Lens thickness and insulin dependent diabetes mellitus: a population based twin study

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Abstract

Aim—To investigate the relation between lens thickness and duration of insulin dependent diabetes mellitus (IDDM).

Methods—From the new population based Danish twin register, containing 20 888 twin pairs born between 1953 and 1982 (inclusive), all twin pairs having one or both partners affected with IDDM were searched. Among the 45 twin pairs available for clinical eye examination there were 15 monozygotic pairs, 14 dizygotic pairs of same sex, and 16 dizygotic pairs of opposite sex. Lens thickness was measured by ultrasonography. Using a twin control design, the relation between lens thickness and duration of IDDM was assessed by estimating the correlation between the intrapair difference in lens thickness and the intrapair difference in diabetes duration.

Results—In monozygotic twin pairs a statistically highly significant correlation between duration of diabetes and lens thickness was found (right eye: \( r=0.58 \), \( p<0.0001 \); left eye: \( r=0.58 \), \( p<0.0001 \)). In dizygotic twin pairs of the same sex the correlations were \( r=0.45 \) (p=0.029) and \( r=0.53 \) (p=0.053) for right eye and left eye, respectively. For dizygotic twin pairs of opposite sex the correlations were \( r=0.45 \) (p=0.025) and \( r=0.35 \) (p=0.005) for right eye and left eye, respectively. The slope in regression analysis were similar for monozygotic twin pairs (0.025, common for both eyes) and dizygotic twin pairs grouped (0.024, common for both eyes). Conclusions—There is a statistically significant positive correlation between duration of IDDM and lens thickness, as assessed by the twin control method. The higher correlation in monozygotic twins compared with dizygotic twins suggests that genetic factors play an additional role in the determination of lens thickness. The similar slopes in regression analysis indicate that the effect of diabetes duration on lens thickness is independent of zygosity.

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The genetic influence on refraction and its components has been investigated previously in twin studies.\(^1\)–\(^5\) Refraction is also influenced by environmental factors and disease conditions.\(^6\)\(^7\) Thus, diabetes mellitus may affect refraction with short term fluctuations and more permanent alterations. The generally accepted view is that short term fluctuations alter the refraction of the lens, primarily by alterations in osmotic pressure caused by changes in the blood glucose level. There is no general agreement regarding the direction of these refractive changes.\(^8\) It has been suggested that there is a higher degree of myopia, when there is a high blood glucose level, and a hyperopic shift when the blood glucose level normalises.\(^9\)\(^10\) Other studies, however, suggest alterations in a hyperopic direction at high blood glucose levels.\(^11\)\(^12\) Furthermore, some investigations have shown an increased prevalence of low degree myopia among diabetic patients.\(^13\)\(^14\)

The lens is a major modifiable determinant of refraction. Several reports have shown increased lens thickness in diabetic patients.\(^15\)–\(^18\) Since lens thickness increases with age, it is difficult to separate the effect of diabetes and, particularly, diabetes duration from the effect of increasing age.

Investigations in twins offer unique opportunities for eliminating the effects of age and other confounding factors in studies of the association between diabetes duration and lens thickness. Partners of monozygotic (MZ) twin pairs are genetically identical and matched for age and most environmental influences that determine growth and development. Partners of dizygotic (DZ) twin pairs have the same features, except for sharing only 50% of their genes on average. The twin control method utilises intrapair differences in exposures (diabetes duration) and outcomes (lens thickness) to eliminate confounding factors in the assessment of a possible association between exposure and outcome.

We here report the results of a twin control study of the association between duration of IDDM and lens thickness. The twin pairs have been ascertained from the new part of the Danish twin register\(^19\) as part of a larger twin study on IDDM.\(^20\)

Material and methods

TWIN SAMPLE

The new part of the Danish twin register includes 20 888 twin pairs, born in Denmark 1953–82 (inclusive). It has been established on the basis of the Danish Civil Registration System and is considered a representative sample comprising 74.4% of all Danish twin pairs born 1953–67, and virtually complete (97.4%) concerning twin pairs born 1968–82.\(^19\) Among 19 180 twin pairs responding to a questionnaire survey on IDDM,\(^20\) 102 pairs had one or both partners affected with IDDM. Of these, 54 pairs were not available...
for further examination. Among the remaining 48 pairs, 45 were included for analysis in the present study (Table 1).

