Retinal tissue thickness in type 1 and type 2 diabetes

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Background: The objective was to investigate full retinal and inner retinal thickness in individuals with type 1 and type 2 diabetes.
Methods: Eighty-four individuals with type 1 diabetes (T1DM), 67 individuals with type 2 diabetes (T2DM) and 42 non-diabetic individuals (control group) were enrolled. Participants underwent full retinal thickness evaluation in the central retinal, parafoveal and perifoveal zones and in the retinal nerve fibre layer (RNFL) and ganglion cell complex (GCC), using spectral domain optical coherence tomography. As a preliminary step, the key variables of interest – age, sex, diabetic retinopathy (DR), duration of diabetes and HbA_{1c} levels – were analysed and compared between the three groups. Full retinal thickness, RNFL and GCC thicknesses were also compared between the groups. The relationship between the type of diabetes and retinal tissue thickness was explored, adjusting for the five potential confounders.
Results: Compared to individuals with T1DM, individuals with T2DM had significantly reduced full retinal thickness in the parafovea and perifovea and reduced RNFL and GCC thickness. The mean differences were six ($p = 0.020$), seven ($p = 0.008$), six ($p = 0.021$) and four micrometres ($p = 0.013$) for the parafovea, perifovea, RNFL and GCC thicknesses, respectively. Thicknesses within the central zone ($p = 0.018$) and at the parafovea ($p = 0.007$) were significantly reduced in T2DM when compared to the control group. After adjusting for age, sex, diabetic retinopathy, duration of diabetes and HbA_{1c} levels, the relationship between type of diabetes and retinal tissue thickness was not statistically significant ($p > 0.056$).
Conclusion: Retinal tissue thickness is not significantly different between type 1 and type 2 diabetes, when adjusted for age, sex, diabetic retinopathy, duration of diabetes and HbA_{1c} levels.

Key words: diabetic retinopathy, ganglion cell complex, retinal nerve fibre layer, retinal thickness, type 1 diabetes, type 2 diabetes

Diabetes is a multi-system disorder with a world-wide prevalence of 2.8 per cent (171 million) in the year 2000 that is predicted to rise to 4.4 per cent (366 million) in the year 2030.[1] Type 1 diabetes (T1DM) results from an autoimmune process that destroys the pancreatic beta cells ultimately leading to absolute insulin deficiency.[2] Type 2 diabetes (T2DM) is characterised by insulin resistance or impaired insulin secretion or both.

In humans, differences between T1DM and T2DM have been observed in ocular structure and visual function. Individuals with T1DM have cataracts with vacuoles and snow-flake-like opacities with light-scattering properties, whereas those with T2DM have cataracts that is similar in appearance to that of age-related cataracts.[3,4] In a study that examined retinal function and structure using multifocal electroretinography (mfERG), optical coherence tomography and retinal vessel calibre measurement in adolescents with T1DM and T2DM, the T2DM group had significantly delayed implicit time, abnormal mfERG amplitude and significantly reduced retinal thickness in comparison to that of the control group.[5] A significantly larger venular diameter was noted in T2DM when compared to the T1DM group.[5]

The retinal nerve fibre layer thickness has been reported to be inversely related to the duration of diabetes.[6] Since a longer duration of diabetes may be more commonly observed in individuals with T1DM than those with T2DM, it is likely that the neural tissue thickness in T1DM may be relatively more compromised compared with that of T2DM. Considering these differences reported in the literature, a key question is whether the retinal tissue thickness is different in T1DM and T2DM.

Investigation of this research question is challenging because of a number of potentially confounding factors – namely, age, sex, diabetic retinopathy, duration of diabetes and HbA_{1c} levels. Retinal thickness is reported to be compromised with increasing age,[7–9] higher degrees of myopia[9] and in women compared to men.[10,11] Similarly, the inner retinal thickness is reported to be compromised with age,[12,13] longer axial length[12,13] and in women compared to men.[13] Retinal tissue thickness is reported to be compromised in the presence of diabetic retinopathy[14–16] and is inversely correlated with longer duration of diabetes and HbA_{1c} levels[17]. Therefore, it is essential to account for the above factors, when examining the retinal tissue thickness.

