Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Autonomic nervous system function assessed by conventional and spectral analysis might be useful in terms of predicting retinal deterioration in persons with type 1 diabetes mellitus

L. Duvnjak [a,b], M. Tomić [a], K. Blaslov [a,*], S. Vučković Rebrina [a]

[a] Vuk Vrhovac Clinic for Diabetes, Endocrinology and Metabolic Diseases, University Hospital Merkur, Zagreb, Croatia
[b] School of Medicine Zagreb, Croatia

ARTICLE INFO

Article history:
Received 1 February 2016
Received in revised form
1 April 2016
Accepted 21 April 2016
Available online 27 April 2016

Keywords:
Type 1 diabetes mellitus
Cardiac autonomic dysfunction
Hearth rate variability

ABSTRACT

Aims: To determine whether cardiac autonomic dysfunction represents a risk factor for diabetic retinopathy (DR) development and progression in persons with type 1 diabetes mellitus (T1DM).

Methods: The study comprised 154 normoalbuminuric persons with T1DM divided into two groups according to the DR presence: with and without DR. Cardiovascular autonomic functioning was measured at baseline using conventional and spectral analysis. Participants were re-examined for the DR presence 18 months after.

Results: The group with DR had longer disease duration compared to the group without DR (20 *vrs* 11.5 years, $p < 0.001$), heart rate coefficient of variation (HRV-CV) at rest and during deep breathing were lower in participants with DR ($p = 0.001$ and 0.004), as well did spectral indices of HRV: low frequency (LF) band, high frequency (HF) band ($p = 0.003$ and 0.022) while LF/HF ratio indicating sympathovagal balance was higher ($p = 0.037$). No difference in glycaemic control or blood pressure value were observed. Twenty-one (13.36%) participants developed non proliferative DR or progressed to proliferative DR. Cox proportional regression showed that the 18 months risk from retinal deterioration was reduced by 33.4% by each increase in the HRV-CV of 1%, 12.7% for the same HRV-CV increase during deep breathing while LF band of 1 ms^2 results in 8.6% risk reduction.

Conclusions: This study provides evidence that DR should not be considered merely a metabolic control manifestation and that HRV-CV as well as spectral indices of HRV might serve as a practical tool to identify a subgroup of T1DM patients with higher risk of retinal deterioration.

1. Introduction

Diabetic retinopathy (DR) is the most frequent cause of visual impairment and legal blindness among adults with type 1 diabetes mellitus (T1DM) [1]. The pathogenesis of its development and progression is not completely understood. To date, dysglycemia, elevated blood pressure, dyslipidemia and longer diabetes duration are the most pronounced risk factors

* *Corresponding author at:* Vuk Vrhovac Clinic for Diabetes, Endocrinology and Metabolic Diseases, University Hospital Merkur, Dugi dol 4a, Zagreb, Croatia. Tel.: +385 12353829; fax: +385 12331515.
E-mail address: kblaslov@gmail.com (K. Blaslov).
http://dx.doi.org/10.1016/j.diabres.2016.04.042
0168-8227/

for DR development and progression [2–4]. Diabetic kidney disease, often accompanied with urine albumin excretion above 30 mg/24 h coincides with DR [5,6]. Moreover, the structural changes in the kidney which include glomerular basement membrane thickening, micro aneurysm formation and mesangial nodule formation represent the similar small histological finding seen in DR [7,8].

Cardiovascular autonomic neuropathy (CAN) is defined as impairment of autonomic control of the cardiovascular system in the setting of diabetes after exclusion of other causes with prevalence ranging from 16% to 20% among persons with diabetes [9]. There is a well established causative role of CAN in diabetic kidney disease development and progression in persons with T1DM [10,11] while an association between CAN and DR has been reported in several cross-sectional studies [6,12–14]. Clinical symptoms of CAN: resting tachycardia and a fixed heart rate represent the characteristic of structural vagal nerve impairment and may not appear until long after diabetes onset [9]. Subclinical CAN however represents functional abnormalities of the autonomic nervous system, i.e. the imbalance between the sympathetic and parasympathetic nervous system that can be discerned by using spectral analysis of heart rate variability (HRV) [15–17].

