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Biometry of the crystalline lens in early-onset diabetes

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Abstract

Lenticular biometry on non-cataractous lenses has been studied by means of Scheimpflug photography and digital image analysis in 153 patients with early-onset insulin-dependent diabetes and 153 non-diabetic controls. Anteroposterior axial lens thickness, cortical thickness, nuclear thickness, anterior and posterior lenticular curvatures, and anterior chamber depth were assessed. Highly significant differences between the lenses of the diabetic subjects and non-diabetic controls were found. After the effect of age had been accounted for within the diabetic subgroup, diabetic duration was found to be a highly significant determinant of lens dimensions, such that age-related dimensional changes for various biometric parameters were accelerated by between 52% and 121% after the onset of diabetes. Because the diabetic duration of the early-onset diabetic subjects studied in this work was accurately known, this report is the first in which a precise assessment of the effect of 'true' diabetic duration on lens biometry has been possible.

The crystalline lens of the eye is the only human organ which undergoes a steady increase in size due to growth throughout the life of the individual.[1-3] Mitosis in the pre-equatorial lenticular epithelium provides a constant supply of new lens fibres, which are added externally to earlier generations of fibres.[4] While accretion of new fibres continues, older generations of fibres compact within the deeper layers of the lens substance.[3 5] Anteroposterior lens growth is proportionally greater than equatorial growth, so the front and back curves of the lens steepen (radii of curvature decrease) with increasing age.[6]

The crystalline lens of the eye is affected by the diabetic state in a number of ways. The anterior clear zone (first zone of discontinuity) has been noted to be enlarged in young diabetics,[7] and lenses of diabetic patients are larger than those of non-diabetics, after the effect of age has been accounted for.[8] Diabetics are in addition at risk for the development of cataractous changes,[9-16] this risk being especially obvious in younger diabetics.[12 13] True juvenile diabetic cataract is fortunately not common and is associated with diabetes which is metabolically severely out of control.[17 18] This type of cataract probably has a specific mechanism, and may occasionally be reversible if the blood sugar concentration is kept normal.[19]

Diabetes therefore affects the lens in a number of important ways. Previous studies have not differentiated between early and late onset diabetes, and the effects of 'true' diabetic duration have therefore not previously been assessed. The present study examines lens biometry in relation to early-onset insulin-dependent diabetics and controls.

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Material and methods

SUBJECTS

One hundred and fifty-three diabetic subjects (96 male) were recruited from general diabetic clinics, a paediatric diabetic clinic, ocular diabetic clinics, and from a population survey of diabetics. Eligible subjects had early-onset insulin-dependent diabetes, defined as diabetes requiring insulin treatment from initial diagnosis, with age at onset being 30 years or less. Recruitment was stratified for age and duration of diabetes. An equal number of control subjects were recruited (79 male), mainly from a population based ocular survey, supplemented by subjects from eye hospital clinics and an ophthalmic casualty department. Controls were included 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.[20 21]

Individual eyes of diabetics and controls were included if the lenses were non-cataractous, had normal anterior ocular segments, and vision sufficiently good for the eye to hold fixation during Scheimpflug photography. Cataractous lenses were excluded because such lenses may have abnormal biometry,[2 22 23] though the following minor opacities as defined by the Oxford clinical cataract classification and grading system[24] were permitted: nuclear brunescence and white nuclear scatter up to and including grade 2, spoke opacities and waterclefts of grade 1, and isolated vacuoles, retrodots, and focal dots. No anterior or posterior subcapsular opacities were permitted, as subcapsular opacities were specifically known to be associated with reduced lens size.[22] There were thus a total of 597 eyes eligible for study in the 306 subjects; 299 were right eyes and 298 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

Subjects were recruited to the study by the primary investigator (JS). At the time of their assessments a brief medical history was taken and Snellen visual acuity determined. After the anterior chamber depth had been checked and the presence of iris supported intraocular lens implants excluded, the subject's pupils were