We examined the full retinal and the inner retinal thicknesses in T1DM and T2DM and

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went on to further examine the relationship between the type of diabetes and retinal tissue thickness, taking into account the potential confounders - namely, age, sex, diabetic retinopathy, duration of diabetes and HbA_{1c} levels.

METHODS

Ethics approval was obtained from the Queensland University of Technology and Princess Alexandra Hospital Human Research Ethics Committees and the study adhered to the Tenets of Declaration of Helsinki as revised in 2008. One hundred and fifty-one people with diabetes (84 with type 1 and 67 with type 2 diabetes) and 42 people without diabetes (controls) were enrolled. Participants were recruited from the Centre for Diabetes and Endocrine Research at Princess Alexandria Hospital in Brisbane and from the broader Brisbane community.

Written informed consent was provided by all participants prior to involvement. The type of diabetes was self-reported or ascertained from general practitioner reports. For individuals identifying as having diabetes by self-report, the diagnosis was verified from their medical practitioner reports. Information about the duration of diabetes was by self-report based on the date of detection by a medical practitioner.

Ophthalmic assessment

Participants underwent visual acuity assessment, slitlamp biomicroscopy, intraocular pressure measurement and three-field fundus photography. Individuals with visual acuity 6/9 or better, spherical refractive error within 6.00 D sphere and astigmatism within 3.00 D cylinder were eligible. Individuals with cataract that prevented a good view of the posterior segment with fundus photography or optical coherence tomography, history of retinal photocoagulation, unilateral or bilateral diagnosis or reasonable suspicion of glaucoma from optic nerve head appearance, unilateral or bilateral evidence or known history of intra-ocular pressure above 22 mmHg or history of any neurological condition that might affect retinal nerve fibres (for example, Parkinson's disease[18] or multiple sclerosis[19]) were excluded from participating in the study.

Participants who fit the eligibility criteria underwent testing in the eye on the side of the dominant hand unless contraindicated by the above exclusion criteria, in which case, the eye on the non-dominant side was tested.

For the control group, individuals identifying as 'without diabetes' underwent fasting plasma glucose testing and were included, only if the fasting levels were in the normal range per our local pathology provider. Anyone with a failed fasting plasma test underwent an oral glucose tolerance test. Although the protocol allowed impaired fasting glucose, all individuals in the control group had fasting glucose in the normal range.

Diabetic retinopathy was graded according to the Early Treatment Diabetic Retinopathy Study scale[20] by an ophthalmologist, who was masked to the details of the participant.

Optical coherence tomography (RTVue, Model RT-100, ver.4.0, Fremont, California, USA) was used to examine full retinal and inner retinal thickness. Full retinal thickness is measured along 12 radial lines, each six millimetres long, centred at the fovea and averaged at three regions. The outermost region is the perifoveal zone that has an inner circle of diameter three millimetres and an outer circle of diameter six millimetres. The parafoveal zone has an inner circle of diameter of one millimetre and an outer circle of diameter three millimetres. The innermost zone is that within the circle of diameter one millimetre and includes the fovea. Figure 1 illustrates the examined retinal zones.

Retinal nerve fibre layer (RNFL) thickness is measured between the inner plexiform layer and the nerve fibre layer along a circle of 3.45 millimetres diameter centred at the optic nerve head. The ganglion cell complex, which is a composite of the inner plexiform layer, ganglion cell layer and nerve fibre layer, is measured along 15 vertical lines and one horizontal line, covering a zone of seven by seven millimetres that is centred at one millimetre temporal to fovea. Figure 2 illustrates the retinal nerve fibre layer and ganglion cell complex regions.

