SCIENTIFIC REPORT

Decreased optical coherence tomography-measured pericentral retinal thickness in patients with diabetes mellitus type 1 with minimal diabetic retinopathy

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Aim: A comparison of retinal thickness (RT) measurements with optical coherence tomography (OCT) in patients with type 1 diabetes mellitus (DM) and no or minimal diabetic retinopathy (DR) versus healthy controls.

Methods: Fifty-three patients with type 1 DM with no or minimal DR underwent full ophthalmic examination, fundus photography and OCT. Mean RT measured by OCT was calculated for the central fovea, the fovea, the pericentral and the peripheral area of the macula, and compared to healthy controls.

Results: Mean RT in the pericentral area was lower in patients with minimal DR ($267 \mu\text{m} \pm 20 \mu\text{m}$; $n=23$) compared to healthy controls ($281 \mu\text{m} \pm 13 \mu\text{m}$; $p=0.005$; $n=28$). Mean pericentral RT in patients without DR ($276 \mu\text{m} \pm 14 \mu\text{m}$; $n=30$) was less than pericentral RT in healthy controls, but higher than in patients with minimal DR, without being statistically significant. None of the other regions showed a significant change.

Conclusion: In this study a significantly decreased pericentral RT was measured in patients with minimal DR compared to healthy controls. This could be explained by a loss of intraretinal neural tissue in the earliest stage of DR.

Diabetic retinopathy (DR) is one of the leading causes of blindness in the developed countries, especially in patients between 20 and 60 years of age. Early detection of DR is important to prevent loss of vision in patients with diabetes mellitus (DM). DR classically presents with micro-aneurysms and small haemorrhages in an early stage of the disease, and is detected with slit-lamp biomicroscopy and fundus photography.

Although DR is generally regarded as a vascular disease, several studies have indicated that neural loss may also occur in a very early stage of DR, even before any sign of vasculopathy can be observed.^{1–8} Human^{1–4} and experimental^{1–8} animal studies have shown apoptosis of neural and glial cells in the retina in a very early stage of retinopathy. Functional deficits in patients with DM have been described, such as a disordered multifocal electroretinogram,^{9–14} colour vision disturbances^{15–20} and abnormal microperimetry.^{10 21–23} These abnormalities were present in the earliest stages of DR, even before development of micro-aneurysms or haemorrhages. However, gross neuroglial cell loss, as observed in rodents with experimental DM, has not been confirmed in humans as yet.

A loss of neuroglial tissue should decrease retinal thickness (RT) in the macular area. This effect of neuroglial loss would be most pronounced in the pericentral ring around the fovea, where the neuroglial cell layer is thickest. Optical coherence

tomography (OCT) is the most sensitive, clinically available, non-invasive method to measure RT, able to detect even very small changes.

To investigate whether neuroglial loss is a very early manifestation of DR we used OCT to compare pericentral RT in patients with type 1 DM, with no or minimal DR, to a healthy control group.

MATERIALS AND METHODS

Patients

Patients were recruited from the outpatient clinic of the department of Internal Medicine at the Academic Medical Centre (University Hospital, Amsterdam, the Netherlands) between July 2004 and June 2005 and were asked to participate in an observational cross-sectional study. Ethics Committee approval was obtained and all participants gave written informed consent.

Eligibility criteria included diagnosis of DM type 1 and no or minimal DR, as detected by slit-lamp biomicroscopy and stereoscopic fundus photographs. Patients were excluded if they had refractive errors of more than S +5, or S –8 dioptres, significant media opacities, glaucoma, uveitis or any other clinically relevant ocular disease. Minimal DR was defined as the presence of two or more micro-aneurysms and/or minor haemorrhages in the central retina and a healthy peripheral retina, as seen on slit-lamp biomicroscopy or stereo fundus photography.

A healthy control group ($n=28$) was matched for gender and age. These individuals did not have a history of ocular disease, no family history of glaucoma nor any relevant systemic disease.

All patients underwent a physical examination, with review of medical history and current medication. Age, gender and onset of DM type 1 were recorded. The following parameters were measured: glycosylated haemoglobin (HbA1c), total cholesterol, triglycerides, serum creatinine, urine creatinine, micro-albuminuria, thyroid stimulating hormone and free thyroxine.

On the same day, patients underwent a full ophthalmic examination. Visual acuity was measured using an early treatment diabetic retinopathy study chart at 4 m. Best corrected visual acuity was recorded as Snellen equivalent. After pupil dilation with 0.5% phenylephrine hydrochloride and 0.1% tropicamide, patients were examined with slit-lamp biomicroscopy, and stereo fundus photographs of the 50° central posterior segment were taken.

