ozalp S, et al. Is there a correlation between diabetes mellitus and central corneal thickness? *J Glaucoma*. 2010;19(9):613–616.
6. Roszkowska AM, Tringali CG, Colosi P, et al. Corneal endothelium evaluation in type I and type II diabetes mellitus. *Ophthalmologica*. 1999;213(4):258–261. https://doi.org/10.1159/000027431.
7. Su DH, Wong TY, Wong W-L, et al. Diabetes, hyperglycemia, and central corneal thickness: the Singapore Malay Eye Study. e961 *Ophthalmology*. 2008;115(6):964–968. https://doi.org/10.1016/j.ophtha.2007.08.021.
8. Adnan, Suheimat M, Efron N, et al. Biometry of eyes in type 1 diabetes. *Biomed Opt Express*. 2015;6(3):702–715. https://doi.org/10.1364/BOE.6.000702.
9. Inoue K, Kato S, Inoue Y, et al. The corneal endothelium and thickness in type II diabetes mellitus. *Jap J Ophthalmol*. 2002;46(1):65–69.
10. Keoleian GM, Pach JM, Hodge DO, et al. Structural and functional studies of the corneal endothelium in diabetes mellitus. *Am J Ophthalmol*. 1992;113(1):64–70. https://doi.org/10.1016/S0002-9394(14)75755-1.
11. Wiemer NG, Dubbelman M, Kostense PJ, et al. The influence of chronic diabetes mellitus on the thickness and the shape of the anterior and posterior surface of the cornea. *Cornea*. 2007;26(10):1165–1170. https://doi.org/10.1097/ICO.0b013e31814fa82f.
12. Ziadi M, Moiroux P, d'Athis P, et al. Assessment of induced corneal hypoxia in diabetic patients. *Cornea*. 2002;21(5):453–457.
13. Cahill M, Eustace P, de Jesus V. Pupillary autonomic denervation with increasing duration of diabetes mellitus. *Br J Ophthalmol*. 2001;85(10):1225–1230.
14. Hreidarsson A. Pupil size in insulin-dependent diabetes: relationship to duration, metabolic control, and long-term manifestations. *Diabetes*. 1982;31(5):442–448. https://doi.org/10.2337/diab.31.5.442.
15. Lei H-L, Yang K-J, Sun C-C, et al. Obtained mydriasis in long-term type 2 diabetic patients. *J Ocul Pharmacol Therapeut*. 2011;27(6):599–602. https://doi.org/10.1089/jop.2011.0090.
16. Pittasch D, Lobmann R, Behrens-Baumann W, et al. Pupil signs of sympathetic autonomic neuropathy in patients with type 1 diabetes. *Diabetes Care*. 2002;25(9):1545–1550. https://doi.org/10.2337/diacare.25.9.1545.
17. Yang Y, Yu Y, Yao K. Pupillary dysfunction in type 2 diabetes mellitus to refine the early diagnosis of diabetic autonomic neuropathy. *Neuro Ophthalmol*. 2006;30(1):17–21. https://doi.org/10.1080/01658100600599527.
18. Zaczek A, Zetterström C. The effect of phenylephrine and pilocarpine on pupil size and aqueous flare intensity in patients with diabetes mellitus. *Acta Ophthalmol*. 1998;76(4):413–416. https://doi.org/10.1034/j.1600-0420.1998.760405.x.
19. Shrestha S, Kaini KR. The influence of diabetes mellitus on lenticular thickness. *Am J Publ Health Res*. 2015;3(5A):91–94. https://doi.org/10.12691/ajphr-3-5A-19.
20. Bron A, Sparrow J, Brown N, et al. The lens in diabetes. *Eye*. 1993;7(2):260–275. https://doi.org/10.1038/eye.1993.60.
21. Brown N, Hungerford J. The influence of the size of the lens in ocular disease. *Trans Ophthalmol Soc U K*. 1982;102:359–363.
22. Fledelius HC, Miyamoto K. Diabetic myopia-is it lens-induced? An oculometric study comprising ultrasound measurements. *Acta Ophthalmol*. 1987;65(4):469–473. https://doi.org/10.1111/j.1755-3768.1987.tb07025.x.
23. Løgstrup N, Sjølie A, Kyvik K, et al. Lens thickness and insulin dependent diabetes mellitus: a population based twin study. *Br J Ophthalmol*. 1996;80(5):405–408. https://doi.org/10.1136/bjo.80.5.405.
