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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

**Table 1**
Basal characteristics of the population according to glucometabolic state.
Abbreviations: NGT: Normal Glucose Tolerance; IGT: Impaired Glucose Tolerance; T2DM: Type 2 Diabetes Mellitus; BMI: Body Mass Index; 6MWT: Six Minutes Walking Test; BUN: Blood Urea Nitrogen; HDL chol: High-density lipoprotein cholesterol; LDL chol: Low-density lipoprotein cholesterol; hs-CRP: high sensitivity C-Reactive Protein.

| Population | NGT N = 17 | IGT N = 25 | T2DM N = 18 |
|---|---|---|---|
| Clinical variables | | | |
| Age | 69.4 ± 7 | 69.8 ± 13 | 72.3 ± 13 |
| Sex: M/F | 15/2 | 21/4 | 17/1 |
| Body weight, kg | 77.6 ± 13 | 78.9 ± 13 | 82.9 ± 13 |
| Waist circumference, cm | 101.7 ± 9 | 102.5 ± 10 | 104.1 ± 12 |
| BMI, kg/m$^2$ | 27.6 ± 4 | 27.4 ± 6 | 29.0 ± 4 |
| Ejection fraction % | 58.2 ± 7 | 53.6 ± 11 | 47.3 ± 8 |
| Systolic BP, mm Hg | 112.6 ± 10 | 110.4 ± 12 | 112 .9 ± 8 |
| Diastolic BP, mm Hg | 82.4 ± 12 | 82.7 ± 21 | 81.2 ± 19 |
| Resting heart rate, bpm | 78 ± 14 | 80 ± 11 | 77 ± 16 |
| 6MWT, m | 344.2 ± 79 | 291.8 ± 66 | 265 ± 71 |
| Previous myocardial infarction | 7 | 14 | 11 |
| Number of vessels involved (one/two/three) | 4/7/6 | 5/13/7 | 2/7/9 |
| Hypertension (N) | 13 | 17 | 15 |
| Dyslipidemia (N) | 9 | 16 | 14 |
| Atrial fibrillation (N) | 4 | 3 | 6 |
| Laboratory values | | | |
| Hemoglobin, gr/dl | 11.0 ± 1.5 | 11.8 ± 2.2 | 12.1 ± 1.5 |
| Creatinine, mg/dl | 1.1 ± 0.2 | 1.2 ± 0.3 | 1.1 ± 0.2 |
| BUN, mg/dl | 40.7 ± 18 | 42.1 ± 16 | 42.9 ± 14 |
| Creatinine clearance, ml/min | 80.3 ± 16 | 80.0 ± 21 | 79.4 ± 19 |
| Microalbuminuria, mg/die | 41.3 ± 12 | 44.6 ± .14 | 48.5 ± 11 |
| Uricemia, mg/dl | 5.9 ± 2 | 5.3 ± 2 | 5.7 ± 1 |
| Alanine transaminase, UI/l | 20.8 ± 4 | 21.4 ± 4 | 18.3 ± 5 |
| Aspartate transaminase, UI/l | 24.5 ± 7 | 22.5 ± 5 | 26.1 ± 6 |
| Gamma-GT, UI/L | 28.5 ± 7 | 31.6 ± 4 | 28.6 ± 5 |
| Triglycerides, mg/dl | 148.1 ± 39 | 146.4 ± 36 | 154.3 ± 44 |
| Total cholesterol, mg/dl | 148.5 ± 32 | 150.9 ± 37 | 163.5 ± 41 |
| HDL chol, mg/dl | 31.0 ± 5 | 32.6 ± 7 | 28.6 ± 4 |
| LDL chol, mg/dl | 93.0 ± 38 | 98.0 ± 41 | 105.0 ± 34 |
| hs-CRP, mg/l | 4.6 ± 1.2 | 5.5 ± 1.9 | 7.9 ± 2.2 |
| Therapy | | | |
| Beta blockers (N) | 14 | 23 | 14 |
| ACE-inhibitors (N) | 16 | 22 | 18 |
| Statins (N) | 13 | 21 | 13 |
| Calcium channel antagonists (N) | 6 | 9 | 6 |
| Antiplatelet agents (N) | 17 | 25 | 18 |
| Diuretics (N) | 11 | 18 | 10 |

decreased (from 14.2 ± 4.0 and 21.2 ± 3.6 to 8.6 ± 1.6 and 18.2 ± 2.1 respectively) after 4-week training program. There was a statistically significant correlation between changes in IL6 and HOMA index ($r = 0.42$; $p < 0.05$). CRP, IL6 and TNF were not related to fasting blood glucose.