The diagnosis of IDDM has been based on internationally accepted clinical criteria combined with no or low fasting C peptide. Onset of diabetes was defined as the month and year when the first insulin injection was given. The zygosity diagnosis was established on 11 blood and enzyme type systems, providing a more than 99% reliable classification.

<table>
<thead>
<tr>
<th>Twin pair No</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration of IDDM (years)</th>
<th>Difference in lens thickness (mm)</th>
<th>Differences in lens thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14:8</td>
<td>M</td>
<td>0 -</td>
<td>0.3</td>
<td>4.36 - 3.52 - 3.49 - 3.62  -0.03 -0.10</td>
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<tr>
<td>2</td>
<td>39:7</td>
<td>M</td>
<td>17.6 - 16.9</td>
<td>1.0</td>
<td>3.72 - 3.72 - 3.72 - 3.72 -0.12 -0.07</td>
</tr>
<tr>
<td>3</td>
<td>25:3</td>
<td>M</td>
<td>3 -</td>
<td>3.0</td>
<td>4.04 - 4.14 - 4.02 - 4.04 -0.02 -0.10</td>
</tr>
<tr>
<td>4</td>
<td>36;8</td>
<td>M</td>
<td>3.4 - 0.3</td>
<td>3.1</td>
<td>4.16 - 4.27 - 4.08 - 4.03 -0.04 -0.24</td>
</tr>
<tr>
<td>5</td>
<td>24:5</td>
<td>F</td>
<td>3.4 - 3.4</td>
<td>3.4</td>
<td>3.05 - 3.05 - 3.72 - 3.72 -0.13 -0.02</td>
</tr>
<tr>
<td>6</td>
<td>31:7</td>
<td>M</td>
<td>18.9 - 15.1</td>
<td>3.8</td>
<td>4.10 - 4.29 - 4.03 - 4.09 -0.07 -0.20</td>
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<td>7</td>
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<td>M</td>
<td>13.9 - 9.1</td>
<td>4.8</td>
<td>3.75 - 3.75 - 3.82 - 3.74 -0.07 -0.01</td>
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<td>5 -</td>
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<td>3.73 - 3.66 - 3.73 - 3.70 -0.10 -0.04</td>
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<td>30:1</td>
<td>F</td>
<td>6 -</td>
<td>5.0</td>
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<td>M</td>
<td>13.8 - 9.8</td>
<td>5.0</td>
<td>3.64 - 3.65 - 3.70 - 3.70 -0.04 -0.01</td>
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<td>M</td>
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<td>13</td>
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<td>F</td>
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<td>10.7</td>
<td>3.74 - 3.77 - 3.74 - 3.74 -0.22 -0.22</td>
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<td>30.1 - 30.1</td>
<td>30.1</td>
<td>4.41 - 4.26 - 3.46 - 3.46 -0.95 -0.80</td>
</tr>
</tbody>
</table>

**Table 2: Age, sex, duration of diabetes, and intrapair difference in diabetic duration, as well as lens thickness and intrapair difference in lens thickness, for all the twins in analysis**

