Relationship between insulin resistance assessed by HOMA-IR and exercise test variables in asymptomatic middle-aged patients with Type 2 diabetes

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ABSTRACT. We investigated the relationship between index of insulin resistance (IR) and exercise test variables in middle-aged asymptomatic patients with Type 2 diabetes. Methods: 90 patients (48 men, 42 women; age: 49±6 yr) were included in the study. We used homeostasis model assessment for IR (HOMA-IR) index as index of IR. All patients were subjected to treadmill exercise test. Four subjects were tested positive (4.4%). Study patients were separated into three groups: group I (no.=26) HOMA-IR index <2.24; group II (no.=26) index 2.24-3.59; group III (no.=38) index >3.59. Results: group I had less frequency of cardiovascular risk factors than group II and III (p=0.001). Systolic blood pressure baseline as well as peak exercise values, were higher in group III than in group I and II (p=0.048 vs p=0.01, respectively). Higher total exercise time and peak workload were found in group I than group II and III (p=0.04). The recovery of heart rate (Δ HR) was similar among the study groups. We found significant negative correlations between HOMA-IR and total exercise time and peak workload. In addition we found significant negative correlations between age vs chronotropic index (CI), Δ HR and peak workload. There were also similar negative correlations between duration of diabetes vs CI and Δ HR. Conclusions: IR is associated with a variety of cardiovascular risk factors. Some exercise test variables point out changes of autonomic tone during exercise in elevated IR group. Negative correlation between HOMA-IR and peak exercise capacity (METs) may well confirm increased mortality in hyperinsulinemia.

INTRODUCTION
Diabetes can affect the heart in many ways, including premature and extensive coronary heart disease (CHD), neuropathies, cardiomyopathy, and disease of the microcirculation. Of all patients with diabetes, approximately 80% die of cardiovascular disease. Increased risk of CHD occurs in the prediabetic state of impaired glucose tolerance (2- to 3- fold risk), in the insulin resistance syndrome (or metabolic syndrome) (2-fold risk), and in Type 2 diabetes (3- to 4-fold risk). Given the growing epidemic of Type 2 diabetes, this represents a major global healthcare challenge. The identification of asymptomatic diabetic patients who are at increased risk and who benefit from aggressive primary prevention has the potential to reduce cardiovascular morbidity and mortality in diabetics. It is controversial whether exercise test should be used to screen asymptomatic non-diabetics as well as diabetics for cardiovascular risk. While several studies have found certain exercise test variables (e.g., reduced exercise capacity, ischemic ST-segment depression, chronotropic incompetence, and heart rate recovery) to be associated with increased morbidity and mortality in men and women, it is not known if these have similar prognostic value in diabetic patients (1-13). The fundamental defect in Type 2 diabetes mellitus is insulin resistance. Insulin resistance has also been associated with increased CHD and mortality (14-16). Bonora et al. (17) showed that insulin resistance assessed by the homeostasis model assessment for insulin resistance (HOMA-IR) was a predictor of cardiovascular disease. However, there are no data on the relationship between insulin resistance and exercise test variables in asymptomatic patients with Type 2 diabetes. In the present prospective study, we investigated the relationship be-
between insulin resistance (as estimated by HOMA-IR) and exercise test variables in unselected consecutive middle-aged asymptomatic patients with Type 2 diabetes without any documented evidence of CHD.

MATERIALS AND METHODS

Subjects

Ninety asymptomatic Type 2 diabetic patients (according to World Health Organization criteria) (48 men, 42 women; age: 49±6 yr, range 36 to 60) without any documented evidence of CHD, were recruited from the Diabetic Clinic of Endocrinology and Metabolism Department. The duration of diabetes in study patients is 4±4.2 yr (range 1 to 21). In 38% of the study population the duration of diabetes was determined to be at least 1 yr. All patients used sulfonylureas. 33% of patients were added biguanide to their therapy. No patient used thiazolidinediones. Exclusion criteria were: Type 2 diabetes for <1 yr, history of myocardial infarction, history of typical chest pain, heart failure, uncontrolled hypertension (blood pressure >180/110 mmHg), significant heart valve disease, cardiomyopathy, known serious arrhythmias, left bundle branch block, previous coronary artery bypass surgery, atrial fibrillation, digoxin treatment, severe chronic disease or acute illness, renal disease other than diabetic nephropathy, urinary tract infection, and patients who were on insulin therapy.

Clinical data

Demographic and clinical data were collected with a standardized interview sheets: sex, age, duration of diabetes, smoking habits, family history of CHD, previous diseases, current drug therapy. Weight (to the nearest 0.5 kg) and height (to the nearest 0.5 cm) were measured while the subjects were fasting overnight and wearing only underwear. Body mass index (BMI) was calculated by weight (kg) divided by height (m²). Subjects with BMI>25 kg/m² were categorized as overweight; these subjects included obese individuals (BMI>30 kg/m²). Waist and hip circumferences (to the nearest 0.5 cm) were measured using a plastic tape meter at the level of the umbilicus and of the greater trochanters. In addition, waist-to-hip ratio (WHR) was also calculated. Blood pressure was measured with a standard sphygmomanometer on the left arm after at least 10 min of rest. Mean values were determined by two independent measurements. Hypertension was diagnosed according to standard criteria.

