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Intensive cardiac rehabilitation improves glucometabolic state of non-diabetic patients with recent coronary artery bypass grafting

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ABSTRACT

Background: The aim of this study is to examine the effect of an intensive CR program early after coronary artery bypass grafting on glucometabolic state of non-diabetic patients with CAD.
Methods: 60 patients were included in the study. All patients underwent Oral Glucose Tolerance Test (OGTT), Homeostasis Model Assessment (HOMA) Index and Six Minutes Walking Test at baseline and at the end of CR. The patients were then included in a 3-month follow-up program.
Results: At baseline 61% of the patients had normal fasting glucose, while after OGTT 28.3% had normal glucose tolerance, 41.6% had impaired glucose tolerance (IGT), and 30.1% had type 2 diabetes mellitus (T2DM). At the end of the CR program the number of patients with T2DM was significantly lower (−22%, $p < 0.05$) while the number of normal glucose tolerance patients had significantly increased (+26%; $p < 0.05$). T2DM and IGT patients showed worse performances at Six Minutes Walking Test than normal glucose tolerance patients at baseline but had a similar improvement after 4 weeks of training. After 3 months follow-up fasting blood glucose, insulin levels and HOMA index were increased compared to 4 week values, but were lower than baseline.
Conclusion: OGTT is important to evaluate glucometabolic state of CAD patients. Intensive CR improves glucometabolic state and insulin resistance in CAD patients with impaired glucose metabolism.

1. Introduction

It is well known that individuals with type 2 diabetes mellitus (T2DM) have an increased cardiovascular morbidity and mortality [1,2] and that patients with coronary artery disease (CAD) and T2DM have significantly worse outcomes than patients with CAD but without diabetes [3–6]. Impaired glucose tolerance (IGT) is also a strong risk factor for future cardiovascular events as fatal or non-fatal re-infarction, stroke, and severe heart failure in patients with recent myocardial infarction [7]. The glucometabolic state of patients admitted to the coronary care units with acute myocardial infarction, with or without diagnosis of diabetes, is an important marker of risk for long-term mortality. The Glucose in Acute Myocardial Infarction (GAMI) study [8] suggested that patients with myocardial infarction have a high prevalence of previously unknown T2DM and IGT and recent data from the EURO Heart Survey on Diabetes [9] have shown a high prevalence of T2DM or IGT in patients with chronic CAD.

Nearly 20% of patients with myocardial infarction have a previously diagnosed T2DM [2,10]; however if an Oral Glucose Tolerance Test (OGTT) is performed, the prevalence of diabetes becomes higher, presumably as high as 40–45% [8,11].

Patients with CAD undergoing cardiac rehabilitation (CR) early after coronary artery bypass grafting have often impaired glucose metabolism, irrespective of a previous history of diabetes, as a consequence of that stressful condition. OGTT is more accurate than fasting blood glucose alone in order to identify CAD patients with impaired glucose metabolism [12,13]. Detection of impaired glucose metabolism during hospitalization in patients with CAD in the acute and post-acute phases may therefore be a target for novel secondary preventive efforts.

Among preventive interventions, exercise training has a well established role on treating impaired glucose metabolism as underlined by guidelines in patients with T2DM and IGT.

The aim of our study was to examine the real prevalence of glucose metabolism alterations in patients with CAD, without previous diagnosis of T2DM, and to evaluate the potential beneficial effect of physical training on glucometabolic state of these patients.

2. Methods

From January 2010 to June 2011 we screened 136 consecutive CAD patients who were admitted to our CR Unit to undergo a cycle of in-hospital rehabilitation early after coronary artery bypass (less than

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10 days). After clinical stabilization and optimization of therapy, the patients underwent a cycle of in-hospital rehabilitation that started two weeks after CABG.

We included in the study patients with no previous history of T2DM, fasting blood glucose at admission <126 mg/dl, and full ability to start physical training within three days after admission. Exclusion criteria were: previous diagnosis of T2DM (it was considered present if the patient had been informed of this diagnosis and/or was on anti-diabetic treatment), physical disabilities contraindicating training, ventricular arrhythmias, primary valve disease, pericardial effusion, severe chronic obstructive pulmonary disease and claudication.

Demographic and clinical data were recorded at admission to our Unit; on the first morning after admission fasting blood glucose, serum lipid profile (total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides), serum renal and liver function (creatinine, BUN, uricemia, SGOT, SGPT, γ-GT) and coagulation parameters were assessed. Low density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula. All patients were tested for physical abilities. After evaluation of inclusion and exclusion criteria patients were asked to join the study and to sign the consent form previously approved by the local ethics committee.