**MEASUREMENT OF LENS THICKNESS**

Lens thickness was measured by ultrasonography on a Teknar Ophthalmic Auto A Scan. All lenses were checked for a cataract by slit-lamp examination in mydriasis, and photographs of the lenses in retroillumination were taken for registration of lens opacities. There was no actual cataract formation in any of the patients. Ten of the diabetic twins and two of the non-diabetic twins had a few vacuoles peripherally in the lens in both eyes. Speed of ultrasound was set to 1550 m/s for aqueous and vitreous, and 1641 m/s for the lens. The ultrasound device was calibrated on a special probe and several times during the investigation period. All measurements were made on the same device and by the same trained ophthalmologist (NL). Only measurements with narrow and well defined echoes of equal height from anterior and posterior lens surfaces and with no internal spikes, as well as well defined echo from the vitreoretinal interface were accepted to obtain correct measurement of lens thickness and to ensure correct alignment and axial direction of the measurements. The mean of three measurements was taken, and all measurements were made 30 minutes after cyclopellagra by installation of one drop of cyclopentolate hydrochloride 1% and one drop of phenylephrine hydrochloride 10% in each eye twice, with an interval of 10 minutes.

**ANALYSIS OF DATA**

Within twin pairs, the partner with longer duration of IDDM was labelled 'A', and the partner with shorter duration or no IDDM was labelled 'B'. Unaffected twins were assigned the value of 0-0 years of IDDM duration. Within each twin pair the difference in IDDM duration was calculated as the difference in duration between twin 'A' and twin 'B' (A-B). The corresponding intrapair differences in lens thickness have been calculated for right and left eye separately. Standard procedures for regression analysis have been employed to obtain estimates of the correlation coefficients and regression coefficients (slopes) for right and left eye independently, and with MZ twin pairs, DZ twin pairs of same sex (ss), and of opposite sex (os). The statistical test of differences between two correlation and regression coefficients was performed as suggested in Documenta Geigy.21

**Results**

Measurements of lens thickness were obtained from 92 right and 91 left eyes. One pair of MZ twins did not want to have their pupils dilated, and one 12-year-old MZ twin and one 15-year-old twin did not cooperate with lens thickness measurements. Further, one DZs twin had an aphakic left eye due to ocular trauma.

Complete ultrasonic measurements of lens thickness for both eyes of both cotwins were thus obtained in 15 MZ pairs, 14 DZs pairs, and 15 DZs pairs. In addition, measurements

**Table 1: Summary of study material**

- Twins born 1953-82 registered in the new Danish twin register: 20888
- Twins with IDDM identified by questionnaire: 102
- One or both unwilling to participate: 39
- One twin partner had died: 7
- One twin partner had emigrated: 5
- Non-response in one twin partner: 5
- Twins investigated: 48
- Did not want pupils dilated: 1
- Did not cooperate to ultrasonic measurements: 0
- Twins pairs in analysis: 45

*No data, due to aphakia.

A=A twins with longest duration of IDDM (years); B=twins with shortest duration of IDDM (years); or no IDDM (·); A-B=intrapair difference in diabetic duration (years); R(A)=lens thickness (mm), right eye, twin A; L(A)=lens thickness (mm), left eye, twin A; R(B)=lens thickness (mm), right eye, twin B; L(B)=lens thickness (mm), left eye; Lrdif=intrapair difference in lens thickness (mm), left eye; Ldif=intrapair difference in lens thickness (mm), left eye.
The intrapair differences in duration of diabetes (A–B) as well as the corresponding intrapair differences in lens thickness for right (Rdiff) and left (Ldiff) eye are also shown in Table 2. In the group of DZss twins, where there were no concordant pairs, the intrapair difference in diabetic duration is identical to the diabetic duration for the cotwin with diabetes. In order to estimate the influence of diabetes duration on lens thickness, the intrapair differences were plotted for each of the three groups shown in Figure 1. Regression lines for left and right eye are shown separately.

The slopes and intercepts for the regression analysis, with 95% confidence intervals, as well as correlation coefficients with p values, are shown in Table 3. There is a clear positive relation between increasing duration of diabetes and lens thickness, especially among the MZ twins, where the slopes for right and left eyes are almost identical, and highly statistically significantly different from zero. In the DZss and DZos groups the slopes vary more, and the lower limits for 95% confidence intervals are close to zero, and one of them not statistically significantly positive (DZss left eye). After testing that the slopes, intercepts, and correlation coefficients for DZss and DZos, right and left eyes respectively, are not statistically significantly different, we have calculated the combined values (DZ) shown in Table 3. The intercepts are not statistically significantly different from zero in any of the groups, implying that it seems reasonable to look at influence of IDDM duration on lens thickness only from the clinical onset of IDDM. The correlation coefficients are highly statistically significant in the MZ group, and significantly higher than the correlation coefficients in the DZ group (p=0.034 and p=0.041, for right and left eye respectively).

