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Association of visual function and ganglion cell layer thickness in patients with diabetes mellitus type 1 and no or minimal diabetic retinopathy

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ABSTRACT

Diabetic retinopathy (DR) classically presents with micro-aneurysms, small haemorrhages and/or lipoprotein exudates. Several studies have indicated that neural loss occurs in DR even before vascular damage can be observed. This study evaluated the possible relationship between structure (spectral domain–optical coherence tomography) and function (Rarebit visual field test) in patients with type 1 diabetes mellitus and no or minimal diabetic retinopathy (DR). Results demonstrated loss of macular visual function and corresponding thinning of the ganglion cell layer (GCL) in the pericentral area of the macula of diabetic patients (Rs = 0.65, $p < 0.001$). In multivariable logistic regression analysis, GCL thickness remained an independent predictor of decreased visual function (OR 1.5, 95% CI 1.1–2.1). Early DR seems to include a neurodegenerative component.

1. Introduction

One of the most frequent causes of blindness among adults in the Western world is diabetic retinopathy (DR) (Fong et al., 2004). The clinical hallmarks of DR are primarily vascular, including micro-aneurysms, hemorrhages, capillary occlusions, and lipoprotein exudates. In addition to vascular changes, neurodegenerative changes have been described including neural apoptosis, loss of ganglion cell bodies, glial reactivity and reduction in thickness of the inner retinal layers in the earliest stages of DR (Abu-El-Asrar, Dralands, Missotten, Al-Jadaan, & Geboes, 2004; Antonetti et al., 2006; Barber, 2003; Barber et al., 1998, 2005; Gardner, Antonetti, Barber, LaNoue, & Levison, 2002; Gastinger, Kunselman, Conboy, Bronson, & Barber, 2008; Gastinger, Singh, & Barber, 2006; Kern & Barber, 2008; Li & Puro, 2002; Martin, Roon, Van Ells, Ganapathy, & Smith, 2004; Park et al., 2003; Rungger-Brandle, Dosso, & Leuenberger, 2000). These findings of structural neuropathy may explain the neuroretinal functional deficits that are known in patients with diabetes, even before the presence of frank retinopathy. Several studies have shown electro-retinogram abnormalities, loss of dark adaptation and contrast sensitivity and color vision disturbances independent of vascular retinopathy (Bearse, et al., 2006; Bronson-Castain et al., 2009; Di Leo et al., 1992; Dosso et al., 1996; Hardy, Lipton, Scase, Foster, & Scarpello, 1992; Kurtenbach, Flogel, & Erb, 2002; Lopes de Faria, Katsumi, Cagliero, Nathan, & Hirose, 2001; Ng, Bearse, Schneck, Barez, & Adams, 2008; Realini, Lai, & Barber, 2004).

Conventional threshold perimetry and visual function tests are insensitive measures of minor neuro-visual damage (Frisen & Quigley, 1984; Kerrigan-Baumrind, Quigley, Pease, Kerrigan, & Mitchell, 2000). The Rarebit technique, which includes Rarebit Perimetry (RBP) and the Rarebit Fovea Test (RFT), was developed to improve detection of subtle defects (Frisen, 2002). The Rarebit technique is based on the principle of detection of very small and bright stimuli. The small stimulus corresponds to half the minimum angle of resolution at the tested retinal location. The test avoids simultaneous stimulation of more than one receptive field, defined as the group of photoreceptors converging on the same ganglion cell (Fischer, 1973). In a previous study employing the Rarebit technique, Nilsson et al. detected foveal dysfunction in patients with diabetes mellitus type 1 without DR (Nilsson, Von, Wanger, & Martin, 2007).

With optical coherence tomography (OCT) the retinal thickness (RT) can be measured with high accuracy. The retinal thickness in diabetic patients with no or minimal DR is thinner than in normals.

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(Asefzadeh, Fisch, Parenteau, & Cavallerano, 2008; Biallosterski et al., 2007; Bronson-Castain et al., 2009; Browning, Fraser, & Clark, 2008; Nilsson et al., 2007; Oshitari, Hanawa, & Adachi-Usami, 2009; Van Dijk et al., 2009). The high resolution of spectral domain–OCT (SD–OCT) allows measurement of the thickness of all individual retinal layers (Garvin et al., 2008), especially if the layers are segmented automatically in three-dimensions (Garvin et al., 2009). Results of a recent study showed that the decreased total RT in type 1 diabetic patients with minimal DR is predominantly caused by a thinning of the ganglion cell layer (GCL) in the pericentral area and retinal nerve fiber layer (RNFL) thinning in the peripheral area of the of the macula (Van Dijk et al., 2010), i.e. both axons and nerve bodies are involved in thinning.

The purpose of the present study is to evaluate the hypothesis that GCL thickness measured with SD–OCT and the function of the macula tested with the Rarebit technique are associated in patients with type1 diabetes mellitus (DM) and no or minimal DR.

2. Materials and methods

2.1. Patients

Patients with type 1 DM were recruited from the outpatient clinic of the department of Internal Medicine at the Academic Medical Center (AMC University Hospital, Amsterdam, The Netherlands) for an ongoing longitudinal observational study. In September 2008 they were invited to participate in this observational cross-sectional study. Additionally, healthy age-matched individuals served as controls. The study adhered to the tenets of the Declaration of Helsinki, and Institutional Review Board approval was obtained at both the AMC and the University of Iowa. All subjects provided written informed consent.