General clinical variables

All participants underwent tests that assessed the following general clinical measures: HbA_{1c} (per cent), body mass index (BMI), systolic and diastolic blood pressure (BP) and total cholesterol levels.

Data analysis

Comparisons between the three groups (T1DM, T2DM and controls) were made in respect of the following three data sets:

1. the five key variables of interest, namely age, sex, diabetic retinopathy, duration of diabetes and HbA_{1c} levels
2. general clinical variables and

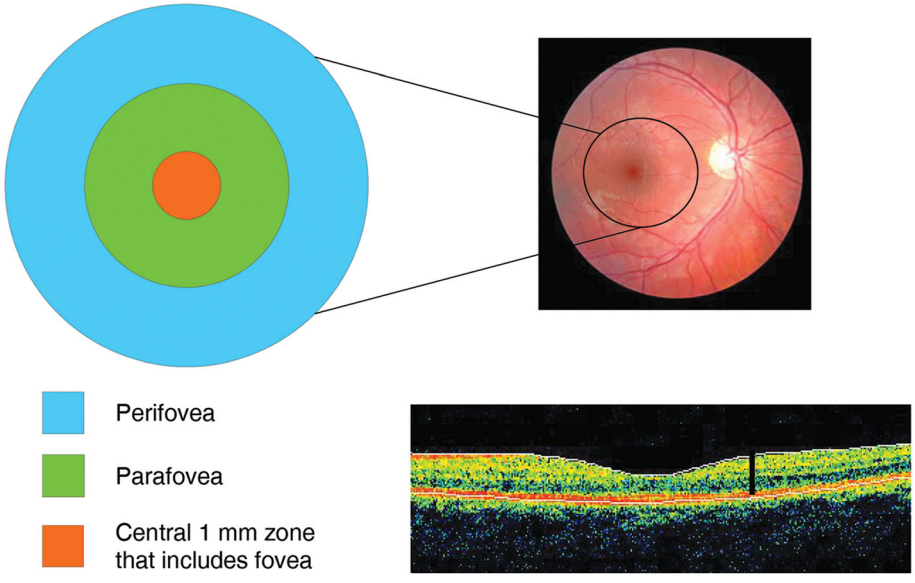

Figure 1. Retinal thickness is measured from the internal limiting membrane to the inner segment – outer segment junction of the photoreceptors (indicated by the black line in the lower right hand image), at three concentric zones. The central zone measured within a circle of one millimetre diameter centred at the fovea; the parafovea has an inner circle of diameter of one millimetre and outer circle diameter of three millimetres and the perifovea that has an inner circle of diameter of three millimetres and outer circle of diameter of six millimetres.

3. full retinal and inner retinal tissue thicknesses. The relationship between type of diabetes and the retinal tissue thickness was explored taking into account the above five variables.

Statistical analysis

The normality of data distribution was assessed using a Kolmogorov–Smirnov test. A Chi-square test was applied for comparing proportions. Predictive Analytics SoftWare (PASW) version 21.0 (IBM, Armonk, New York, USA) was used for analyses. A p-value of less than 0.05 was considered statistically significant and significant p-values were adjusted for multiple comparisons.

To examine the relationship between the type of diabetes and retinal tissue thickness, a univariate general linear model was used. The thicknesses in the central zone, parafovea, perifovea, RNFL and ganglion cell complex were entered as dependent variables and analysed in separate regression models. The type of diabetes, presence of diabetic retinopathy and sex of the individuals were coded and entered as factors. Age, duration of diabetes and HbA_{1c} levels were entered as covariates in each of the regression models. Main effects were assessed for type of diabetes, age, sex, diabetic retinopathy, duration of diabetes and HbA_{1c} levels on the thicknesses of the central zone, parafovea, perifovea, RNFL and ganglion cell complex thicknesses. Interactions were analysed between type of diabetes versus age, diabetic retinopathy and duration of diabetes.