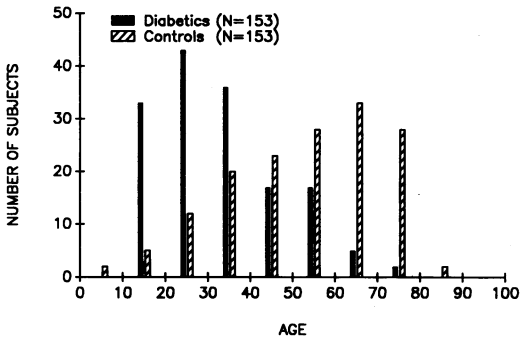

Figure 1 Frequency distribution of the ages of male and female subjects.

dilated with tropicamide eyedrops 1% and phenylephrine eyedrops 10%, repeated if necessary.

After pupillary dilatation the crystalline lens was examined at a slit-lamp biomicroscope to exclude cataractous changes as described above. Scheimpflug slit-image photography with a Brown Scheimpflug camera[25-27] was then performed, and the photographic images were subjected to digital image analysis by an image analysis system developed by the authors.

Measurements obtained from this system are uncompensated for optical distortions produced by the Scheimpflug camera optics and the corneal and crystalline lenticular magnifications, though separate horizontal and vertical calibration was used for curvature measurements.[28] Anteroposterior biometry (lens thickness, cortical thickness, nuclear thickness, anterior clear zone thickness, and anterior chamber depth) were all measured by a standard method using a linear density trace running down the axis of the Scheimpflug photograph, measurement being facilitated by simultaneous display of both the density trace and the image on adjacent computer screens. Anterior and posterior lens curvatures were measured by defining three points on the curve, the computer program then working out the radius of curvature (calibrated horizontally and vertically).

STATISTICAL METHODS

Biometric measurements were in general obtained from both eyes, though 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 of biometry against age for the diabetic and non-diabetic groups. To take account of the within-subject inter-eye correlation, the intra-class correlation model was employed in the analysis.[29-30] All dependent variables were continuous and approximately normally distributed. The 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. Age was therefore treated as a co-variate, compensating for the imperfect age matching of the diabetic and non-diabetic groups where these were being compared.

Significant effects were sought for various patient characteristics. Three series of analyses were performed, the first included all subjects (n=306), the second included only the early onset diabetics (n=153), and the third included only the non-diabetic controls (n=153). Terms were included into the models in a fixed, predetermined order, and this order is adhered to in the summary table of the analysis (Table II). Certain terms were always included in the model (obligatory terms), while others were included only if they were found to be significant at the 5% level (optional terms). Where very powerful effects were found for continuous independent variables (namely, age and duration of diabetes) multiple linear regression slopes for these variables are reported. In this analysis the age slope derived from the control group was imposed on the regression model for the diabetic group, the duration slope therefore being exclusively the additional effect of duration over and above the effect of age. (This method circumvents the statistical problems associated with the fact that age and duration are partially correlated variables.) The analysis was performed by the Generalised Linear Interactive Modelling (GLIM) System of the Numerical Algorithms Group on the Oxford University mainframe computer (VAX cluster).

TABLE 1 *Age by diabetic duration of the early onset diabetes study population*

	Diabetic duration (years)					
Age	*0 to <10*	*10 to <20*	*20 to <30*	*30 to <40*	*40 to <50*	*Total*
0 to <10	0	–	–	–	–	0
10 to <20	22	11	–	–	–	33
20 to <30	20	16	7	–	–	43
30 to <40	5	17	11	3	–	36
40 to <50	–	6	7	3	1	17
50 to <60	–	–	6	6	5	17
60 to <70	–	–	–	4	1	5
70 to <80	–	–	–	–	2	2
Total	47	50	31	16	9	153

0 to <10=up to but excluding 10 years, and so on.

