Biometry of the crystalline lens in late onset diabetes: the importance of diabetic type


Abstract
Lenticular and anterior chamber biometry were studied in non-cataractous eyes by means of Scheimpflug photography and digital image analysis. The study population consisted of 91 late onset diabetic subjects and 115 non-diabetic controls. Anteroposterior axial lens thickness, cortical thickness, nuclear thickness, anterior clear zone thickness, anterior chamber depth, and anterior and posterior lenticular curvatures were assessed. Age played an important role in determining lens biometry in all subjects, and small but significant differences were found between late onset diabetics and non-diabetics. In the late onset diabetic subgroup, apart from age, diabetic retinopathy was the only significant parameter found which determined lens biometry. These biometric findings in late onset diabetics are in marked contrast to the large overall effect of diabetes and the powerful effect of diabetic duration which we previously reported in early onset diabetes. Further analysis of the data from our previous study has been provided, which clearly demonstrates differences between the impact of early and late onset diabetes on the biometry of the anterior ocular segment.

Mitotic activity in the pre-equatorial lenticular epithelium results in steady growth of the human crystalline lens throughout life.1-5 Overall lens growth is determined by a dynamic balance between external accretion of secondary lens fibres and the central compaction of older nuclear or perinuclear fibres.6 Lenticular growth is proportionally greater than equatorial growth, anterior and posterior lens curvatures therefore become steeper (shorter radii of curvature) with increasing age.7 Lenticular biometry is disturbed in diabetes,3,8-10 with early onset diabetics showing markedly abnormal lens growth with a powerful dependency upon diabetic duration.3 The anterior clear zone (first zone of disjunction) of the lens behaves independently of the other lenticular zones. This zone, which is neither age dependent nor dependent upon diabetic duration, has been found to be markedly increased in early onset diabetics.3 The increased anterior clear zone thickness and the powerful dependency of other biometric parameters on diabetic duration imply that the lenses of early onset diabetics may not simply be over-hydrated, but that they may be in a state of accelerated growth, with either more (hyperplastic mechanism) or individually larger (hypertrophic mechanism) secondary lens fibres being formed. Intracellular ‘swelling’ of individual lens fibres would be theoretically possible although such swelling would need to be confined to the newly formed (metabolically active) fibres to be compatible with the powerful duration effect observed in early onset diabetes.1 In order for extracellular swelling of the lens to explain the observed effect of duration it would be necessary to postulate that such swelling increased over time with diabetic duration. This is conceivable, as ongoing cumulative damage to membrane structures could take place over periods of years.

Previous studies have not examined specifically the effect of late onset diabetes on lenticular biometry.3,8-10 The present study examines biometry in clear lenses of late onset diabetics and controls, and draws comparisons between the impact of diabetes on the lens in late and early onset diabetes.

Material and methods

SUBJECTS
A total of 91 late onset diabetics (57 males) and 115 non-diabetic controls (64 males) were included in the study. These patients formed part of a population-based comparative lens study.1 The diabetics were survivors of the Oxford Community Diabetes Study,12 and community-based controls were selected to group match the diabetics by age and sex. In the present study only the late onset diabetics were included. Late onset diabetics were regarded simply as all those diabetics who did not fit the inclusion criteria used in our earlier study for early onset diabetes. In effect this meant that late onset diabetics were defined as any diabetic whose age at onset was more than 30 years regardless of the type of diabetic treatment, or diabetics whose age at onset was 30 years or less, but who did not require continuous insulin treatment. Controls were all community based, and were accepted if they had no history of diabetes or impaired glucose tolerance, and a non-fasting whole venous blood glucose of less than 7.8 mmol/l.13

Individual eyes of diabetics and controls were included in the present study if the lenses were non-cataractous, and had normal anterior ocular segments and vision sufficiently good to hold fixation during Scheimpflug photography. Cataractous lenses were excluded because such lenses may have abnormal biometry.13,16 although certain minor opacities as defined by the Oxford Clinical Cataract Classification and Grading System17,18 were accepted: nuclear brunescence and white nuclear scatter up to and including Grade 2, spoke opacities and water-clefs of Grade 1, and isolated vacuoles, retrodots and focal dots. No anterior or posterior sub-
capsular opacities were permitted, as subcapsular opacities were specifically known to be associated with reduced lens size. There were thus a total of 378 eligible eyes in 206 subjects; 188 were right eyes and 190 were left eyes.