Careful physical examination was performed by each subject. All subjects underwent 12-lead electrocardiogram (ECG) which was interpreted according to the Minnesota code (18). Subjects with typical chest pain and/or typical ECG alterations suggestive of myocardial ischemia were not included in the study. Patients underwent fundoscopic evaluation to detect retinopathy and testing of creatinine clearance and 24-hr urine albumin excretion to detect nephropathy. Neurological history was taken and a physical examination was performed focusing on symptoms and signs of distal symmetric sensorimotor polyneuropathy. Electromyogram was performed to detect distal symmetric sensorimotor polyneuropathy.

Laboratory data

Fasting venous blood was tested using standard assays for glucose, total, LDL- and HDL-cholesterol, triglycerides, creatinine, glycosylated hemoglobin (HbA₁c), insulin, C-peptide, fibrinogen, ferritin. 24-h urine was collected for urinary albumin excretion.

Treadmill exercise testing

Subjects were requested to discontinue any antihypertensive medication having anti-ischemic properties, including calcium antagonists and β-blockers, for at least 5 half-lives before exercise testing. A maximum symptom-limited exercise stress test was performed according to the Bruce protocol using the Cardifox ECG-9320K (Nihon Kohoden, Japan) exercise treadmill between 09:00 and 11:00 h. The patients were encouraged to reach symptom-limited maximal exercise; the achievement of the age-predicted heart rate (HR) (220 - the patient's age) alone was not a sufficient reason for the termination of testing. A standard 12-lead ECG was recorded initially under basal conditions subsequently just before the test, at the end of each 3-min step, at the appearance of ECG signs of ischemia, at peak exercise and every minute during recovery period. Blood pressure was measured with cuff sphygmomanometer at 3-min intervals during exercise and at every minute during recovery. Testing was terminated at fatigue or by the medical staff in the event of >4 mm ST depression. The rate-pressure product (RPP: HR x systolic blood pressure) was calculated under basal condition, at peak exercise and at 1 min of recovery period. Peak workload (as determined on the basis on the standard tables), expressed in metabolic equivalents (METs; METs equals 3.5 ml of oxygen uptake per kilogram of body weight per minute), was based on total exercise time. A test was defined as suboptimal if the patient failed to achieve 85% of age-predicted HR. Chronotropic response during exercise was assessed by calculating the ratio of HR reserve expended to metabolic reserve expended at peak exercise as previously described (19). For any given stage of exercise, the percent metabolic reserve expended is: ([METs_peak - METs_basal] / [METs_basal]) x 100. In analogous fashion, the percent heart rate (HR) reserve expended was: [(HR_peak - HR_basal) / (age-predicted HR - HR_basal)] x 100. Thus chronotropic incompetence can be defined as a percent HR reserve expended to percent metabolic reserve expended ratio of <0.8; this will be referred to as a low chronotropic index (CI). We considered the ratio of HR reserve expended to metabolic reserve expended at peak exercise, when, by definition, the proportion of metabolic reserve expended has a value of one. Using this approach, CI was based entirely on directly measured variables, namely HR_basal, HR_peak and age (19). The value for the recovery of HR (Δ HR) was defined as the change from HR_peak to that measured at 1 min of recovery (that is, Δ HR =HR_peak - HR_recovery at 1 min recovery). A positive ECG response was defined as the occurrence of at least 1 mm ST segment depression in comparison with the baseline tracing. The ischemia threshold was defined as the appearance of a 1 mm horizontal or downsloping ST segment depression 0.08 sec after the J point in comparison with baseline ECG. Tests were analyzed by an observer (A.A.) who was blinded to the patient's status.

Assessment of insulin resistance and sensitivity

Insulin resistance was measured with the HOMA-IR. HOMA-IR index was calculated [formula: fasting plasma glucose (mmol/l) x fasting serum insulin (µU/ml) / 22.5]. Gokcel et al. (20) recently showed the mean values of HOMA-IR in healthy subjects and Type 2 diabetic patients were 2.24 and 3.59 in the Turkish population, respectively. According to HOMA-IR index, patients were separated into three groups: group I (no. =26) HOMA-IR index <2.24; group II (no. =26) index 2.24-3.59; group III (no. =38) index >3.59. These values divided our study patients into nearly equal tertiles. Low HOMA-IR index indicate high insulin sensitivity, whereas high HOMA-IR index indicate low insulin sensitivity (insulin resistance).