Results

The age distributions of the diabetics and controls are shown in Figure 1, and the age by duration distributions of the diabetics appear in Table 1. Figures 2 to 8 show the results of the preliminary regression analysis of biometry against age. These graphs illustrate that age was an important determinant of the biometry of the anterior ocular segment (an exception to this was the anterior clear zone thickness). Further it can be seen from these graphs that the regression lines for the early onset diabetics differed from those of the non-diabetics. In general the lenses of diabetics appeared larger than those of non-diabetics (Fig 2), this effect being more obvious in the cortex (Fig 3) than in the nucleus (Fig 4). The anterior clear zone of the diabetics was also considerably larger than that of the non-diabetics (Fig 5). The larger diabetic lenses were associated with shallower anterior chambers (Fig 6), and with steeper curvatures (smaller front (Fig 7) and back (Fig 8) radii of curvature).

Formal analysis confirmed these preliminary findings. A summary of p values from the formal analysis appears in Table 2. From the all-subjects analysis (306 subjects) in this table it is apparent that age was a powerful determinant of biometry. These effects were such that older age was associated with larger lens dimensions,

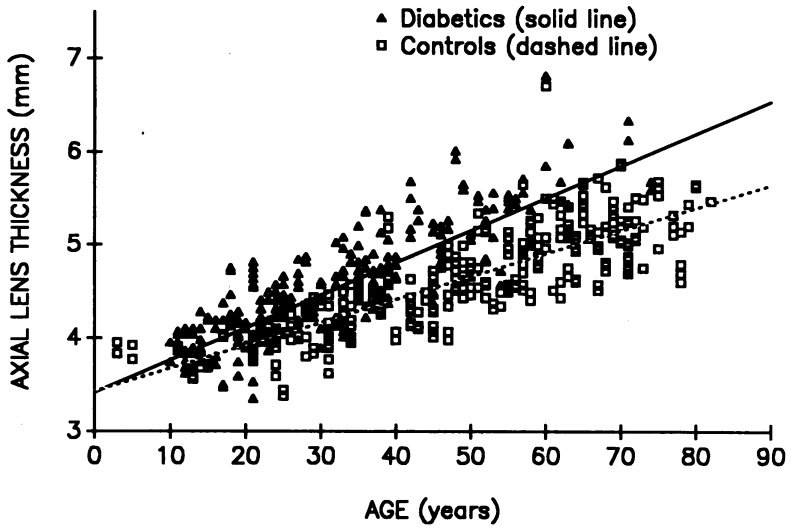

Figure 2 Plot of anteroposterior axial lens thickness in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

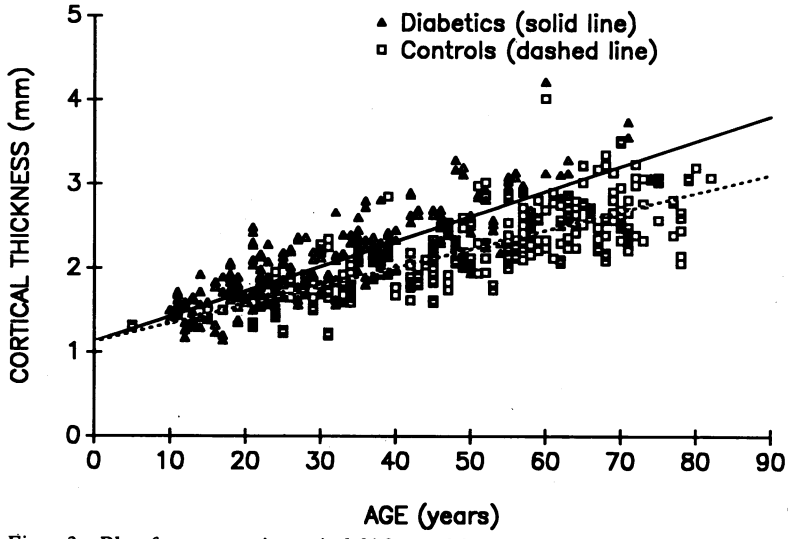

Figure 3 Plot of anteroposterior cortical thickness of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