Abbreviations: DM, diabetes mellitus; DR, diabetic retinopathy; OCT, optical coherence tomography; RT, retinal thickness; TSH, thyroid stimulating hormone

Figure 1 Definition of the optical coherence tomography (OCT) scanning areas around the fovea in patients with diabetes mellitus type 1 and healthy controls. The crossing of the six radial scan lines is the central fovea, area A1 is the fovea (right). The pericentral ring consists of the areas A2 to A5 (left) and the peripheral ring consists of the areas A6 to A9 (middle).

OCT measurements

Subsequently, all subjects were examined with the *StratusOCT* (Model 3000, Carl Zeiss Meditec, Dublin, CA, USA, software version 4.0.1). Both the fast macular thickness and regular macular thickness OCT scan protocols were performed on both eyes. Both scan protocols obtain six cross-sectional scan lines, 6 mm in length, at equally spaced angular orientations (30°) in a radial spoke pattern centred on the fovea. RT is defined by the software algorithm as the distance between the surface of the retina and the first highly reflective layer visible at the level of the outer retina and retinal pigment epithelium. An interpolated RT map is constructed from the six scan lines by the software.

For analysis of the RT, the mean RT was calculated in four areas: the central fovea (the cross-section of the six radial scans), the fovea (central circle, with a diameter of 1 mm, area A1), the pericentral area (donut shaped ring with an inner diameter of 1 mm and an outer diameter of 3 mm, area A2–5) and the peripheral area (inner diameter of 3 mm and outer diameter of 6 mm, area A6–9) (fig 1). As the results of RT measurements by the two scan protocols did not differ ($r = 0.98$, $p < 0.0001$), we used the fast macular thickness scan protocol for further analysis. As the mean RT in the left and right eye of the same subject showed a significant correlation ($r = 0.93$, $p < 0.0001$), we used the right eye of all patients and healthy controls for further analysis. The mean RT in all four areas was compared between patients with minimal DR, patients with no DR and healthy control subjects.

Figure 2 Box plot of the mean pericentral RT in patients with and without DR compared to controls.

RT measurements were repeated for all patients with diabetes after a period of 4 months.

Statistical analysis

Statistical analyses were performed using SPSS 12.0.1 for Windows (SPSS, Chicago, USA). Analysis of variance (ANOVA) was used to compare the differences in demographics between the patients with diabetes with minimal DR, the patients with no DR and the healthy control group. Mean RT measurements were compared using the unpaired Student *t* test. A $p < 0.05$ was considered statistically significant.

RESULTS

In total, 53 consecutive patients with DM type 1 were included in the study, of which 30 (57%) had no DR and 23 (43%) showed minimal DR. There was a significant difference in age ($p = 0.007$, 95% CI -12.33 to -2.02) and mean duration of DM ($p < 0.001$, 95% CI -12.22 to -3.95) between patients with

Table 1 Characteristics of the patients with diabetes mellitus type 1 with and without diabetic retinopathy and healthy controls

Parameters	Reference values	Patients without DR (n = 30)	Patients with minimal DR (n = 23)	Healthy controls (n = 28)
Age (years)	NA	28* ± 10	36* ± 8	34 ± 11
Gender (male:female)	NA	11:19	10:13	15:13
Duration of DM (years)	NA	13.1* ± 7	21.2* ± 8	NA
Systolic BP (mmHG)	<140	126 ± 14	122 ± 14	–
Diastolic BP (mmHG)	<90	76 ± 10	76 ± 8	–
HbA1c (%)	4.2–6.5	8.1 ± 1.1	8.2 ± 0.9	–
Total cholesterol (mmol/l)	3.7–6.5	4.4 ± 1.2	4.5 ± 0.8	–
Triglycerides (mmol/l)	0.5–2.0	0.8 ± 0.5	1.0 ± 0.7	–
Creatinine S (μmol/l)	65–95	63 ± 9	67 ± 16	–
Micr.alb/creat U (mg/mmol)†	M <2.5 and F <3.5	10%	9%	–
TSH (mE/l)	0.4–4.0	1.7 ± 1.1	1.3 ± 1.1	–
FT4 (pmol/l)	10.0–23.0	13.0 ± 4.2	14.8 ± 4.2	–

BP, blood pressure; DM, diabetes mellitus; DR, diabetic retinopathy; F, female; FT4, free thyroxine; HbA1c, glycosylated haemoglobin; M, male; S, serum; TSH, thyroid stimulating hormone; U, urine. The values are the mean ± SD for all subjects in each group. NA, not applicable; –, not done. *Significant difference as compared between the two patient groups with diabetes. †Percentage of the patients with diabetes with a micro-albuminuria/urine creatinine ratio >2.5 mg/mmol for males and >3.5 mg/mmol for females.