**Discussion**

Our study has confirmed previous studies reporting a positive association between diabetes and lens thickness. The estimated correlations in our analyses seem to be higher than previously reported. This may be due to the application of the twin control design, by which the influence of confounding factors has been eliminated, or at least reduced. Our sample of twin pairs is small, but considered to be representative. It is particularly important that the distribution between MZ, DZss, and DZos twins is roughly equal, which is expected according to principles of population genetics.

The validity of assigning the value of 0 to the diabetes duration in unaffected twins relies upon the assumption that the effect of IDDM on lens thickness is exerted only from the clinical onset of IDDM. This seems to be a realistic assumption because of the belief that the increased lens thickness in IDDM patients is caused by the effect of hyperglycaemia which first manifests immediately preceding clinical onset in most IDDM patients. The fact that all estimated intercepts did not differ statistically

![Figure 1 Scatterplot of intrapair difference in insulin dependent diabetes mellitus (IDDM) duration versus intrapair difference in lens thickness. (A) Monozygotic twin pairs; (B) dizygotic twin pairs of same sex; (C) dizygotic twin pairs of opposite sex.](image)
significantly from 0.0 provides further support for the validity of the assumption.

The high degree of correlation found in our study may partly be explained by a few outlying values. Therefore, we have repeated the analyses after exclusion of such outliers. The point estimates of the slopes were only slightly changed and maintained the level of statistical significance; however, the difference in the correlation coefficients between MZ and the combined DZ groups did not reach statistical significance, probably due to the small sample size. Therefore, the exclusion of outliers did not change our conclusion qualitatively. The almost similar slopes in the group of MZ twins compared with the group of DZ pairs suggest that the effect of IDDM duration on lens thickness is similar for MZ twins and DZ twins, thus independent of genetic factors. The higher correlation coefficients in MZ twin pairs compared with DZ twin pairs suggest that, when adjusting for the effect of IDDM, there is an additional genetic component that determines lens thickness. Since there were no statistically significant differences in correlation coefficients between the DZ groups of same sex and opposite sex, there seems to be no influence of sex on the effect of diabetes on lens thickness. The design of the present study does not permit further analyses and conclusions on this aspect, since this requires investigation on a representative sample of non-diabetic MZ and DZ pairs.

Since the twin pairs included in our study are young and affected exclusively with IDDM we cannot generalise our findings from IDDM to non-insulin dependent diabetes mellitus (NIDDM). Previous studies have demonstrated that the type of diabetes was of importance for lens thickness. In IDDM a significant relation between duration of diabetes and lens thickness was found, whereas in NIDDM no relation between lens thickness and duration of diabetes was found.18 The duration effect in IDDM on lens thickness could be caused by accumulated damage by oxidation or non-enzymatic glycosylation involved in the regulatory mechanisms in the lens membrane.22 There is also evidence that different insulin-like growth factors could stimulate lens fibroblasts.24-26 Further, it has been speculated that retina derived growth factors may be responsible for lens hyperplasia and hypertrophy.27 This also agrees with the finding that lens thickness is associated with proliferative diabetic retinopathy.27 Simple osmotic swelling of the lens may be responsible for the short term alterations in refraction seen with high blood glucose levels where part of the glucose is transformed via the sorbitol pathway, but does not explain the strong relation that we found between duration of IDDM and lens thickness. In our study of young diabetic patients with generally short duration of diabetes only two developed proliferative retinopathy; consequently we could not investigate the possible association between IDDM duration, biometry of the lens, and diabetic retinopathy. We intend, however, in future follow up studies of the diabetic twin pairs in the Danish twin register to throw further light on these aspects.

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