RESULTS

Clinical and metabolic measures

Results for clinical and metabolic measures are presented in Table 1. People with T2DM were older than those with T1DM and the control group (mean difference of six years [$p < 0.001$] and four years [$p = 0.034$], respectively). The mean HbA_{1c} levels were not significantly different between T1DM and T2DM but both the diabetic groups had elevated HbA_{1c} levels (by 2.6 per cent [$p < 0.001$] and 2.4 per cent [$p < 0.001$], respectively) compared with controls.

Forty-six per cent of those with T1DM had diabetic retinopathy compared to 35 per cent among those with T2DM. A chi-square test of independence showed no significant relationship between the type of diabetes and diabetic retinopathy ($\chi^2_{(1, 151)} = 1.725$, $p = 0.189$). There were 53 per cent of males and 64 per cent of males in T1DM and T2DM groups, respectively, but there was no significant relationship between gender and type of diabetes ($p = 0.189$).

Individuals with T1DM had a more prolonged duration of diabetes (mean difference of six years) than the T2DM group ($p < 0.001$).

A summary of the other clinical measures in T1DM, T2DM and controls is presented in Table 1. The body mass index in T2DM was 3.0 kg/m^2 higher than T1DM and 5.0 kg/m^2 higher than the control group ($p < 0.001$ for both). There was no significant difference in total cholesterol levels between the two diabetic groups; however, both groups had lower total cholesterol levels compared to controls (1.7 mmol/L and 0.9 mmol/L, respectively; $p < 0.001$ for all). Systolic and diastolic blood pressures were not significantly different in the three-group comparison.

Retinal tissue thicknesses

Table 2 provides a summary of central zone, parafovea, perifovea, RNFL and ganglion cell complex thicknesses for the three groups. Individuals with T2DM had reduced thickness in the parafovea, perifovea, RNFL and ganglion cell complex compared to those with T1DM; the mean differences were six micrometres ($p = 0.020$), seven micrometres ($p = 0.008$), six micrometres ($p = 0.021$) and four micrometres ($p = 0.013$), respectively. Thickness in the central zone ($p = 0.018$) and parafovea ($p = 0.007$) was reduced in T2DM compared to controls.

The association between the main effects and the interactions between the type of diabetes and a range of variables, namely age, diabetic retinopathy and duration of diabetes is presented in Table 3. Neither HbA_{1c} ($p > 0.555$) nor sex ($p > 0.314$) was significantly related to retinal tissue thickness in these models. The relationship between the type of diabetes and retinal tissue thickness was not statistically significant ($p > 0.056$).

DISCUSSION

Type1 diabetes is characterised by an autoimmune process that destroys the pancreatic beta cells, ultimately leading to absolute insulin deficiency.[2] Type 2 diabetes on the other hand, is characterised by insulin resistance at the level of tissues or impaired insulin secretion or both. Other than the pathophysiological features, differences between T1DM and T2DM have been observed in the morphological appearance of cataracts[3,4] and also in venular diameter.[5] Considering these differences reported in the literature, an interesting question is whether the retinal tissue thickness is different in T1DM and T2DM. Our study sought to explore retinal structural integrity as assessed by full retinal and inner retinal thickness in T1DM and T2DM. Unadjusted thicknesses in the parafovea, perifovea, RNFL and ganglion cell complex are significantly lower in T2DM than T1DM.

In the study by Bronson-Castain and colleagues,[5] a significantly larger venular diameter in T2DM compared to T1DM was