Spectral analysis involves decomposing the series of sequential R–R intervals into a sum of sinusoidal functions of different amplitudes and frequencies by several possible mathematical approaches, such as fast Fourier transformation [18]. The result (power spectrum) reflects the amplitude of the HRV present at different oscillation frequencies. The power spectrum of HRV has been shown to consist of two major peaks: low-frequency (LF) component which in absolute values expresses modulation to the heart of parasympathetic more than sympathetic nervous system parasympathetic/vagal nerve contribution to HRV-CV at rest and high-frequency (HF) component which reflects parasympathetic contribution to HRV-CV during normal respiration.

It would be of a special interest to investigate whether early, subclinical CAN contributes to the risk of DR and whether it might represent an independent risk factor for its development and progression in normoabuminuric type 1 diabetic (T1DM). We aimed to determine whether CAN assessment accompanied by detailed spectral analysis might serve as a practical tool to identify a group of T1DM patients with a higher risk for retinal deterioration.

2. Materials and methods

2.1. Study population

One hundred fifty-four randomly selected normoalbuminuric persons with T1DM referred to Vuk Vrhovac University clinic for Diabetes, Endocrinology and Metabolic diseases, Zagreb, Croatia between January 2011 and December 2014 were included in the study after informed consent was obtained. T1DM was diagnosed according to World Health Organization (WHO) criteria (<35 years at the age of onset of diabetes, a previous episode of ketoacidosis or documented ketonuria, positive autoantibodies and permanent insulin treatment initiated within 1 year of diagnosis) [19]. Eligible participants were at least 18 years old, minimum duration of T1DM of 1 year, no medical history of cardiovascular diseases or electrocardiogram (ECG) evidence of ischemic heart disease, absence of any systemic disease and absence of any infections in the previous month. Urine albumin excretion (UAE) was measured from at least two 24-h urine samples and determined as the mean of 24-h urine collections in order to minimise variability. Normoalbuminuria was defined as a UAE < 30 mg/24 h [20]. Fasting venous blood samples were collected for the determination of a glycated haemoglobin (HbA1c,%, reference interval 3.5–5.7, i.e. 15–39 mmol/mol in the IFCC units), C-reactive protein (CRP), serum creatinine in order to exclude a wide range of disorders that might affect the study results. HbA1c was measured spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA).

Blood pressure was measured in the sitting position with a mercury sphygmomanometer with a cuff appropriate to the length and circumference of the arm after a resting period of 10 min and expressed in mmHg. Patients taking blood pressure medications or with blood pressure >140/90 mmHg were considered to have hypertension.

Participants were re-examined after 18 months to update their glycaemic control, UAE and retinopathy status. The study protocol complied with the Declaration of Helsinki as well as local institutional guidelines.

2.2. Data acquisition

Complete eye examination included best corrected visual acuity (BCVA), Goldmann applanation tonometry, slit lamp biomicroscopy of the anterior eye segment, binocular indirect slit lamp fundoscopy and fundus photography after mydriasis with eye drops containing 0.5% tropicamide and 5% phenylephrine. Color fundus photographs of two fields (macular field, disc/nasal field) of both eyes were taken with a suitable 45° fundus camera (VISUCAM, Zeiss) according to the EURODIAB retinal photography methodology [21]. Macular field: positioned in such a way that the exact centre of the optic disc laid at the nasal end of the horizontal meridian of the field view. Disc/nasal field: such that the optic disc was positioned one disc-diameter in from the temporal edge of the field, on the horizontal meridian. EURODIAB classification scheme was used because it uses two-field 45° fundus photography and standard photographs to grade retinal lesions. In each person the “worse” eye was graded for retinopathy using fundus photographs.

Autonomic nervous system testing was carried out on VAGUS 2100 (Sigma Medizin Technik, Thum, Germany) Test conditions was standardised as suggested by Spallone et al. [17] as follows: testing was conducted between 9 and 12 a.m., at least 2 h after a light breakfast, a tested subject did not consume coffee, black tea or nicotine and blood glucose was checked prior to testing. Three disposable, self-adhesive ECG electrodes and breathing sensor were applied to the patients chest with self adhesive tape. The length of ECG recordings was 7 min in rest conditions and during spontaneous breathing.