Journal of Diabetes and Its Complications 30 (2016) 469–476

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Abnormalities of retinal ganglion cell complex at optical coherence tomography in patients with type 2 diabetes: a sign of diabetic polyneuropathy, not retinopathy

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ARTICLE INFO

Article history:
Received 12 October 2015
Received in revised form 23 December 2015
Accepted 28 December 2015
Available online 30 December 2015

Keywords:
Type 2 diabetes
Optical coherence tomography
Ganglion cell complex
Diabetic polyneuropathy
Diabetic retinopathy

ABSTRACT

Aims: To compare optical coherence tomography (OCT)-derived neuro-retinal parameters in patients with type 2 diabetes and non-diabetic controls and to evaluate their correlation with diabetic retinopathy (DR) and polyneuropathy (DPN).
Methods: One-hundred consecutive patients with type 2 diabetes were examined by spectral–domain (SD) OCT for evaluating ganglion cell complex (GCC) and retinal nerve fibre layer (RNFL) thickness and two new pattern-based quantitative measures of GCC damage, global and focal loss volume (GLV and FLV). Fifty sex- and age-matched non-diabetic subjects served as control.
Results: RNFL thickness (101.0 ± 10.6 vs. 106.4 ± 10.3 μm, $P = 0.003$) was significantly lower and GLV (6.58 ± 4.98 vs. 4.52 ± 3.10 %, $P = 0.008$) and FLV (1.90 ± 1.97 vs. 0.89 ± 0.84 %, $P < 0.0001$) were significantly higher in diabetic versus control subjects. The OCT parameters did not differ significantly according to DR grade. Conversely, RNFL thickness was lower and GLV and FLV were higher in patients with versus those without DPN, and the extent of changes increased significantly with quartiles of DPN score. At both bivariate and multivariate analysis, OCT parameters, especially FLV, correlated significantly with DPN measures.
Conclusions: The GCC is significantly affected in patients with type 2 diabetes and SD-OCT might represent a useful tool to detect DPN, but not DR in these individuals.

1. Introduction

Diabetic polyneuropathy (DPN) is a common long-term complication of diabetes characterized by the involvement of sensory, motor, and autonomic nerves, leading to disability, pain, foot ulceration, amputation, cardiovascular disease (CVD), and sudden death (Boulton, Malik, Arezzo, & Sosenko, 2004). Yet, DPN is often under-diagnosed as current procedures are either semi-quantitative or laborious, time-consuming, and even invasive; moreover, most of these methods are relatively insensitive for detecting early stages of the disease (Spallone et al., 2011).

The eye is a superficial organ which is easily accessible to a variety of non-invasive techniques. Diabetic retinopathy (DR), the most common microvascular complications of diabetes, is characterized by capillary degeneration leading to retinal ischemia and subsequent neovascularization and may be detected by fundus examination (Cheung, Mitchell, & Wong, 2010). However, the eye is densely innervated and, hence, it may also be affected by DPN, that can be eventually identified at this level, provided that damage to eye nerves parallels that to distal nerves of the lower limbs (Shahidi et al., 2010; Tavakoli, Petropoulos, & Malik, 2013). Previous studies have shown that corneal confocal microscopy is able to detect abnormalities of small unmyelinated corneal nerve fibers which correlate with loss of intraepidermal nerve fibers at skin biopsy (Petropoulos et al., 2013; Tavakoli et al., 2010) and neuropathy disability score (Quattrini et al., 2007).

Conflict of interest: The authors declare no competing financial interests.

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http://dx.doi.org/10.1016/j.jdiacomp.2015.12.025
1056-8727/

The retina is also richly endowed with sensory neurons and, therefore, is another potential site for DPN-related damage. In fact, increasing evidence indicates that diabetes results in changes of the neural retina, including loss of photoreceptors, horizontal, amacrine, and particularly ganglion cells (GCs), with thinning of the retinal nerve fiber layer (RNFL) formed by the unmyelinated GC axons, which become myelinated beyond the lamina cribrosa (Kern & Barber, 2008). Histological studies in autoptic samples from diabetic humans and eye tissues from experimental animal models of diabetes have provided evidence that GCs die from apoptosis and that those surviving may undergo morphological changes (Kern & Barber, 2008). These abnormalities might account for early loss of retinal function, as manifested by impaired night vision (Bailey & Sparrow, 2001), reduced contrast sensitivity (Lopes De Faria, Katsumi, Cagliero, Nathan, & Hirose, 2001), and altered electroretinogram pattern (Juen & Kieselbach, 1990), which occur before microvascular changes are detected. However, it is unclear whether GC complex (GCC) abnormalities represent an early sign of DR, which heralds the development of microvascular lesions (Simó, Hernández, & European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR), 2014), or they reflect the presence and extent of DPN (Shahidi et al., 2010). A number of studies have been conducted using a variety of techniques, including optical coherence tomography (OCT), which provides high-resolution images of the retina and is usually referred to as an "optical biopsy" (Fujimoto et al., 1995). However, a reduction of RNFL thickness in patients with type 2 diabetes vs. control subjects and in patients with DR vs. those without has not been consistently reported, possibly due to differences in sample size and type of OCT device, though a recent meta-analysis showed an overall significant trend toward a reduction of this parameter (De Clerck et al., 2015).

