Redox Biology 5 (2015) 301–307

Contents lists available at ScienceDirect

Redox Biology

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

Research paper

The correlations of glycated hemoglobin and carbohydrate metabolism parameters with heart rate variability in apparently healthy sedentary young male subjects

Andriy Cherkas [a,b,c,*], Orest Abrahamovych [c], Sergii Golota [d], Armen Nersesyan [e], Christoph Pichler [e], Victoria Serhiyenko [b], Siegfried Knasmüller [e], Neven Zarkovic [f], Peter Eckl [g]

[a] Department of Medicine, Lviv College of Physical Culture, Lviv, Ukraine
[b] Department of Endocrinology, Danylo Halytskyi Lviv National Medical University, Lviv, Ukraine
[c] Department of Internal Medicine #1, Danylo Halytskyi Lviv National Medical University, Lviv, Ukraine
[d] Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Halytskyi Lviv National Medical University, Lviv, Ukraine
[e] Institute of Cancer Research, Internal Medicine I, Medical University of Vienna, Vienna, Austria
[f] Laboratory for Oxidative Stress, Rudjer Boskovic Institute, Zagreb, Croatia
[g] Department of Cell Biology, University of Salzburg, Salzburg, Austria

ARTICLE INFO

Article history:
Received 27 April 2015
Received in revised form
28 May 2015
Accepted 29 May 2015
Available online 3 June 2015

Keywords:
Sedentary lifestyle
Glycated hemoglobin
Heart rate variability
Insulin sensitivity
Correlations

ABSTRACT

Introduction: Sedentary lifestyle is a major risk factor for diabetes, cardiovascular and many other age-related diseases. Heart rate variability (HRV) reflects the function of regulatory systems of internal organs and may sensitively indicate early metabolic disturbances. We hypothesize that quantitative and qualitative changes of HRV in young subjects may reflect early metabolic derangements responsible for further development of clinically significant disease.
Aim: The aim of our study was to determine whether the parameters of carbohydrate metabolism (fasting blood glucose, HBA_{1c} and surrogate insulin sensitivity/resistance indices) correlate with anthropometric data and HRV.
Methods: The study group consisted of 30 healthy sedentary male subjects aged 20–40, nonsmokers, mainly office and research employees, medical staff and students. Athletes, actively training more than one hour per week, severely obese and men of physical work were excluded from the study. HRV parameters were derived from short term ECG records (five minutes intervals) in supine position and during orthostatic test. Anthropometric data included height, weight, body mass index (BMI), age and body composition (estimation by bioelectric impedance method). The fasting blood glucose, insulin and C-peptide, homeostatic model assessment (HOMA-IR) index and glycated hemoglobin (HbA_{1c}) were evaluated. Linear correlation coefficient (r) was calculated using Statistica 10.0 software.
Results and discussion: HOMA-IR index correlated positively with body weight, visceral fat and BMI ($p=0.047$, 0.027 and 0.017 respectively). In supine position pNN50 positively correlated with glucose/insulin ratio ($p=0.011$) and heart rate with HOMA-IR ($p=0.006$). In orthostatic test negative correlations of HBA_{1c} with standard deviation, total and low frequency power were determined ($p=0.034$, 0.400 and 0.403 respectively), which indicates a gradual worsening of functional capacity of cardiovascular system with low-grade increase (under the conventional threshold) of HBA_{1c}.
Conclusions: In apparently healthy sedentary subjects HRV reduction correlates with the age advancement, subclinical deteriorations of carbohydrate metabolism and excessive fat accumulation.

Abbreviations: ANS, autonomous nervous system; BMI, body mass index; CVS, cardiovascular system; ECG, electrocardiogram; FBG, fasting blood glucose; HBA_{1c}, glycated hemoglobin; HF, the power of high frequency oscillations; HOMA, homeostatic model assessment; HR, heart rate; HRV, heart rate variability; HSS, healthy sedentary subjects; IR, insulin resistance; LF, the power of low frequency oscillations; OT, orthostatic test; pNN50, percentage of differences between adjacent normal RR intervals exceeding 50 milliseconds; RMSSD, square root of the mean squared differences of successive RR intervals; SAN, sinoatrial node; SDNN, standard deviation of normal RR intervals; TP, total power of RR-intervals oscillations; VLF, the power of very low frequency oscillations

* Corresponding author at: Knyagyni Olgy St. 1, Lviv, 79044, Ukraine. Tel.: +380322382794; fax: +380322382793.
E-mail address: cherkasandriy@yahoo.com (A. Cherkas).

http://dx.doi.org/10.1016/j.redox.2015.05.007

1. Introduction

Sedentary lifestyle, obesity, hypertension, dyslipidemia and type 2 diabetes (T2D) are among the most important risk factors of cardiovascular morbidity and mortality [1,2]. These factors contribute to approximately 19.5 million deaths per year, which is more than 1/3 of all fatalities [3]. Due to economic development and gradual elimination of physical work the share of people with physical inactivity (low level of activity) dramatically increases and spreads worldwide from mainly developed countries in the past [4]. It is well known that the development of cardiovascular diseases, in particular atherosclerosis, often starts at young age, sometimes even in childhood and adolescence without the evidence for the presence of these risk factors. Research is mainly focused on already developed disease and little is known about early stages where the main homeostatic parameters (e.g. blood tests) remain within the physiological range and all the changes are on early subclinical stages. Being clinically invisible and generally ignored these conditions gradually progress and it is only a matter of time when they will manifest in the form of the disease. But most of the known risk factors are highly modifiable, and early interventions may be extremely beneficial, cost-effective, and could prevent or at least significantly delay the onset of the disease.

