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Delayed heart rate recovery after exercise as a risk factor of incident type 2 diabetes mellitus after adjusting for glycometabolic parameters in men

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ABSTRACT

Background: Some studies have reported that delayed heart rate recovery (HRR) after exercise is associated with incident type 2 diabetes mellitus (T2DM). This study aimed to investigate the longitudinal association of delayed HRR following a graded exercise treadmill test (GTX) with the development of T2DM including glucose-associated parameters as an adjusting factor in healthy Korean men.

Material and methods: Analyses including fasting plasma glucose, HOMA-IR, HOMA-β, and HbA1c as confounding factors and known confounders were performed. HRR was calculated as peak heart rate minus heart rate after a 1-min rest (HRR 1). Cox proportional hazards model was used to quantify the independent association between HRR and incident T2DM.

Results: During 9082 person-years of follow-up between 2006 and 2012, there were 180 (10.1%) incident cases of T2DM. After adjustment for age, BMI, systolic BP, diastolic BP, smoking status, peak heart rate, peak oxygen uptake, TG, LDL-C, HDL-C, fasting plasma glucose, HOMA-IR, HOMA-β, and HbA1c, the hazard ratios (HRs) [95% confidence interval (CI)] of incident T2DM comparing the second and third tertiles to the first tertile of HRR 1 were 0.867 (0.609–1.235) and 0.624 (0.426–0.915), respectively (p for trend = 0.017). As a continuous variable, in the fully-adjusted model, the HR (95% CI) of incident T2DM associated with each 1 beat increase in HRR 1 was 0.980 (0.960–1.000) (p = 0.048).

Conclusions: This study demonstrated that delayed HRR after exercise predicts incident T2DM in men, even after adjusting for fasting glucose, HOMA-IR, HOMA-β, and HbA1c. However, only HRR 1 had clinical significance.

1. Introduction

Delayed heart rate recovery (HRR) after exercise is known to be associated with an increased risk of all-cause mortality [1–3]. The autonomic nervous system (ANS) plays a major role in HRR after exercise [4]. The physiology of HRR after exercise cessation involves an increment in parasympathetic activation and a decrement in sympathetic activation [5]. Therefore, dysfunction of the ANS can lead to delayed HRR. Autonomic neuropathy has also been reported in individuals with prediabetes, as well as those with type 2 diabetes mellitus (T2DM) [6]. In this regard, delayed HRR might precede incident T2DM and could eventually be a risk factor of the development of T2DM.

Some studies have reported that ANS dysfunction is associated with incident T2DM [7–11]. However, there have been few studies in which glycometabolic parameters have been taken into consideration. Risk factors reflecting glucose metabolism are correlated with autonomic neuropathy [12–15]. Therefore, the relationship between HRR and the development of T2DM should be investigated considering glucose-associated parameters. Moreover, it is well known that beta-blockers lower maximum heart rate and HRR; however, little effort has been directed toward excluding subjects taking beta-blockers or to the consideration of beta-blockers as a confounding factor.

Thus, we designed this retrospective cohort study to investigate how the longitudinal effects of HRR after exercise influence incident T2DM and to include glycometabolic parameters as confounding factors in healthy men who are not taking beta-blockers.

Abbreviations: HRR, heart rate recovery; T2DM, type 2 diabetes mellitus; GTX, graded exercise treadmill test; ANS, autonomic nervous system; BMI, body mass index; BP, blood pressure; TG, triglyceride; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of beta-cell; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HR, hazard ratios; CI, confidence interval.

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2. Materials and methods

2.1. Population and measurements

A retrospective longitudinal cohort study was designed to evaluate the association between HRR and the development of T2DM. Adults aged ≥20 years were recruited from a medical health check-up program at the Health Promotion Center of Samsung Medical Center, Sungkyunkwan University, Seoul, Republic of Korea [16]. The check-up included a medical history, smoking status, anthropometric data, and laboratory data collected either annually or biennially. A total of 24,185 participants who attended four or more follow-up check-ups between January 2006 and December 2012 were assessed for eligibility.

HRR values following a graded exercise treadmill test (GTX) were available for 2557 men. We excluded men with baseline T2DM (n = 263), CVD (cardiovascular disease; myocardial infarction, bypass surgery, stroke, n = 230), those who were using beta-blockers (n = 72), those who had an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 (n = 24), or those with abnormal EKG (WPW syndrome, atrial fibrillation, left bundle branch block, n = 13). Those who had missing data were also excluded (n = 311). Several participants met more than two criteria. After these exclusions, the final study population included 1774 men (Fig. 1). The observation period continued until the participant was first diagnosed with T2DM or until the last follow-up visit if they were not diagnosed with T2DM. The study was approved by the Institutional Review Board (IRB) of Samsung Medical Center and was carried out in accordance with recommendations from the Declaration of Helsinki.

Weight, height, systolic blood pressure (BP), and diastolic BP were measured at each visit. BP was measured by trained nurses using a mercury sphygmomanometer on the right arm after participants were seated comfortably for at least 5 min. Body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of the height in meters (kg/m^2). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [17]. Insulin resistance was assessed using the homeostatic model assessment of insulin resistance (HOMA-IR), calculated as the product of fasting plasma insulin level (μU/ml) and fasting plasma glucose (FPG) level (mg/dl), divided by 405. Insulin secretion was assessed using the homeostatic model assessment of beta-cell [HOMA-β (%)], calculated as the product of 360 and fasting plasma insulin level (μU/ml), divided by glucose minus 63 [18].