24. Løgstrup N, Sjølie AK, Kyvik KO, et al. Long term influence of insulin dependent diabetes mellitus on refraction and its components: a population based twin study. *Br J Ophthalmol*. 1997;81(5):343–349. https://doi.org/10.1136/bjo.81.5.343.
25. Pierro L, Brancato R, Zaganelli E, et al. Correlation of lens thickness with blood glucose control in diabetes mellitus. *Acta Ophthalmol*. 1996;74(6):539–541. https://doi.org/10.1111/j.1600-0420.1996.tb00730.x.
26. Saw S-M, Wong TY, Ting S, et al. The relationship between anterior chamber depth and the presence of diabetes in the Tanjong Pagar Survey. *Am J Ophthalmol*. 2007;144(2):325–326. https://doi.org/10.1016/j.ajo.2007.03.038.
27. Sparrow JM, Bron AJ, Brown N, et al. Biometry of the crystalline lens in early-onset diabetes. *Br J Ophthalmol*. 1990;74(11):654–660. https://doi.org/10.1136/bjo.74.11.654.
28. Wiemer NG, Dubbelman M, Hermans EA, et al. Changes in the internal structure of the human crystalline lens with diabetes mellitus type 1 and type 2. *Ophthalmology*. 2008;115(11):2017–2023. https://doi.org/10.1016/j.ophtha.2008.06.032.
29. Wiemer NG, Dubbelman M, Kostense PJ, et al. The influence of diabetes mellitus type 1 and 2 on the thickness, shape, and equivalent refractive index of the human crystalline lens. *Ophthalmology*. 2008;115(10):1679–1686. https://doi.org/10.1016/j.ophtha.2008.03.019.
30. Adnan, Pope JM, Sepehrband F, et al. Lens shape and refractive index distribution in type 1 diabetes. *Invest Ophthalmol Vis Sci*. 2015;56(8):4759–4766. https://doi.org/10.1167/iovs.15-16430.
31. Adnan, Suheimat M, Mathur A, et al. Straylight, lens yellowing and aberrations of eyes in type 1 diabetes. *Biomed Opt Express*. 2015;6(4):1282–1292. https://doi.org/10.1364/BOE.6.001282.
32. Davies NP, Morland AB. Color matching in diabetes: optical density of the crystalline lens and macular pigments. *Invest Ophthalmol Vis Sci*. 2002;43(1):281–289.
33. Lutze M, Bresnick G. Lenses of diabetic patients yellow at an accelerated rate similar to older normals. *Invest Ophthalmol Vis Sci*. 1991;32(1):194–199.
34. Liu J, Wang X, Wang J, et al. Optical quality and intraocular scattering in the diabetic eye without diabetic retinopathy. *Optom Vis Sci*. 2019;96(4):248–255. https://doi.org/10.1097/OPX.0000000000001360.
35. Jacobsen N, Jensen H, Lund-Andersen H, et al. Is poor glycaemic control in diabetic patients a risk factor of myopia? *Acta Ophthalmol*. 2008;86(5):510–514. https://doi.org/10.1111/j.1600-0420.2007.01104.x.
36. Fledelius HC. Is myopia getting more frequent? A cross-sectional study of 1416 Danes aged 16 years+. *Acta Ophthalmol*. 1983;61(4):545–559. https://doi.org/10.1111/j.1755-3768.1983.tb04344.x.
37. Song E, Qian DJ, Wang S, et al. Refractive error in Chinese with type 2 diabetes and its association with glycaemic control. *Clin Exp Optom*. 2018;101(2):213–219. https://doi.org/10.1111/cxo.12606.
38. Shahidi M, Blair NP, Mori M, et al. Optical section retinal imaging and wavefront sensing in diabetes. *Optom Vis Sci*. 2004;81(10):778–784.
39. Valeshabad AK, Wanek J, Grant P, et al. Wavefront error correction with adaptive optics in diabetic retinopathy. *Optom Vis Sci*. 2014;91(10):1238–1243. https://doi.org/10.1097/OPX.0000000000000252.
40. Adnan, Efron N, Mathur A, et al. Amplitude of accommodation in type 1 diabetes. *Invest Ophthalmol Vis Sci*. 2014;55(10):7014–7018. https://doi.org/10.1167/iovs.14-15376.
41. Gwinup G, Villarreal A. Relationship of serum glucose concentration to changes in refraction. *Diabetes*. 1976;25(1):29–31.