Table 2 Retinal thickness measurements in patients with diabetes mellitus type 1 with no or minimal diabetic retinopathy compared to healthy controls

Parameters	Patients without DR (n = 30)	p Value	Patients with minimal DR (n = 23)	p Value	Healthy controls (n = 28)
CF	171 μ $\pm$ 30 μ	0.218	168 μ $\pm$ 21 μ	0.378	162 μ $\pm$ 22 μ
F	209 μ $\pm$ 29 μ	0.774	200 μ $\pm$ 23 μ	0.256	207 μ $\pm$ 20 μ
Pericentral R	276 μ $\pm$ 14 μ	0.193	267 μ $\pm$ 20 μ	0.005*	281 μ $\pm$ 13 μ
Peripheral R	241 μ $\pm$ 13 μ	0.571	238 μ $\pm$ 14 μ	0.207	243 μ $\pm$ 13 μ

CF, central fovea; DR, diabetic retinopathy; F, fovea; R, ring. The values are the mean $\pm$ SD for all subjects in each group. *Significant difference compared to healthy controls.

minimal DR and patients without DR. Most patients were in reasonable glycaemic control (mean HbA1c = 7.9%; SD = 1.4%) and the mean lipid profile was normal as was the thyroid function. Micro-albuminuria was present in 19% of patients with diabetes (table 1). No significant difference was found in any of the metabolic parameters between patients with and without retinopathy. All eyes included in the analysis had a visual acuity of at least 20/25.

Mean ($\pm$ SD) RT in all patients with diabetes compared to healthy controls is shown in table 2. A statistically significant RT difference was found in the pericentral ring around the fovea between diabetic patients with minimal retinopathy and controls ($p = 0.005$, 95% CI -23.10 to -4.46). This is also shown in fig 2 where mean pericentral RT in patients with diabetes with and without minimal DR is compared to controls. In the other macular areas, no significant difference in RT measurements could be found compared to the control group or between the two groups with diabetes.

Repeated RT measurements after 4 months showed the same mean RT values in the four measured areas in all patients with diabetes (data not shown).

DISCUSSION

In this study we demonstrated a significantly thinner pericentral RT at two different time points, in patients with DM type 1 and minimal DR compared to a healthy control group, supporting the hypothesis of neuroglial loss in the earliest stage of DR.

In contrast, most previous papers about RT measurements with either OCT or the retinal thickness analyser in patients with DM have shown an increased RT in the perifoveal area.^{24–33} Several explanations for this difference may be put forward.

The retinal thickness analyser computes the RT from oblique laser slit projections on the posterior pole of the eye. Five partially overlapping scan areas covering a rectangular region of 6 $\times$ 6 mm are obtained. A thickness map of the retina is then calculated by the analysis software. Results in thickness measurements are not directly comparable between both methods. The difference in imaging and calculation of the RT between both systems could explain the inconsistent results between our study and the studies using the retinal thickness analyser.^{24–26–29}

The strength of this study compared to other studies is the strict inclusion of patients with type 1 DM only. We feel that this group of patients, with a well known duration of their disease, is a more homogeneous group of patients compared to a mix of type 1 and type 2 patients as used in other studies.^{24–33} The distinctive differences in pathophysiology and treatment between type 1 and type 2 diabetes may result in differences in the development of retinopathy.

Other less likely explanations for retinal thinning in the pericentral area are changes in reflectivity or a decrease in intercellular matrix volume and/or the intracellular volume within the retina.

We think a loss of neural tissue is the most likely explanation for the loss of RT in the early phase of DR. This is supported by several reports on apoptosis of neuroglial tissue in DM in humans and experimental animals, and subtle changes in retinal function observed in DM before the development of DR.^{1–23} Other studies have suggested that retinal nerve fibre layer loss occurs in patients with DM and no or minimal DR, another indirect proof of neural loss.^{34–39} We also measured the peripapillary retinal nerve fibre layer thickness using OCT and could detect a trend towards a thinner retinal nerve fibre layer thickness in the superior quadrant of the peripapillary area in patients with diabetes compared to controls (data not shown). In conclusion, we feel our findings support the concept of DR as a neurodegenerative disease.

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