At baseline weight, height, body mass index (kg/m^2), waist circumference, and systolic and diastolic blood pressure were collected. All patients underwent an OGTT (ingestion of 75 g of glucose dissolved in 200 ml of water) according to WHO standards, including fasting basal blood glucose and fasting blood insulin and blood glucose and insulin measurements 30, 60, 90 and 120 min after glucose load. At baseline and prior to the OGTT, glycated hemoglobin (HbA1c), inflammatory markers (high sensitivity-C Reactive Protein, IL-6, TNF-α), creatinine clearance and microalbuminuria were assessed. Insulin resistance was estimated by the homeostasis model assessment (HOMA) index [14]. A baseline standard 12-lead electrocardiogram and a full transthoracic echocardiogram were performed for all patients. Functional capacity was only measured through the distance walked at Six Minutes Walking Test that was performed according to a standardized procedure [15]. The test was supervised by a physical therapist. The patients were asked to walk at their own maximal pace in a 100 m long hospital corridor with 10 m signs on the floor. Every minute a standard phrase of encouragement was told. The patients were allowed to stop if signs or symptoms of significant distress occurred (dyspnea, angina), though they were instructed to resume walking as soon as possible. Results of Six Minutes Walking Test were expressed as distance walked (meters).

After baseline assessment the patients entered a 4 week program of intensive CR. The physical rehabilitation program was performed according to the AHA guidelines: each exercise session included warm-up, cool-down and flexibility exercises and 30–60 min of aerobic exercise with cycling or treadmill [16] for two exercise sessions every day for six days/week. The patients underwent an additional assessment by OGTT, HbA1c, HOMA index, transthoracic echocardiogram and Six Minutes Walking Test at the end of the in-hospital rehabilitation program.

All the patients were then included in an outpatient physical training program for 3 further months and were given a nutritional and exercise program (walking fast at least 30 min for 3 times/week). At the end of the 3 month period all the patients underwent a follow-up visit with assessment of body weight, height, body mass index, waist circumference, fasting glucose and insulin, HBA1c and HOMA index. The patients were asked to express their compliance to the home-based exercise program through an exercise questionnaire in which the level of compliance was considered high/moderate (exercise > 3 times/week) or low (exercise < 3 times/week).

2.1. Definitions

The glucometabolic state was classified based on the WHO criteria: normal glucose tolerance was recognized as a fasting blood glucose < 110 mg/dl (6.1 mmol/l) and 2-h post-load glucose < 140 mg/dl (7.8 mmol/l); IGT was defined as fasting blood glucose < 126 mg/dl (7 mmol/l) and 2 h post load glucose ≥ 140 mg/dl (7.8 mmol/l) and <200 mg/dl (11.1 mmol/l); and T2DM as fasting blood glucose ≥ 126 mg/dl (7 mmol/l) or a 2 h post load glucose ≥ 200 mg/dl (11.1 mmol/l). The term abnormal glucose tolerance was used to describe the presence of newly detected T2DM or IGT.

2.2. Laboratory analysis

2.2.1. Serum inflammatory cytokine assessment

Once processed, serum samples were immediately stored at −80 °C. TNF-α and IL-6 (R&D System) were examined by ELISA method according to manufacturer's instructions.

2.2.2. Glucose and insulin assessment

Glucose and insulin were measured after an overnight fasting. The blood samples were collected in 5-ml tubes, immediately placed on ice, and transferred to the biochemistry laboratory where samples were processed. Plasma insulin levels were measured by immunoradiometric assay with a commercially available kit (DiaSorin, Inc., Reutlinger, Germany).

2.3. Statistical methods

Values were expressed as mean ± SD or as percentages where appropriate. Differences in baseline characteristics between groups were evaluated by the chi-square and unpaired *t* test. Within-group changes in the reported variables were evaluated by the paired *t*-test or Wilcoxon signed rank test for non normally distributed variables. Between group comparisons were performed by the unpaired *t*-test and Mann–Whitney rank sum test. All analyses were performed with a commercially available statistical package (SPSS for Windows version 12.0, Chicago, Illinois).

3. Results

136 consecutive CAD patients admitted over a 12 month period (January 2011 to June 2011) to our Cardiac Rehabilitation Unit, early after coronary artery bypass grafting (average 5.6 days) were screened for the study. 37 of these were diabetic, and 39 were unable to start physical training within 3 days from admission because of acute complications or severe physical disability. Sixty patients resulted non diabetic and were able to start physical training, so they were included in the study.

At baseline 61% of the patients had normal fasting glucose, 85% of the patients had body mass index ≥ 25; mean waist circumference of our sample was 101.7 ± 9.5 cm (23 men > 102 cm, 6 women > 88 cm). The first OGTT was performed 2 weeks after CABG. Basing on baseline OGTT results, the patients were divided into 3 groups: 17 patients (28.3%) had normal glucose tolerance, 25 (41.6%) had IGT, and 18 (30.1%) had T2DM.

Clinical characteristics of patients included in the study according to their glucometabolic state are shown in Table 1. At baseline IGT and T2DM groups had higher HOMA index, higher levels of microalbuminuria and higher blood levels of IL6 and TNF-α than normal glucose tolerance group.

At the end of 4-week CR program, there were no significant changes on BMI and waist circumference. According to post-CR OGTT, 55% of the patients resulted to have normal glucose tolerance, 38% IGT and 7% T2DM. Overall there was a significant improvement in 2 h glucose levels (170.2 ± 56.2 mg/dl vs 146.8 ± 54.8 mg/dl; p = 0.002). Fasting glycemia (−8.5%), fasting insulinemia (−34.2%), 2 h insulinemia and glycemia and HOMA index (−44%) significantly decreased after 4 weeks CR (Table 2). High sensitivity C-Reactive Protein significantly decreased compared to baseline. Levels of IL6 and TNF-α also significantly