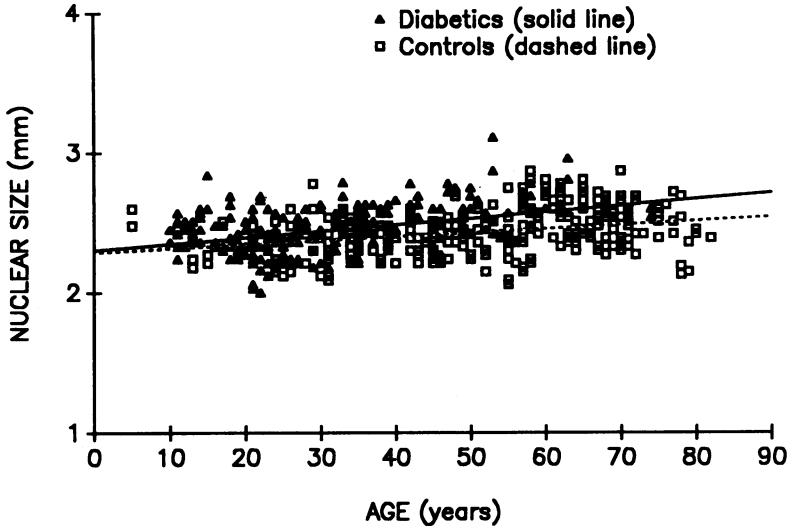

Figure 4 Plot of anteroposterior nuclear size of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

shallower anterior chambers, and steeper surface curvatures. Diabetic status was also a powerful determinant of biometry, with diabetic lenses being larger, being associated with shallower anterior chambers, and having steeper front and back curvatures than those of controls. The significant age by status interactions (Age. Sta) for axial lens thickness, cortical thickness, and anterior chamber depth were such that the slopes of the regression lines against age for the diabetics were significantly steeper than those of the controls (see Figs 2, 3, 5). The effect of sex was such that female sex was associated with decreased cortical thickness, with increased nuclear size, and with decreased anterior chamber depth.

In the early onset diabetes subgroup (153 subjects) age was powerfully associated with biometry. Diabetic duration was generally also a powerful determinant of biometry. Female sex was associated with decreased cortical thickness. Higher daily insulin dose was associated with reduced nuclear size and increased anterior clear zone thickness. The presence of diabetic retinopathy was associated with a larger lens nucleus, with increased anterior clear zone thickness and with steeper surface curvatures.

In the non-diabetic controls subgroup (153 subjects) age was again powerfully associated with biometry. Among the controls female sex was associated with smaller cortical thickness and larger nuclear size.

The linear regression slope for age alone in the non-diabetic controls subgroup, and the multiple linear regression slope for duration in the diabetic subgroup (effect of age fixed to that of the control group), are displayed in Table 3. Also displayed are associated p values from the intraclass correlation analysis, and the duration/age slope ratios. (Anterior clear zone was excluded because age and diabetic duration were not powerful determinants of this feature.) These duration slopes indicate the additional effect of diabetic duration over and above the normal effect of age. For the various biometric parameters in Table 3 the ratio of the slopes of age and duration demonstrate that the independent effect of diabetic duration per year on biometry is between 52% and 121% of the effect of age per year, with the effect on overall lens thickness being 68% and that on anterior chamber depth being 100%.

Discussion

The present work confirms earlier findings that the diabetic state profoundly affects the biometry of the crystalline lens,[7,8] and it has extended this knowledge in terms of the biometry of the anterior ocular segment as a whole in non-cataractous early onset diabetics and non-diabetic controls. In addition other patient characteristics have been examined, and it is clear from the results of this study that duration of diabetes is of paramount importance in the determination of anterior segment biometry in early onset diabetics. The data show that in these diabetics, from the time of diagnosis, the rate of change of lenticular biometry per year increases markedly. Other subject features (sex, daily insulin dose,