The study was approved by the Central Oxford Research Ethics Committee (ref no 1211), and informed consent was obtained from participants.

PROCEDURE

The procedure followed has been described. Briefly, subjects were contacted and recruited by the primary investigator (JS). Following a short history and Snellen acuity testing pupils were dilated (tropicamide 1% and phenylephrine 10%) with due regard to the usual precautions. Lenses were assessed for cataract at the slit-lamp biomicroscope, and Scheimpflug photographs were taken using a Brown Scheimpflug camera. Biometric measurements on digitised images were performed by a masked observer (JS) using the Oxford Modular Cataract Image Analysis System which was developed by the authors. As in our previous study of lens biometry in early onset diabetes the biometric parameters measured were: anteroposterior axial lens thickness, cortical thickness, nuclear thickness, anterior clear zone thickness, anterior chamber depth, and anterior and posterior lenticular curvatures. Cortical thickness was derived arithmetically as the difference between lens and nuclear thickness.

STATISTICAL METHODS

Biometric measurements were in general obtained from both eyes, although certain patients contributed measurements on only one eye. A preliminary analysis was performed by plotting the biometric data against age and performing simple linear regression for the diabetic and non-diabetic groups separately. In the main analysis the within-subject intereye correlation was accounted for by employing the intraclass correlation model of Rosner for calculating significance levels and confidence intervals. The dependent variables were continuous and were approximately normally distributed. The main analysis took the form of a multiple linear regression analysis with groups (factors), the biometric measures being used as dependent variables in a series of model fitting exercises. Adjustment for minor imbalances in the case/control age distribution was achieved by treating age as a covariate in the relevant analyses. To facilitate comparison with our earlier study of lens biometry in early onset diabetes the analyses were performed in broadly the same manner as in that study. The orders of the fitting of terms to the models are indicated in the tables. Using the data from the previous study as well as the data from the present study additional analyses were performed comparing the overall effects of early and late onset diabetes with non-diabetic controls, and comparing early and late onset diabetics directly. These analyses provide the average group differences (with 95% confidence intervals) between both types of diabetes and controls, and between early and late onset diabetics, after taking account of the (confounding) effects of age and sex. The analysis was performed using the Generalised Linear Interactive Modelling (GLIM) System of the Numerical Algorithms Group (NAG, Wilkinson House, Jordan Hill Road, Oxford OX2 8DR).

Results

The age distribution of the late onset diabetics and controls is presented in Figure 1. The age/duration distributions for the diabetics alone are presented in Table 1. Figures 2 to 8 illustrate the preliminary regression analyses of biometry against age. These graphs demonstrate the important effect of age on anterior segment biometry. For certain of the biometric features studied there appear to be small differences between the late onset diabetics and controls.

These impressions were investigated in the formal analysis summarised in Table 2. The late onset diabetics and controls' analysis (206 subjects, 378 eyes) confirmed that age was an important determinant of biometry. Modest differences existed between diabetics and non-diabetics for axial lens thickness, cortical thickness, and front radius of curvature. These changes were such that lenses of diabetics were 'thicker' with steeper front curvatures. The significant age by diabetic status interaction term (age.xa) for front radius of curvature indicated that the younger diabetics were relatively more affected, this being well demonstrated in Figure 7 (regression lines non-parallel). A substantial difference in anterior clear zone thickness between diabetics and non-diabetics was found, with diabetics having increased clear zone thick-
ness. Female sex was associated with decreased cortical thickness.