This study was aimed at comparing OCT-derived GCC parameters, including two new pattern-based quantitative measures of GCC damage called global loss volume (GLV) and focal loss volume (FLV), in patients with type 2 diabetes and non-diabetic control subjects and to assess whether they correlate with DR or DPN and, hence, may represent a useful tool to detect these complications.

2. Material and Methods

2.1. Subjects

One-hundred consecutive Caucasian patients with type 2 diabetes (52 males, 48 females, aged 66.3 ± 8.7 years) attending the yearly follow-up visit for the Study on the Assessment of determinants of Muscle and Bone strength Abnormalities in diabetes (SAMBA) between October 2014 and April 2015 were considered for this cross-sectional analysis. The SAMBA is an observational, prospective, cohort study (registered with ClinicalTrial.gov, NCT01600924, URL https://clinicaltrials.gov/ct2/show/NCT01600924), aimed at assessing the independent correlates of impaired muscle and bone strength in diabetic patients encompassing a wide range of vascular and peripheral nerve function. For the purpose of the current analysis, in addition to the assessment of cardiovascular risk factors and a variety of measures of complications according to the SAMBA protocol (Balducci et al., 2014), patients underwent also an OCT. Fifty healthy non-diabetic volunteers, with similar sex distribution (26 males, 24 females) and age (65.8 ± 10.4 years), served as a control group for the OCT parameters. Exclusion criteria were a positive history of glaucoma and/or the detection of an intraocular pressure ≥21 mmHg, altered foveal profile, history of other retinal diseases, optic nerve diseases, neurodegenerative diseases, and ocular surgery, a visual acuity 5/9 or worse, spherical refractive error > −6 or > +3 diopters or cylindrical refractive error > +/− 1.25 diopters, and advanced cataract or cloudy media opacity precluding fundus examination or imaging.

The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The protocol was approved by the Ethics Committee of Sant'Andrea Hospital and participants gave written informed consent.

2.2. OCT parameters

All diabetic and non-diabetic participants underwent an OCT scan. Both eyes were examined by spectral domain (SD)-OCT (RTVue Premier; OptovueInc, Fremont, CA, USA) after pupillary dilation for the assessment of GCC and RNFL thickness. RNFL thickness was calculated from the images of 6 circular and 12 linear scans along a 3.45-mm diameter circle around the optic disc, whereas GCC thickness, as defined as the distance from the internal limiting membrane to the boundary of the outer inner plexiform layer, was calculated from a 7 × 7 mm grid of the macula 1-mm temporal to the fovea. Eyes were divided in 2 sectors, superior and inferior. RNFL and GCC were expressed as the average thickness (in μm) of both sectors (AvgRNFL; AvgGCC) as well as of the superior (SupRNFL; SupGCC) and inferior (Inf RNFL; Inf GCC) sector.

In addition, the RTVue SD-OCT device is equipped with a software that allowed the analysis of diffuse and focal GCC defects by calculating GLV and FLV, respectively. The former, which corresponds to "the overall thinning of the topography of the GCC", is computed as the sum of the negative fractional deviation in the entire area, whereas the latter, which represents "the potholes in the topography of the GCC", is computed as the total sum of statistically significant GCC volume loss divided by the GCC map area.

Results were expressed as the mean of values from the two eyes or the value from the worst eye.

2.3. CVD risk factors

All diabetic patients underwent a structured interview in order to collect the following information: demographics, lifestyle habits, known diabetes duration, and current treatments.

Body mass index (BMI) was calculated from body weight and height; and waist circumference was measured at the umbilicus. Blood pressure (BP) was measured with a mercury sphygmomanometer with the patients seated with the arm at the heart level.

Hemoglobin (Hb) A_{1c} was assessed by a DCCT-aligned high-performance liquid chromatography method (Adams TMA1C HA-8160, Menarini Diagnostics, Florence, Italy). Fasting plasma glucose, triglycerides, total and HDL cholesterol were measured by standard analytical methods using the VITROS 5,1 FS Chemistry System (Ortho-Clinical Diagnostics, Inc, Raritan, NJ, USA), whereas LDL cholesterol was calculated by the Friedwald formula.

2.4. Complications

Prevalent CVD was assessed from medical history by recording previous documented major acute CVD events, including myocardial infarction, stroke, foot ulcer, gangrene and amputation, and revascularization procedures (Solini et al., 2012). In addition, carotid intima-media thickness (IMT) and ankle–brachial index (ABI) were assessed as surrogate measures of diabetic macroangiopathy by color-coded duplex sonography (Agilent HP ImagePoint HX, Hewlett Packard, Rome, Italy) and a mercury sphygmomanometer plus a handheld continuous wave Doppler device (Super Doppler 2, Huntleight Healthcare, Lewis Center, OH), respectively. Patients were then classified as having or not CVD, either asymptomatic or symptomatic, based on whether they had abnormal IMT and ABI values and/or prior CVD events.

Diabetic nephropathy was evaluated by assessing serum creatinine and albuminuria. Serum creatinine was measured by the modified Jaffe method and estimated glomerular filtration rate (eGFR) was then calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (http://www.qxmd.com/calculate-online/nephrology/ckd-epi-egfr). Albuminuria was assessed as albumin/creatinine ratio (ACR) by measuring albumin and creatinine