**Table 2**
Changes observed on metabolic parameters at 4 weeks and 12 weeks in the overall study-population; inflammatory markers at baseline and 4 weeks in the overall study-population.
Abbreviations: BMI: Body Mass Index; HOMA index: Homeostasis Model Assessment Index. HbA1c: glycated hemoglobin.

| | Basal | 4 weeks | 12 weeks |
|---|---|---|---|
| BMI, kg/m$^2$ | 29.8 ± 3.4 | 29.6 ± 2.7 | 31.4 ± 3.5 |
| HOMA index | 3.0 ± 1.6 | 1.7 ± 0.8* | 2.3 ± 1.2** |
| Fructosamine, μm/l | 269 ± 34.9 | 260 ± 19.9 | 328 ± 48.1** |
| Fasting insulinemia, μU/ml | 12.3 ± 3.5 | 8.1 ± 4.0* | 9.5 ± 4.4 |
| Fasting glycemia, mg/dl | 95.6 ± 17.3 | 87.5 ± 10.8* | 93.7 ± 16.1 |
| HbA1c, % | 5.7 ± 0.4 | 4.2 ± 0.3* | 5.8 ± 0.4** |
| Inflammatory markers | | | |
| IL6 | 14.2 ± 4.0 | 8.6 ± 1.6* | |
| TNF-α | 21.2 ± 3.6 | 18.2 ± 2.1 | |

* $p < 0.05$ between baseline and 4 weeks.
** $p < 0.05$ between 4 weeks and 3 months.

At baseline and at 4 weeks NGT patients had significantly better performances at Six Minutes Walking Test than IGT and T2DM patients. However the three groups had a similar increase of distance walked at Six Minutes Walking Test after physical training (normal glucose tolerance = +166.3 ± 45; IGT = +153.8 ± 64; T2DM = +193.4 ± 61).

At 3 month follow-up visit, the level of compliance to the home-based exercise training, as expressed through the exercise questionnaire, was low at 78% of the subjects. There was a significant increase of body weight and waist circumference compared to both baseline and 4 week values. Fasting glycemia, fasting insulinemia, and HOMA index (+35%) were all increased compared to 4 week levels; conversely their levels remained lower than baseline. Levels of high sensitivity C-Reactive Protein were similar to 4-week assessment but lower than baseline.

## 4. Discussion

The first finding of this study is the high prevalence of impaired glucose metabolism in our sample of CAD patients undergoing intensive CR early after coronary artery bypass grafting. In our population of subjects without history of diabetes, less than one third of them had normal glucose tolerance after the first OGTT evaluation. Our results are in agreement with similar findings reported in other studies [10,17]. Boas Soja et al. [12] showed a prevalence of impaired glucose metabolism of 49–68% in a cohort of CAD patients undergoing CR. In the Euro Heart Survey [18] only 29% of the patients with acute CAD and 34% of those with stable CAD had normal glucose tolerance.

Our study underlines the importance of using OGTT in addition to fasting plasma glucose for the screening of impaired glucose metabolism in patients with CAD, especially in the context of cardiac rehabilitation/secondary prevention programs. According to our data, many subjects with impaired glucose metabolism would remain undiagnosed by using fasting plasma glucose alone. In our population more than half of the patients (61%) had a normal fasting glycemia. 30% of the patients with unrecognized T2DM and 40% of the patients with IGT would have been misclassified if they had not undergone an OGTT test. Our findings are in agreement with those of Norhammar that in the GAMI and DIGAMI studies underlined the usefulness to perform an OGTT test in patients with acute ischemic syndromes [8,18]. Similarly Boas Soja et al. [12] showed that one-fifth of patients with unrecognized T2DM would remain undiagnosed when using the fasting glucose criteria alone. Discovering a previously unknown impaired glucose metabolism could help physicians to better stratify the risk of patients: IGT is related to a rate of cardiovascular mortality twice higher than normal glucose tolerance [1,7,19]. Only in the recent decade blood glucose levels have been recognized as an independent risk factor for cardiovascular morbidity and mortality [6,20]; several studies showed that raised blood glucose levels on admission were associated with increased mortality and congestive heart failure [21–25]. Afterwards, in the context of a cardiac rehabilitation unit we could identify high risk patients using both fasting blood glucose and OGTT and select them for a more intensive rehabilitation program that aims at preventing new acute cardiovascular events.