In the late onset diabetic subgroup (91 subjects, 161 eyes) age was an important determinant of lens biometry for all parameters except nuclear thickness and anterior clear zone thickness. Proliferative diabetic retinopathy was associated with increased lens and cortical thickness. Diabetic duration, sex, or type of diabetic treatment (insulin, oral hypoglycaemics, or diet) did not have a demonstrable effect on any of the biometric parameters studied.

Among the controls (115 subjects, 217 eyes) age was an important determinant of biometry, with female sex associated with decreased axial length and cortical thickness and with increased nuclear thickness.

The differences between the late onset diabetics and controls were observed to be less impressive than those previously found for 153 early onset diabetics and 153 controls\(^5\) (the 115 controls in the present study being a subset of the previous 153). For this reason further analyses making a direct comparison between early and late onset diabetics were performed. The first of these analyses is summarised in Table 3, and demonstrated important differences between the two groups of diabetics (after accounting for confounding effects). The differences between the early and late onset groups were such that the lenses of the early onset patients were significantly larger in their axial, cortical, and nuclear thicknesses, had steeper front and back radii of curvatures, and were associated with shallower anterior chambers. The interaction terms between age and type of diabetes (age-type) indicated certain differences in the slopes of the regression lines between the two groups. The regression lines for lens thickness (cortical thickness) and front radius of curvature were each less steep in the late onset diabetics than in the early onset diabetics, indicating that the average change per year in biometry was greater in the early onset group.

The magnitudes of the observed effects (with 95% confidence intervals) are presented in Table 4. These analyses demonstrated the average effects of late onset and early onset diabetes on lens biometry compared with controls, and also compared early and late onset diabetics directly. After adjustment for age and sex, the effect sizes in the early and late onset diabetics compared with controls indicated that the impact of lens biometry of early onset diabetes was between two and three times that found in late onset diabetes.

The final group of analyses in Table 4 provide direct estimates (adjusted for age and sex) for the overall differences between early and late onset diabetics. These estimates show that diabetics demonstrate a particular pattern of disturbance of anterior segment biometry, and that the magnitude of this disturbance is considerably greater among early onset than among late onset diabetics.

Because the early onset diabetics from our previous study\(^7\) were on average younger than the late onset diabetics in the present study, two further analyses were performed to determine whether the observed differences might be due to differences in the age structures of the two diabetic populations. To examine this point attention was directed to the impact of diabetic duration, which, as has been noted above, was a powerful effect among the early onset diabetics,\(^7\) but which appeared to play no role in the late onset diabetics. Firstly, the early onset group...
was examined to determine whether the powerful duration effect persisted across the entire age range. For this the early onset diabetics (age range 10 to 74 years) were grouped into age quartiles. The duration effect for the biometric parameters was then determined separately for each age quartile in a model which pre-fixed the age effect to that of the non-diabetic control group, and maintained a constant y-intercept for the age quartiles. A summary of this analysis appears in Table 5, which gives the duration estimates (and 95% confidence intervals) for each quartile. This analysis demonstrated that in general the duration effect among the early onset diabetics persisted across all the age quartiles. In the second analysis all the diabetics (early and late onset) were grouped in deciles according to their age at onset of diabetes. This approach dispensed with the prior classification of the diabetics into early and late onset groups. After adjusting for age and sex each 'onset decile' group was examined separately for an effect of diabetic duration (Table 6). These analyses demonstrated that for most parameters the effect of diabetic duration on biometry diminished dramatically when age at onset of diabetes exceeded 30 years.