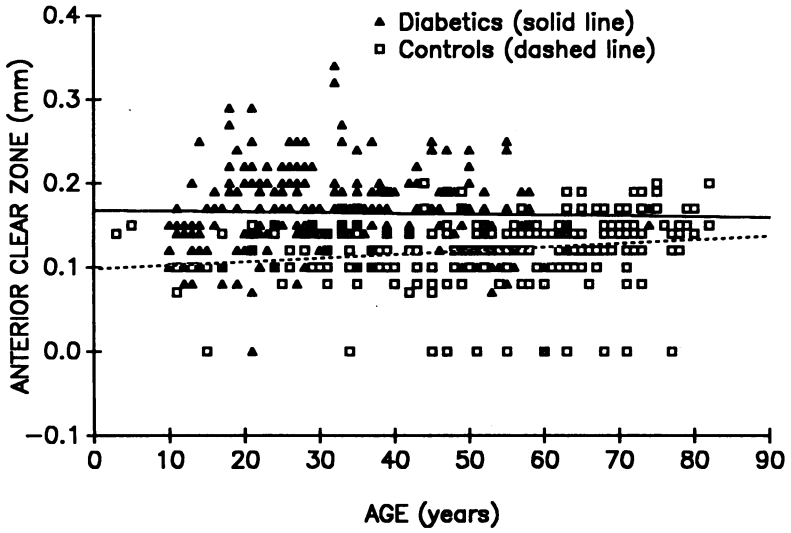

Figure 5 Plot of anterior clear zone thickness of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

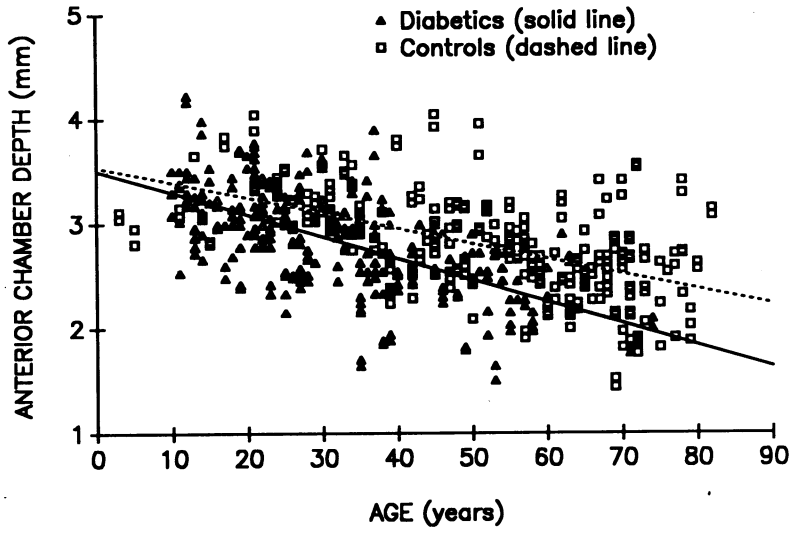

Figure 6 Plot of axial anterior chamber depth of the eye in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

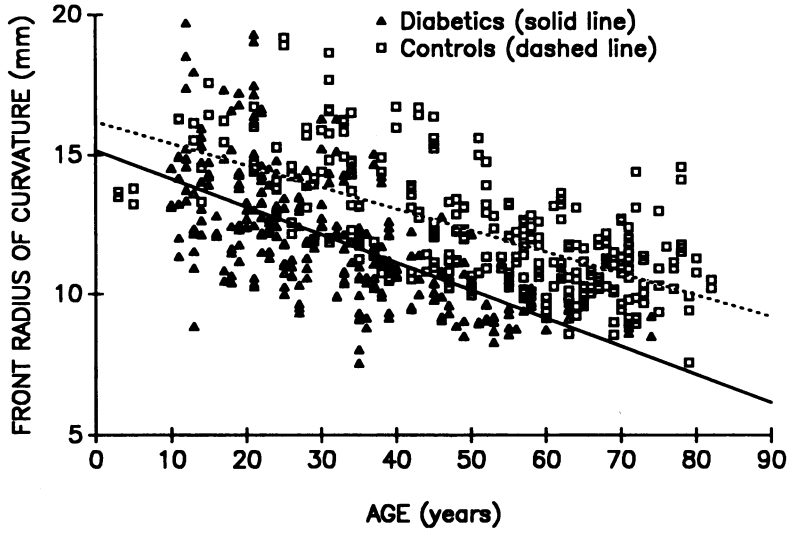

Figure 7 Plot of front radius of curvature of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

and presence of diabetic retinopathy) were of variable importance.

