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Original article

Increase in resting heart rate over 2 years predicts incidence of diabetes: A 10-year prospective study

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Abstract

Objective. – The association between resting heart rate (RHR) and the development of diabetes has yet to be fully elucidated, and the relationship between changes in RHR and incidence of diabetes also remains unclear. Our study aimed to investigate the association between changes in RHR over 2 years and the risk of diabetes.

Methods. – A total of 7416 adults without diabetes were included. All had participated in the Korean Genome and Epidemiology Study, a community-based, 10-year prospective study in which RHR was measured at baseline and 2 years later. Incident diabetes was defined as fasting blood glucose ≥126 mg/dL, 2-h post-load glucose ≥200 mg/dL during a 75-g oral glucose tolerance test or current use of diabetes medication. The relative risk of diabetes associated with the 2-year change in RHR was calculated using Cox models.

Results. – During the 10-year follow-up, 1444 (19.5%) developed diabetes. Compared with RHR increases <5 beats per minute (bpm) over 2 years, increases >10 bpm were significantly associated with development of diabetes (adjusted hazard ratio: 1.31, 95% confidence interval: 1.06–1.60), even after adjusting for glycometabolic parameters and baseline RHR. This significant association was attenuated in people who exercised regularly ($P = 0.650$), but remained significant in those not doing any regular exercise ($P = 0.010$).

Conclusion. – An increase in RHR over a 2-year follow-up period is significantly associated with a risk of diabetes, independently of baseline RHR and glycometabolic parameters. Further investigations into ways to control RHR as a potential preventative measure against the development of diabetes are now needed.

Keywords: Autonomic nerve system; Diabetes; Heart rate; Prospective; Risk factor

1. Introduction

Diabetes is a serious health problem worldwide, and its global patient population is expected to grow from the 171 million sufferers in 2000 to more than 366 million people by 2030 [1,2]. Its increasing prevalence has significant socioeconomic implications, and it is anticipated to be the seventh leading cause of death by 2030 [3]. Factors contributing to the risk of diabetes include obesity or overweight, family history of diabetes, hypertension, dyslipidaemia, history of gestational diabetes mellitus, history

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of polycystic ovary syndrome, and impaired glucose tolerance [4,5].

A high resting heart rate (RHR) was recently reported to be associated with an increased likelihood of having diabetes [6–8]. RHR is a crude index of autonomic nervous system (ANS) status, and diabetes may be associated with an ANS imbalance [9]. Higher RHRs have also been linked to increased sympathetic nervous system (SNS) activity, and may increase both acute and chronic insulin resistance, thereby inducing diabetes [10,11]. SNS overactivity inhibits insulin secretion by beta cells in the pancreas, which is innervated by parasympathetic nerve fibers, thus causing vasoconstriction, which decreases skeletal muscle blood flow and reduces glucose uptake in skeletal muscle [12]. In addition, SNS activation stimulates the renin–angiotensin–aldosterone system (RAAS), associated with increases in heart rate, blood pressure, insulin resistance and the metabolic syndrome (MetS) [8,13]. However, the relationship between changes in RHR over long periods of time and diabetes has remained poorly understood. Thus, the present well-designed 10-year prospective study aimed to investigate whether changes in RHR are associated with the development of diabetes.