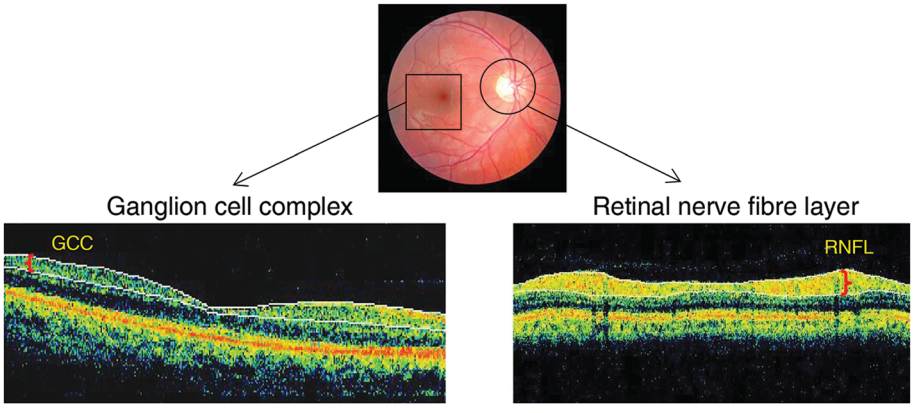

Figure 2. The top picture shows scanned areas for the inner retinal thickness. Bottom left picture shows the ganglion cell complex (GCC) scan. The thickness of the GCC is measured from the inner plexiform layer to the nerve fibre layer at the macula (indicated by the red left brace). Bottom right picture shows retinal nerve fibre layer (RNFL) scan. The RNFL thickness is measured from the inner border of the nerve fibre layer to the outer border of the plexiform layer along a circle of 3.45 millimetres diameter centred at the optic nerve head (indicated by red right brace).

Clinical variables	T1DM (A) Mean ± SD Number Range	T2DM (B) Mean ± SD Number Range	Controls (C) Mean ± SD Number Range	p-value for three-group comparison Post-hoc differences
Age	53.6 ± 9.1	60.4 ± 8.1	55.9 ± 9.6	<0.001
	84	66	42	A, C versus B
	40.1-77.3	41.4-72.1	40.7-72.6	
HbA_{1c} (%)	8.0 ± 1.2	7.5 ± 1.4	5.4 ± 0.3	
	84	66	42	<0.001
	6-13	5-12	5-6	A, B versus C
Duration of diabetes (years)	20 ± 15	14 ± 10		
	84	67		
	1-56	2-64	n/a	<0.001
Diabetic retinopathy n (%)	39 (46%)	24 (35%)	n/a	0.189
Total cholesterol (mmol/L)	4.7 ± 1.0	3.9 ± 0.8	5.6 ± 1.0	
	84	66	42	<0.001
	3.0-8.6	2.6-6.2	4.2-9.2	A, B versus C
Systolic BP (mmHg)	128 ± 16	128 ± 14	126 ± 14	
	84	67	42	0.613
	95-167	87-161	102-163	
Diastolic BP (mmHg)	78 ± 8	75 ± 8	79 ± 9	0.051
	84	67	42	
	53-97	52-91	63-108	
Body mass index (kg/m^2)	28.5 ± 4.8	32.2 ± 6.8	26.9 ± 5.3	<0.001
	84	67	42	A, C versus B
	19.3-47.3	21.1-55.5	19.3-46.9	

T1DM: type 1 diabetes, T2DM: type 2 diabetes, Controls: no diabetes, BP: blood pressure.

Table 1. Clinical variables

observed but the authors found no significant differences in retinal thickness between T1DM and T2DM. We demonstrated differences in structural aspects of retinal layers between T1DM and T2DM, wherein retinal thicknesses at the parafovea, perifovea, the RNFL and ganglion cell complex are reduced in T2DM compared to T1DM; however, after controlling for the effects of age, sex, diabetic retinopathy, duration of diabetes and HbA_{1c} levels, we did not observe statistically significant differences in retinal tissue thickness between T1DM and T2DM.

We observed differences between T1DM and T2DM in certain clinical characteristics, wherein those with T2DM were slightly older than T1DM; however, those with T1DM had a significantly prolonged duration of diabetes than T2DM, an observation that is consistent with the nature of the disease. Therefore, it was deemed important to take into account the potentially confounding effect of these variables in assessing retinal thickness.