The anterior clear zone is of special interest because it behaves independently of the other zones of the lens. This zone has attracted attention in health[32] and disease[33], being reduced in cataractous lenses[22 23] and increased in lenses of diabetics.[7 8] In the present work the finding of an increased anterior clear zone thickness in diabetes is confirmed, though no relationship with duration has been found. This zone appears to represent a phase in the maturation of young cortical fibres, which sink through it into the deeper cortex as they mature. It has been suggested that the size of this zone reflects the rate of growth of the lens at any particular time.[33] If maturation takes a fixed period, then in a situation of accelerated 'growth' more (or larger) fibres would be in this phase of maturation, and the zone would therefore become wider. The converse would apply in lenses where growth was slowed or halted, when the zone could be expected to shrink or even disappear completely. Brown and Tripathi[22] have shown that the clear zone is reduced or absent in lenses with cataracts, posterior subcapsular cataracts in particular, and further that reduction of the clear zone is associated with a 'small for age' axial lens size. Perkins[23] has corroborated these findings by a simple optical method, and has shown that lenses with early cortical and posterior subcapsular cataracts have reduced overall anteroposterior thickness, and that 60% of early cataracts of all types have a deficient anterior clear zone.

The changes in lens dimensions in diabetes may result from an abnormality in the growth of the lens. From the mechanical point of view three possible explanations exist in relation to altered growth characteristics. The rate of new fibre formation might be increased, with more maturing fibres in the anterior clear zone, and more mature fibres making up the increased bulk of the lens. This 'hyperplastic' model would fit with the findings in the present work, in that the dimensional changes as well as the effect of diabetic duration are natural consequences of such a model. Alternatively the number of new fibres produced might be normal, with individual fibres being increased in size. This 'hypertrophic' model could explain the dimensional changes and duration related effects equally well. The hypertrophic change might be limited to the metabolically active superficial nucleated fibres, which would explain the observed events, with hypertrophic fibres, once enlarged, remaining so. A combination of the above two mechanisms might also exist, and there is evidence that cell size and DNA synthesis can be independently regulated by appropriate combinations of cellular growth factors and growth inhibitors.[34] The third possibility in relation to altered 'lens growth' is a reduction in central compaction of mature lens fibres. There may be some support for this notion in the fact that the ratio of the slopes for the effects of duration and age is the highest for nuclear size (Table 3). This may imply less efficient central fibre packing in diabetes. Brown *et al*[35] could not demonstrate any statistically significant difference in superficial cortical fibre size between diabetics and