DR status was evaluated by a retinal specialist through indirect fundoscopy, slit-lamp stereo biomicroscopy and stereoscopic fundus photography. Patients were included if they were diagnosed with minimal or no DR. The definition of minimal DR was conform stage 2 of the International Clinical Diabetic Retinopathy Disease Severity Scale (Wilkinson et al., 2003). Control subjects did not have a diagnosis of any ocular disease, diabetes or other systemic disease, and were randomly recruited from accompanying persons of patients visiting the outpatient clinic of the department of Ophthalmology. Exclusion criteria were refractive errors over S+5, or under S−8 diopters, visual acuity below 20/25, significant media opacities, previous ocular surgery and a previous diagnosis of glaucoma, uveitis, or retinal disease.

Age, gender, duration since diagnosis of diabetes and serum glycosylated hemoglobin (HbA1c) at the time of the study examinations were gathered from the patient charts. Best corrected visual acuity was obtained conform the Early Treatment Diabetic Retinopathy Study, and recorded as Snellen equivalent. All subjects underwent Rarebit Perimetry and the Rarebit Fovea Test (Frisen, 2002). Finally, all subjects underwent papillary dilatation and an ophthalmic examination including slitlamp biomicroscopy with a handheld lens (SuperField; Volk Optical, Inc., Mentor, OH), OCT imaging (3D OCT-1000, Topcon Corporation, Tokyo, Japan) and stereoscopic fundus photography (TRC-50IX; Topcon Corporation, Tokyo, Japan).

2.2. Rarebit perimetry and Rarebit Fovea Test

The RBP and the RFT form a computerized visual function test developed to detect subtle damage to the visual system (Frisen, 2002). The RBP evaluates the central 30° visual field, while the RFT evaluates the central 4° visual field. The test principle is to briefly (200 ms) present zero, one, or two, bright small (<0.5 min of arc) dots against a dark background in a completely dark room. Due to photopic luminance levels for both the fixation mark and the test targets, dark adaptation is not of influence for test results. The subjects are asked to focus on the fixation mark and meanwhile respond by clicking a mouse button once or twice when they detect one respectively two dots anywhere on the screen. The result of the Rarebit test is presented as mean hit rate (MHR). The MHR is a percentage of the stimuli seen by the subject of all presented stimuli. In this study we combined the RFT and RBP and present a combined MHR. The combined MHR is abnormal if below 95% (Malmer & Martin, 2005; Salvetat, Zeppieri, Parisi, & Brusini, 2007).

2.3. Optical coherence tomography imaging and layer segmentation

OCT images of the subjects were obtained with SD–OCT (3D OCT-1000, Topcon Corporation, Tokyo, Japan) using the 3D volume scan protocol ($6 \times 6 \times 2.2$ mm^3), consisting of 128 (y) by 512 (x) by 650 (z) voxels. From this volume, nine intraretinal surfaces defining eight retinal layers were segmented automatically by our algorithm, which uses an extensively validated, robust fully three-dimensional graph search approach (Garvin et al., 2009). The eight layers were interpreted as follows (from inner to outer surface): 1/retinal nerve fiber layer (RNFL), 2/ganglion cell layer (GCL), 3/inner plexiform layer (IPL), 4/inner nuclear layer (INL), 5/outer plexiform layer (OPL), 6/outer nuclear layer (ONL) + inner segments (photoreceptors) (IS), 7/outer segments (photoreceptors) (OS), 8/retinal pigment epithelium (RPE) (Fig. 1).

The pericentral area of the macula – a donut shaped ring centered on the fovea with an inner diameter of 1 mm – was defined by one of the authors (HvD), who was masked for the DR status and demographic features of the patients and controls. The mean thickness of each layer in the pericentral area was automatically calculated with the computer program ImageJ 1.41 (Abràmoff, Magalhães, & Ram, 2004).

2.4. Statistical analysis

For the statistical analyses SPSS 16.0.2 for Windows (SPSS, Chicago, IL) was used. An independent t-test was used to assess differences in mean age and MHR between diabetic patients and controls. A Chi-square test was used to compare distribution of gender between patients and controls. Mean HbA1c, age, duration of diabetes and mean pericentral GCL thickness of diabetic patients with subnormal MHR and diabetic patients with normal MHR were compared using the independent t-test. The presence or absence of DR was compared between patients with subnormal and normal MHR using the Chi-square test. The possible correlation between MHR and pericentral GCL and INL thickness was analyzed using the Spearman rank test. Multivariable logistic regression analyses were performed to identify independent predictors of subnormal MHR. Confidence intervals were computed at the $p = 0.05$ level.

3. Results

Thirty-two patients type 1 diabetes with no or minimal DR and 38 controls were included. There was no significant difference in age and gender between patient groups and controls (see Table 1). Patients were in reasonable glycemic control (mean HbA1c = 8.1%; SD = 1.4).

The mean MHR of patients with DM and controls were 93.5 ± 5.3 and 97.1 ± 2.8, respectively. The mean MHR of the patient group was significantly decreased compared with the control group (95% CI of the difference 1.6–5.6).