After adjusting for the main effects and interactions of the type of diabetes with potential confounders, we did not observe a significant relationship between the type of diabetes and the retinal tissue thickness. This is the first study to investigate the relationship between retinal tissue thickness and type of diabetes, while controlling for the effects of potentially confounding factors.

The T1DM group had a more prolonged duration of diabetes and a slightly higher proportion of individuals with diabetic retinopathy compared with the T2DM group. The T2DM group had higher BMI than the other two groups. These clinical findings are broadly consistent with those reported by Bronson-Castain and colleagues.[5]

With regards to the prevalence of diabetic retinopathy, nearly all individuals with T1DM and over 60 per cent of those with T2DM have some form of retinopathy during the first two decades of diabetes detection.[21] In our study, the proportion of individuals with diabetic retinopathy was 46 per cent in T1DM and 35 per cent in T2DM but the difference was not statistically significant. Duration of diabetes is a strong predictor for the development and progression of diabetic retinopathy.[22] Although in our study those with T1DM had a more prolonged duration of diabetes compared with T2DM, we did not observe significant differences in the prevalence of diabetic retinopathy between these groups, possibly because the two groups differed by a mean diabetes duration of only six years. In addition, duration of diabetes in this work represents duration since detection. Uncertainty

Retinal thickness (μm)	T1DM (A) Mean ± SD Number Range	T2DM (B) Mean ± SD Number Range	Controls (C) Mean ± SD Number Range	p-values for three-group comparison Post-hoc differences
Central 1 mm	249 ± 23 84 140-293	241 ± 24 66 177-289	254 ± 26 42 180-313	0.019 B versus C
Parafovea	311 ± 16 84 259-338	305 ± 16 66 268-342	314 ± 14 42 277-341	0.006 B versus A,C
Perifovea	272 ± 13 84 230-301	265 ± 15 66 201-297	272 ± 13 42 236-301	0.007 A versus B
RNFL	105 ± 10 84 82-132	99 ± 12 67 71-136	102 ± 11 42 74-132	0.026 A versus B
GCC	97 ± 8 84 77-117	93 ± 8 66 71-113	96 ± 7 42 76-108	0.015 A versus B

T1DM: type 1 diabetes, T2DM: type 2 diabetes, Controls: no diabetes, RNFL: retinal nerve fibre layer, GCC: ganglion cell complex.

Table 2. Retinal tissue thickness measures

Interactions between variables	p-values for interactions and main effects at various retinal regions				
	Central 1 mm	Parafovea	Perifovea	RNFL	GCC
Type of diabetes and age	0.927	0.180	0.343	0.243	0.555
Type of diabetes and diabetes duration	0.151	0.440	0.997	0.982	0.740
Type of diabetes and diabetic retinopathy	0.194	0.211	0.255	0.325	0.564
Main effect of the type of diabetes	0.171	0.056	0.075	0.284	0.107

RNFL: retinal nerve fibre layer, GCC: ganglion cell complex.

Table 3. Association of type of diabetes and interaction with key variables at various retinal regions

as to the exact date of onset of diabetes in our cohort is a limiting factor in this work which must be taken into consideration when interpreting the results reported here.

We investigated the influence of diabetic retinopathy as a confounding factor that must be taken into account while examining retinal tissue thickness; however, assessment of retinal tissue thickness in varying severities of diabetic retinopathy was not the primary focus of this work. For this reason, the presence of diabetic retinopathy rather than its severity was included as a categorical variable and was accounted for in the statistical models.

In conclusion, although there were unadjusted differences in retinal tissue thickness between T1DM and T2DM, the differences were not statistically significant after controlling for the effects of potential confounders, namely, age, sex, diabetic retinopathy, duration of diabetes and HbA_{1c} levels.

CONCLUSIONS

Our study has demonstrated no significant differences in structural aspects of retinal layers between T1DM and T2DM, when accounting for age, sex, diabetic retinopathy, duration of diabetes and HbA_{1c} levels.

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