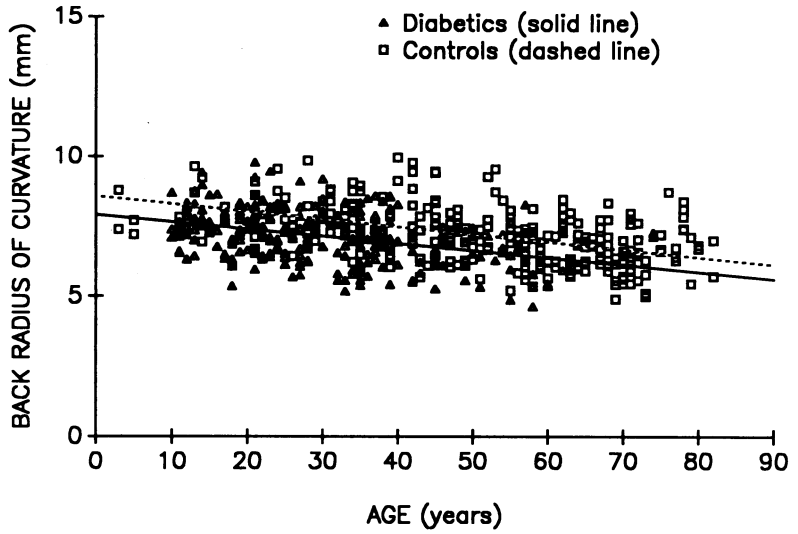

Figure 8 Plot of back radius of curvature of the lens in mm units derived from image analysis of Scheimpflug photographs, against age in years. Separate linear regression lines for diabetics and controls.

non-diabetics, though the numbers of diabetics in this study were small and it is possible that a moderate to small difference may have been missed.

Animal studies have shown that the lenticular epithelium can be stimulated by a number of biological substances. Mitosis can be reinitiated in the epithelium of hypophysectomised frogs by insulin, growth hormone, prolactin and triiodothyronine.[36-38] In the rabbit lens insulin, insulin-like growth factors (IGF 1 and 2), and epidermal growth factor (EGF) can stimulate lens epithelial mitosis in serum free culture medium.[39 40] Fibroblast growth factors (basic and acidic FGF) are both mitogenic and capable of inducing changes in cell culture which are characteristic of fibre differentiation in rat lens epithelial explants.[41 42] Several of these growth factors are known to exist in the ocular tissues. Thus eye-derived growth factors (1 and 2) and retina-derived (endothelial cell) growth factors (β and α) are synonymous with fibroblast growth factors (basic and acidic), and angiogenic factor derived from the retina (retina-derived endothelial growth factor) may also be synonymous with a fibroblast growth factor,[42] though this is disputed.[43 44] Lentropin, derived from vitreous humour, has been identified as an insulin-like growth factor which is capable of initiating fibre differentiation in lens epithelial explants from chick embryos.[45] Modulation of the effects of these growth factors by the plasma membrane Na^+H^+ exchanger (via intracellular pH) may play a part.[46] The above suggests that there are multiple regulatory peptides capable of influencing the mitotic activity of the lenticular epithelium, some of which are structurally similar to insulin, with insulin itself having mitogenic properties. Insulin can also produce a hypertrophic cellular response without stimulation of DNA synthesis.[34].

There is general agreement that growth hormone (GH) is raised in human diabetes.[47] No consensus exists with regard to IGF 1, however, with levels having been reported which are raised, normal, or reduced in diabetics compared with controls.[48] Raised IGF 1 has been associated with the existence of retinopathy,[49] though this association was not found when an adjustment for the presence of proteinuria was made.[48] In the present work an association between retinopathy and increased anterior clear zone thickness, nuclear size, and steeper curvatures was found (renal status not accounted for). A retina-derived growth factor (which may be raised in eyes with retinopathy) may play a part in this association. Recent work indicates that non-diabetic renal transplant patients have increased anteroposterior lens thickness.[50]

The increased size of the anterior clear zone of the lens in early-onset diabetes is associated in the present study with increased daily insulin dose. Insulin is known to have a mitogenic effect on the lenticular epithelium,[39 40] and it can also induce hypertrophy in an epithelial tissue.[34] The possibility exists that the above association could be significant in terms of a causal role for isulin in stimulating lens growth. In individual diabetic patients the insulin dose would vary from time to time, so the prevailing dose at the time of lens photography may not represent a composite statement about insulin dose covering the entire duration of the diabetic state. On the other hand the prevailing insulin dose may be more relevant to the thickness of the anterior clear zone. Too high insulin dosage or high pulses of insulin associated with insulin injections may be relevant in this regard.[51] From the present data there is no way of distinguishing between changes resultant on the effects of 'worse diabetes' (requiring more insulin), and the possible effects of the insulin itself. The association between increased daily

TABLE 2 *Summary of p values from analysis of lens dimensions in early-onset diabetes and controls (clear lenses)*