Discussion

The results of this study have demonstrated important differences in the impact of late onset and early onset diabetes on the biometry of the anterior ocular segment. The impact of late onset diabetes on biometry was modest, and a direct comparison between early onset and late onset diabetics confirmed these biometric differences between the two groups of diabetics. Comparisons between each diabetic type and non-diabetic controls revealed that the impact on biometry of early onset diabetes was two to three times greater than the impact of late onset diabetes. Furthermore, within the diabetic subgroups, no effect of diabetic duration was found among the late onset diabetics, which was in marked contrast to the powerful effect of diabetic duration previously found in early onset diabetes. Further analysis of the data from our earlier study has demonstrated that the duration effect in early onset diabetes persists across all the age quartiles (age range 10 to 74 years). The demonstration that the duration effect persists across the age quartiles is important, because it illustrates that the absence of a duration effect in the late onset diabetics cannot be attributed to the fact that the late onset diabetics were on average older than the early onset diabetics. When the classification of diabetics into early and late onset subjects was dispensed with, age at onset of more than 30 years was noted to be associated with a marked reduction in the effect of diabetic duration after adjustment for the effects of sex and ageing. These findings support the idea that the response of the lens to early onset diabetes is distinct, and is not simply a function of the age of the affected individual. It may be argued that the failure to demonstrate an effect of diabetic duration in the late onset diabetics could be due to the fact that disease duration is frequently not precisely known in such patients. The disease duration of such patients however would in general be underestimated and this would tend to amplify any actual association with duration. Our failure to identify any association with disease duration in
late onset patients is therefore unlikely to arise from inaccurate knowledge of true diabetic duration among late onset diabetics. The statistical power of this study to detect a 'medium' sized duration effect among the late onset diabetics in a multiple regression analysis (13% of the variance of Cohen’s convention) at the 5% probability level for 91 subjects is 87%, and for 161 eyes is 99%. The true power of the study as analysed by the intraclass correlation model will therefore lie between these upper and lower limits, depending on the actual within-subject intereye correlation for each parameter under study. Even if the intereye correlation was high it would be reasonable to suppose that the power of this study to detect a medium size effect at the 5% level is at least 90%, which confirms that any duration effect among the late onset diabetics would have had to be small (and therefore of doubtful importance) to have been missed.

Our definitions of early onset diabetics as diabetics diagnosed at or before 30 years of age and requiring continuous insulin treatment, and late onset diabetics as all other diabetics have the effect of separating off a group of young subjects who almost certainly had Type 1 diabetes. This definition of Type 1 diabetes, although based purely on clinical features and age at onset, has been used extensively in epidemiological studies. A prospective study of 268 newly diagnosed diabetic patients classified on the basis of clinical criteria only found that all patients diagnosed before the age of 40 years who were clinically assessed as insulin-dependent, had fasting C-peptide levels 18 months after diagnosis which were diagnostic of insulin dependence.27 The classification that we used will therefore have ensured that early onset patients were correctly characterised as having minimal endogenous insulin production, although the late onset group is likely to have contained a small number of misclassified patients with true Type 1 (insulin-dependent) diabetes. This might confound comparisons between the early and late onset groups, and it is conceivable (although unlikely) that the ‘weak’ effects of diabetes seen in our late onset group are (partly) due to the misclassification and inclusion of a number of small truly Type 1 diabetics within a group which should ideally contain only Type 2 patients. Thirty (33%) of the late onset diabetics were using insulin at the time of the study, 15 (16%) having had their diabetes diagnosed at age <50 years, and 10 (11%) at age <40 years. The number of potential misclassifications was therefore not very great.

In the present study proliferative diabetic retinopathy was found to be associated with greater lens and cortical thickness, an effect which is in general consistent with our previous finding in early onset diabetics of increased clear zone and nuclear thickness, and steeper front and back curvatures in patients with retinopathy (confounding variables accounted for in each study). These associations raise the possibility that disturbances in lens biometry could be due to the forward diffusion of an (angiogenic) growth factor from the posterior choroidal segment, or they may simply imply that patients with a
may reflect fundamental pathophysiological differences between Type 1 and Type 2 diabetes.

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8 Huggart A. The appearance of the band of disjunction of the lens in diabetes mellitus. Acta Ophthalmol (Kbh) 1953; 31: 227-34.


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