T2DM was defined as fasting glucose ≥126 mg/dl or HbA1c ≥ 6.5%, self-reported physician's diagnosis, or intake of antidiabetic medications.

Venous blood samples were obtained after overnight fast. The levels of FPG, fasting plasma insulin, triglyceride (TG), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), and creatinine were measured.

FPG concentration was measured with hexokinase using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer, Bayer Diagnostics, Leverkusen, Germany), and fasting plasma insulin concentration was measured with an immunoradiometric assay (TFB Co., Ltd., Tokyo, Japan). TG, LDL-C, and HDL-C were measured with an enzymatic colorimetric method using a Modular D2400 chemistry system (Roche Diagnostics, Basel, Switzerland).

2.2. Cardiopulmonary function test

Resting heart rate was obtained in the supine position after at least 5 min of rest. Patients underwent a standard symptom-limited GTX according to the Bruce protocol or the modified Bruce protocol using a treadmill system (Quinton Q-Stress TM65, Bothell, WA). Peak oxygen uptake (ml/kg/min) was defined as the highest value recorded during the test using the TrueOne 2400 system (Parvo Medics, Sandy, UT). The maximum heart rate using 12-lead electrocardiography (Quinton Q-4500, Bothell, WA) was defined as the highest value obtained during the test. Exercise was completed when the subject desired cessation of the treadmill test due to exhaustion, if the heart rate was higher than 90% of the estimated maximum heart rate (220-age), or if the rating of perceived exertion (RPE) was higher than 17 or the respiratory exchange ratio was greater than 1.15. During the recovery phase, the subjects continued to walk for 30 s at a speed of 1.2 mph and then sat down for 5 min, with continuous monitoring. HRR was calculated as peak heart rate minus heart rate after a 1-minute rest (HRR 1), heart rate after a 2-minute rest (HRR 2), and heart rate after a 3-minute rest (HRR 3).

2.3. Statistical analyses

Continuous variables with normal distributions were expressed as mean ± standard deviation, whereas continuous variables with non-normal distributions were expressed as median and interquartile range. Categorical data are expressed as frequencies and percentages. Either Student's *t*-test or the Mann–Whitney U test was used for comparisons of the characteristics of study participants at baseline. Pearson's Chi-square test was used to compare frequency distributions. Characteristics of the study population according to HRR after exercise tertile were compared using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables and Pearson's Chi-square test for categorical variables. HRR after exercise was analyzed in tertile groups as a continuous variable.

Multivariate Cox proportional hazards analysis was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for assessing the relationship between HRR after exercise and incident T2DM and the enter procedure was used for analysis. A collinearity test for the variables used in the multivariate Cox proportional hazards analysis was performed using linear modeling of the outcome variables with calculation of the variance inflation factor (VIF) of the independent predictors. A VIF < 5 was considered optimal to warranty stability. Intervals between the baseline visit and the last follow-up visit or the first diagnosis of T2DM were used for this model. The sets of variables adjusted for in the model were previously selected according to clinical relevance (i.e., smoking status [19]) and the results of Pearson's correlation and multiple regression analysis between HRR after exercise and possible variables.

Two-sided probability values<0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS Software (Version 21, SPSS, Inc., Chicago, IL).

3. Results

Table 1 shows the clinical characteristics and laboratory variables of the study participants with regard to development of T2DM. HRR 1 was lower in participants who developed T2DM (20.6 ± 7.9 beats) compared to those who did not (22.8 ± 7.6 beats, $p < 0.001$). Participants who subsequently developed T2DM had higher baseline BMI, TG, LDL-C, fasting glucose, fasting insulin, and HOMA-IR values but lower HOMA-β values than those who did not develop T2DM. There were no significant differences in age, systolic BP, diastolic BP, smoking status, HDL-C, resting heart rate, peak heart rate, peak oxygen uptake, or exercise capacity (METs; metabolic equivalents) between the two groups.

The baseline clinical characteristics and laboratory variables of the study participants based on HRR 1 tertile are shown in Table 2. Negative relationships between HRR 1 tertile and age, fasting insulin, HOMA-IR, HbA1c, TG level, and resting heart rate existed, while a positive

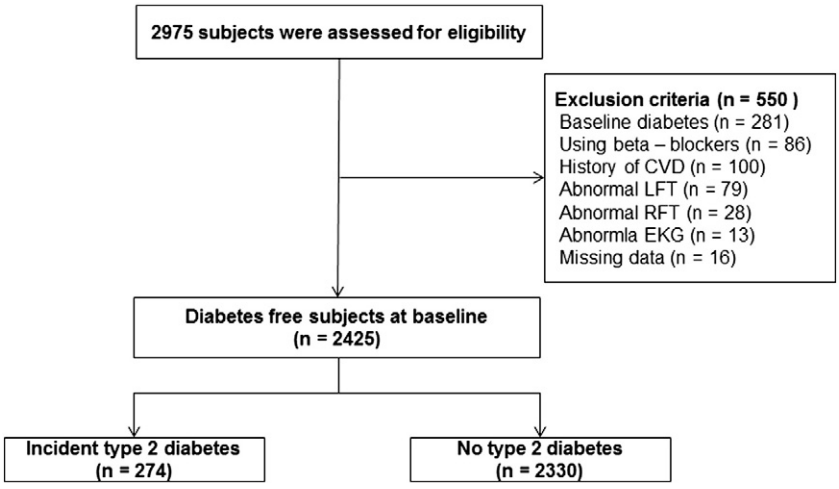

Fig. 1. Selection of study particicpants.