	Lens	*Cortex*	*Nucleus*	*ACZ*	*AC*	*FR*	*BK*
All subjects (n=306)							
Age	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$	0·00037	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$
Status	$<10^{-6}$	$<10^{-6}$	0·00002	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$
Age.Sta	0·00008	0·0021	NS	NS	0·021	NS	NS
Sex	NS	0·0010	0·00061	NS	0·017	NS	NS
Early-onset diabetes (n=153)							
Age	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$	NS	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$
DUR	$<10^{-6}$	0·000002	0·0049	NS	$<10^{-6}$	$<10^{-6}$	0·00002
Sex	NS	0·0070	NS	NS	NS	NS	NS
INS	NS	NS	0·0057	0·045	NS	NS	NS
BGR	NS	NS	0·045	0·0032	NS	0·047	NS
PLR	NS	NS	NS	0·016	NS	NS	0·034
Controls (n=153)							
Age	$<10^{-6}$	$<10^{-6}$	0·00006	0·010	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$
Sex	NS	0·011	0·0012	NS	NS	NS	NS

AC=anterior chamber depth. ACZ=anterior clear zone thickness of lens. FR=front radius of curvature of lens. BK=back radius of curvature of lens. STA=diabetic or non-diabetic status. DUR=diabetic duration. INS=daily insulin dose. BGR=background retinopathy. PLR=proliferative retinopathy.

TABLE 3 *Summary of slopes for age and diabetic duration from multiple linear regression analysis of lens dimensions in early-onset diabetes and controls (clear lenses)*

	Lens	*Cortex*	*Nucleus*	*AC*	*FR*	*BK*
Controls (n=153)						
Age slope	+0·025	+0·022	+0·0029	−0·014	−0·077	−0·027
p	$<10^{-6}$	$<10^{-6}$	0·00006	$<10^{-6}$	$<10^{-6}$	$<10^{-6}$
Early-onset diabetes (n=153)						
DUR Slope	+0·017	+0·013	+0·0035	−0·014	−0·068	−0·014
p	$<10^{-6}$	0·000002	0·0049	$<10^{-6}$	$<10^{-6}$	0·00002
Slope ratio (DUR/age)	0·68	0·59	1·21	1·02	0·88	0·52

p=Probability. DUR=diabetic duration. AC=anterior chamber depth. FR=front radius of curvature of lens. BK=back radius of curvature of lens. The slopes for age from the control groups were imposed upon the diabetic groups in order to avoid unwanted distortion of the age and duration slopes due to the effects of partially correlated variables.

insulin dose and increased nuclear thickness is difficult to interpret.

Extracellular overhydration of the lens as a whole (unless progressive with years of diabetes) cannot easily explain the powerful effect of duration found in the present study. Simple osmotic events related to the polyol pathway[52 53] therefore seem an unlikely explanation. Overhydration at the cellular level, however, remains a possible cause of the biometric changes. Cellular overhydration of metabolically active recently formed fibres only would fit with the 'hypertrophic model', and could satisfactorily explain a duration effect. A number of mechanisms are available by which cellular overhydration could come about. Abnormally functioning membrane pumps might be involved, with damage to Na^+K^+ ATPase by non-enzymatic glycosylation[54] or oxidation[55] possibly playing a role. (Diabetics may be at increased risk of damage by oxidation from autooxidation of monosaccharides[56 57] or depletion of glutathione.[58 59]) Other membrane pumps could be similarly damaged in the diabetic. Thus, not only NA^+K^+ ATPase but also Ca^{++} ATPase and the Na^+H^+ exchanger might be affected. Malfunction of Na^+K^+ ATPase and the Na^+H^+ exchanger could affect cellular hydration and fibre size in keeping with the 'hypertrophic model,' while malfunction of the Na^+H^+ exchanger could also have an effect (by modulation of growth factors) on the mitotic activity of the epithelium.[46 60] The present data do not allow a distinction to be drawn between an abnormality of lens growth and an abnormality of cellular hydration.

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