Moreover, CABG interventions, like other stressful conditions, may unmask IGT and diabetes [26]. According to our study post-CABG IGM, could be often reversible if a comprehensive intervention including exercise training would be performed. According to the results of second OGTT determination (post-CR), the proportion of subjects classified as T2DM and IGT changed significantly. In particular, 64% of the patients previously classified as IGT resulted as NGT, while 77% of the patients previously classified as T2DM resulted as IGT.

The second finding of the present study is that an intense exercise training (six days/week), performed in the contest of a very short cardiac rehabilitation program (4 weeks), leads to a fast improvement of glucose metabolism in patients with CAD early after CABG, without inducing significant changes on body weight and waist circumference. The benefits of exercise in preventing and treating T2DM and

IGT have been widely recognized [27–30]. However available data come, mostly, from long-term interventions. It has been showed that exercise training improves glycemic control, body composition, cardiorespiratory fitness, cardiovascular risk, physical functioning and well-being in patients with T2DM or IGT. The DANSUK study [12] demonstrated that a long-term CR intervention, besides the improvement in exercise capacity, improves several metabolic parameters including fasting plasma glucose among patients with CAD and T2DM or IGT.

The causal mechanisms of these exercise training-induced benefits in T2DM and IGT are complex. They include improvements in insulin resistance [31], increase of insulin dependent glucose uptake [32] and increase of muscle capillarization and blood flow [33].

In this study we focused our attention on insulin resistance as the leading cause of impaired glucose metabolism in our population. IGT and T2DM are associated to insulin resistance causing hyperglycemia on the background of an insulin secretion defect. Moreover, the cause of insulin resistance can change in different clinical conditions. In stable subjects undergoing long-term exercise programs the reduction of insulin resistance is strongly related to body weight decrease. The Finnish Diabetes Prevention Study (DPS) [28] found that a reduction in body weight achieved through an intensive diet and exercise program was associated with a significant reduction of the risk of developing T2DM. The reduction of the risk of progression to diabetes was directly related to the magnitude of the changes in lifestyle. Conversely in the setting of post-coronary artery bypass grafting patients, insulin resistance results from an exaggerated release of stress-hormones and pro-inflammatory cytokines related to the stressful event [26]. The inflammatory response has a well established role in the occurrence of hyperglycemia after cardiac surgery. IL6 and TNF-α cause insulin resistance in both liver and skeletal muscles most likely through the modification of signaling properties of insulin receptor substrates [26].

In our population we evidenced a significant decrease of insulin resistance after the training period that was significantly related to a decrease of the blood levels of inflammatory cytokines. Probably we could conclude that in our population physical activity improved glucose metabolism by modulating the inflammatory response [34,35]. The lack of changes on body weight confirms that the improvement of insulin resistance was body weight-independent. The increase of HOMA index at 12 weeks seems to be related to a low compliance of patients to the prescribed exercise program.

## 5. Study limitations

The most important limitation of this study is the lack of a control group (not exercise training after coronary artery bypass grafting). However post coronary artery bypass grafting patients who were ruled out from the CR program were considered not comparable to the study sample. On the other hand we considered unethical to assign to a not exercise training group subjects who met the CR criteria. Moreover because of the lack of a control group we cannot rule out that the improvement of glucose metabolism observed is due to the longer time period between CABG and second post CR OGTT compared to the first OGTT.

Other important limitations are a small sample size and a short follow-up time. Moreover, among factors affecting insulin resistance, only inflammatory cytokines were investigated while we have no data on stress-hormones.

## 6. Conclusion

In conclusion, the OGTT is useful to better identify the glucometabolic state in CAD patients with normal fasting glucose, also early after coronary artery bypass grafting. So this test should be considered an essential part of routine care management in cardiac rehabilitation settings. Our data suggest that the leading cause involved in the improvement of glucose metabolism after training could be the reduction of insulin resistance.

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