42. Pritchard N, Edwards K, Dehghani C, et al. Longitudinal assessment of neuropathy in type 1 diabetes using novel ophthalmic markers (LANDMark): study design and baseline characteristics. *Diabetes Res Clin Pract*. 2014;104(2):248–256. https://doi.org/10.1016/j.diabres.2014.02.011.

43. Chylack LT, Wolfe JK, Singer DM, et al. The lens opacities classification system III. *Arch Ophthalmol*. 1993;111(6):831–836. https://doi.org/10.1001/archopht.1993.01090060119035.
44. Atchison DA, Smith G. Chromatic dispersions of the ocular media of human eyes. *J Opt Soc Am A*. 2005;22(1):29–37. https://doi.org/10.1364/JOSAA.22.000029.
45. Atchison DA. Age-related paraxial schematic emmetropic eyes. *Ophthalmic Physiol Opt*. 2009;29(1):58–64. https://doi.org/10.1111/j.1475-1313.2008.00598.x.
46. Moffat BA, Atchison DA, Pope JM. Explanation of the lens paradox. *Optom Vis Sci*. 2002;79(3):148–150.
47. Rozema JJ, Dankert S, Iribarren R: Normal Refractive Development from before Birth until Adulthood (in review).
48. Rozema J, Dankert S, Iribarren R, et al. Axial growth and lens power loss at myopia onset in Singaporean children. *Invest Ophthalmol Vis Sci*. 2019;60(8):3091–3099. https://doi.org/10.1167/iovs.18-26247.
49. Mutti DO, Mitchell GL, Sinnott LT, et al. Corneal and crystalline lens dimensions before and after myopia onset. *Optom Vis Sci*. 2012;89(3), 251262. https://doi.org/10.1097/OPX.0b013e3182418213.
50. Xiao Y, Li T, Jia Y, et al. Influence of type 1 diabetes mellitus on the ocular biometry of Chinese children, 2019 *J Ophthalmol*. 2019, 7216490. https://doi.org/10.1155/2019/7216490.
51. Uzel MM, Elgin U, Sen E, et al. Comparison of anterior segment parameters in juvenile diabetes mellitus and healthy eyes. *Eur J Ophthalmol*. 2016;26(6):618–622. https://doi.org/10.5301/ejo.5000764.
52. Öztürk H, Özen B, Manyas H, et al. Can ocular changes be detected early in children and adolescents with type 1 diabetes mellitus without retinopathy by using optical biometry and optical coherence tomography? *Int Ophthalmol*. 2020;40:2503–2514. https://doi.org/10.1007/s10792-020-01430-4.
53. Herse P. Effects of hyperglycaemia on ocular development in rabbit: refraction and biometric changes. *Ophthalmic Physiol Opt*. 2005;25(2):97–104. https://doi.org/10.1111/j.1475-1313.2004.00262.x.
54. Sırakaya E, Küçük B, Sırakaya HA. The influence of type 1 diabetes mellitus on amplitude of accommodation. *Curr Eye Res*. 2020;45(7):873–878. https://doi.org/10.1080/02713683.2020.1726406.
55. Gwiazda J, Bauer J, Thorn F, et al. A dynamic relationship between myopia and blur-driven accommodation in school-aged children. *Vis Research*. 1995;35(9):1299–1304. https://doi.org/10.1016/0042-6989(94)00238-H.
56. Kaštelan S, Gverović-Antunica A, Pelčić G, et al. Refractive changes associated with diabetes mellitus. In: *Sem Ophthalmol*. Taylor & Francis; 2018:838–845. https://doi.org/10.1080/08820538.2018.1519582.
57. Okamoto F, Sone H, Nonoyama T, et al. Refractive changes in diabetic patients during intensive glycaemic control. *Br J Ophthalmol*. 2000;84(10):1097–1102. https://doi.org/10.1136/bjo.84.10.1097.
58. Huntjens B, Charman WN, Workman H, et al. Short-term stability in refractive status despite large fluctuations in glucose levels in diabetes mellitus type 1 and 2. *PLoS One*. 2012;7(12), e52947. https://doi.org/10.1371/journal.pone.0052947.
59. Tai M-C, Lin S-Y, Chen J-T, et al. Sweet hyperopia: refractive changes in acute hyperglycemia. *Eur J Ophthalmol*. 2006;16(5):663–666. https://doi.org/10.1177/112067210601600501.
60. Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. *Neuron*. 2004;43(4):447–468. https://doi.org/10.1016/j.neuron.2004.08.008.