Glycosylated (glycated) hemoglobin (HBA_{1c}) is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to blood glucose and, since erythrocyte's lifetime normally is over a hundred days, HBA_{1c} level highly correlates with average blood concentration of glucose for relatively long periods of time (up to 3 months). The level of HBA_{1c} is often used as a stable cumulative index of glycemia reflecting the average level of blood glucose more reliably than commonly used fasting glucose. Therefore it is a major clinical parameter, especially in diabetes. Besides, it may reflect also the general level of posttranslational protein glycation in the whole organism, because the increased rate of glycation takes place in other body compartments proportionally to the glycemia level [5]. There are close relationships of key parameters of carbohydrate metabolism such as fasting blood glucose (FBG), HBA_{1c}, and homeostatic model assessment (HOMA) of insulin resistance (IR), and cardiovascular risk in diabetic patients. However, in non-diabetic subjects where the levels of HBA_{1c} are within normal range (up to 6.0%) despite its potential importance, this parameter has not been extensively studied until recently. In a recent paper of Chang et al. [13] on a large cohort it has been proven that subclinical coronary atherosclerosis is associated with higher levels of HBA_{1c} in non-diabetic subjects without overt cardiovascular disease [6].

Heart rate variability (HRV) reflects oscillations in heart cycle duration over the time and is generally considered as a measure of regulatory influences, mainly activity of the autonomous nervous system (ANS) to regulate function of cardiovascular system (CVS). Classical interpretation of HRV include the activities of parasympathetic and sympathetic branches of ANS, their balance/ratio and a number of other related parameters [7]. However a growing evidence is accumulating since recently concerning metabolic background of HRV [8–10] and the critical dependence of the amplitude of heart rate oscillation on the intracellular energy supply [11]. There are also some indications that the parameters of HRV in orthostatic test (OT) are of particular importance, since the examined subjects are exposed to a mild level of exertion which causes some stress, requiring adaptation. In fact, at rest initial changes may become hidden by adaptive reactions of the human organism, and only mild physiological activation reveals abnormalities [12]. If this assumption is correct, the changes in HRV parameters in apparently healthy subjects should reflect early metabolic shifts and sensitively indicate the initial stages of health problems related with sedentary lifestyle. The aim of our study therefore was to determine whether the parameters of carbohydrate metabolism (FBG, HBA_{1c} and surrogate insulin sensitivity/resistance indices) correlate with anthropometric data and HRV.

2. Materials and methods

2.1. Study group characteristics and anthropometric parameters

In our study 30 apparently healthy sedentary young male subjects (HSS) aged 20–40, nonsmokers, mainly office and research employees, medical staff and students were enrolled. Any athletes, subjects actively training for more than 1 h per week, severely obese (body mass index above 35.0 kg/m^2), men physically working and subjects suffering from any chronic diseases were excluded from the study. The questionnaire used in the study was adapted from "The General Practice Physical Activity Questionnaire" (translated into Ukrainian), developed by the London School of Hygiene and Tropical Medicine as a validated short measure of physical activity available online at http://www.patient.co.uk/doctor/general-practice-physical-activity-questionnaire-gppaq. Subjects were considered as "sedentary" if their result was classified qualitatively as "Inactive" or "Moderately Inactive" according to the online calculator. Enrolled subjects never smoked or quit smoking not later than 3 years prior to the participation in the study, no one was vegetarian or had any voluntary qualitative or quantitative food restrictions. All subjects underwent physical examination, routine clinical tests and electrocardiography. Anthropometric data included height, weight, body mass index (BMI), and age. Height was measured with a standardized stadiometer, patients were weighed on electronic scales (OMRON Corporation, Kyoto, Japan), and BMI was calculated. Body composition was estimated by the bioelectric impedance method and the following parameters were determined: fat content (% of body weight), visceral fat (%), muscle mass (%) on the Body Composition Monitor BF500 (OMRON Corporation, Kyoto, Japan). It should be noted that the body composition measurements provide approximate results and are used for rough estimation of body composition. The Ethics Committee of Danylo Halytskyi Lviv National Medical University approved the design and protocol of the study. A written informed consent form was obtained from all the subjects enrolled in the study.

2.2. Clinical laboratory investigations, ELISA and glycated hemoglobin

Routine clinical blood cell count was performed by automatic cell counter ABS-Micros 60-OT (Horiba Medical, Montpellier, France). Blood cell morphology evaluation was performed by an experienced clinical laboratory specialist.

Fasting whole blood glucose was determined by the conventional glucose oxidase method routinely used in clinical laboratories, while HbA_{1c} was assessed using a highly sensitive method of ion-exchange liquid chromatography with a D-10™ System analyzer and BIO-RAD D-10™ reagents (Bio-Rad, Hercules, California, USA). The levels of insulin and C-peptide were determined with respective ELISA-assays (DRG Instruments GmbH, Marburg, Germany).

Surrogate methods for insulin resistance/sensitivity evaluation have also been used in the study. A homeostatic model assessment (HOMA) of insulin resistance (IR) derived from the basal (fasting) levels of glucose and insulin is the most commonly used and highly correlates with the "golden standard" euglycemic clamp method, which is technically much more difficult to perform [13]. HOMA-IR index was calculated by the formula $\text{HOMA-IR} = \text{FBG} \times \text{Insulin}/22.5$. As a measure of insulin sensitivity glucose/insulin ratio was calculated.