2. Materials and methods

2.1. Study population

Our study subjects were participants in the ongoing Korean Genome and Epidemiology Study (KoGES), a prospective community-based survey that began in 2001 with 10,030 participants, aged 40–69 years, living in the urban Ansan and rural Ansung communities in South Korea. KoGES was launched by the Korea Centers for Disease Control and Prevention (KCDC), and its findings have been used and validated in previous studies [14,15]. For the present study, current users of steroids ($n = 15$) and those with a diagnosis of diabetes or taking oral hypoglycaemic agents (OHAs) or insulin ($n = 682$) were excluded. Of the remaining 9333 participants, 45 were missing results from a 2-h 75-g oral glucose tolerance test (OGTT), 553 had fasting glucose concentrations ≥126 mg/dL or post-load glucose concentrations ≥200 mg/dL during a 75-g OGTT, and 13 with no baseline RHR data and were also excluded (Fig. S1; see supplementary material associated with this article online). Thus, 8722 participants were included in our analyses of the relationship between RHR at baseline and diabetes risk, of whom 5544 were successfully followed-up for 10 years. However, to examine the relationship between changes in RHR and risk of diabetes, 1306 subjects without 2-year follow-up RHR data had to be excluded. In the end, the association between changes in RHR and diabetes risk was investigated in 7416 subjects, of whom 5336 were followed for 10 years.

The study protocol was approved by the Ethics Committee of the KCDC and the Institutional Review Board of the Severance Hospital (IRB No: 4-2015-1050), and informed consent was obtained from all study participants.

2.2. Clinical data and measurements

KoGES participants are examined biennially, and also complete self-reported questionnaires on their personal and family medical histories, smoking habits, alcohol consumption, exercise status and use of medication. For the present study, participants were categorized according to smoking status (never, past or current smoker) and alcohol consumption (none, <1, 1–4.9 or ≥5 drinks per day) [16]. Exercise status was assessed by self-reported questionnaires on frequency of exercise (none, 1–3 times or ≥4 times per week).

Body weight and height were measured and used to calculate the body mass index (BMI; as kg/m^2). Obesity was defined according to criteria for the Asia–Pacific region (BMI ≥ 25 kg/m^2) [17]. Waist circumference was measured at the narrowest level between the upper iliac crest and lowest rib after normal expiration. Blood pressure was measured by averaging three recordings taken in the morning after at least 10 min of rest in a sitting position. Also, after a 10-min rest in a supine position, baseline RHR was obtained by averaging the results of three measurements of the radial artery pulse over 1 min by well-trained specialists. Changes were calculated by subtracting the baseline RHR from the RHR value at the 2-year follow-up visit, and analyzed as a continuous variable by standard z-scores or as categorical variables by three groups, according to bpm (<5 bpm, 5–10 bpm and >10 bpm).

Laboratory samples were obtained after a 12-h fast. Plasma total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, creatinine, and alanine and aspartate aminotransferases (ALT and AST, respectively) were measured using a Hitachi 747 chemistry analyzer (Hitachi Ltd, Tokyo, Japan). Low-density lipoprotein (LDL) cholesterol was assessed by the Friedewald equation: [total cholesterol–HDL cholesterol–triglycerides/5]. Levels of high-sensitivity C-reactive protein (hsCRP) were measured by immunoradiometric assay (ADVIA 1650 analyzer, Bayer Diagnostics, Tarrytown, NY, USA). Plasma samples were taken at 0 and 120 min during a 75-g OGTT for measurement of plasma glucose and insulin concentrations, using a hexokinase method and a radioimmunoassay kit (LINCO Research, St. Charles, MO, USA), respectively.

In the present study, incident diabetes was defined as the current use of oral diabetes medication or insulin injections, a fasting glucose level ≥126 mg/dL or a post-load glucose level ≥200 mg/dL during the 2-h 75-g OGTT, performed biennially as per the 1997 American Diabetes Association criteria [18]. HbA_{1c} levels were measured by high-performance liquid chromatography (Variant II; Bio-Rad, Hercules, CA, USA). Homoeostasis model assessment for insulin resistance (HOMA-IR) and beta-cell function (HOMA-β) indices were calculated using the following formulas: [fasting plasma insulin (μIU/mL) × fasting plasma glucose (mg/dL)/405] and [fasting insulin (μIU/mL) × 20/fasting glucose (mg/dL) × 0.05551 − 3.5], respectively [19]. MetS was defined according to the revised National Cholesterol Education Program (NCEP) definition (presence of at least three of the following criteria: waist circumference >90 cm in men or >80 cm in women, using Asia–Pacific abdominal obesity criteria; serum