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A randomized trial comparing the effect of weight loss and exercise training on insulin sensitivity and glucose metabolism in coronary artery disease

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ABSTRACT

Aim. The majority of patients with coronary artery disease (CAD) exhibit abnormal glucose metabolism, which is associated with mortality even at non-diabetic glucose levels. This trial aims to compare the effects of a considerable weight loss and exercise with limited weight loss on glucose metabolism in prediabetic, CAD patients.

Methods and Results. Seventy non-diabetic participants with CAD, BMI 28–40 kg/m^2, age 45–75 years were randomized to 12 weeks' aerobic interval training (AIT) at 90% peak heart rate three times weekly or a low energy diet (LED, 800–1000 kcal/day) for 8–10 weeks followed by 2–4 weeks' weight maintenance diet. Glucose tolerance, insulin action, β-cell function and suppression of lipolysis were assessed using a 3-h oral glucose tolerance test. ISI-composite and ISI-HOMA (=1/HOMA-IR) were calculated as surrogate measures of whole-body and hepatic insulin sensitivity, respectively. Magnetic resonance imaging estimated abdominal adipose tissue. Twenty-six (74%) AIT and 29 (83%) LED participants completed intervention per protocol. LED increased ISI-composite by 55% and ISI-HOMA by 70% ($p < 0.01$) while AIT did not change insulin sensitivity ($p > 0.7$) revealing a significant difference between the groups ($p < 0.05$). No concurrent significant changes in lipolysis, β-cell responsiveness or insulin clearance were seen. Changes in ISI-HOMA and ISI-composite were associated with reduced visceral abdominal fat, waist circumference and body weight. Intention-to-treat analyses (n = 64) yielded similar results.

Conclusion. LED is superior to AIT in improving insulin sensitivity in prediabetic CAD patients. Changes in insulin sensitivity are associated with decreased visceral abdominal fat, waist circumference and body weight.

Abbreviations: AIT, Aerobic interval training; AUC, Area under the curve; CAD, Coronary artery disease; FPG, Fasting plasma glucose; FPI, Fasting plasma insulin; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; ISI, Insulin sensitivity index; HOMA, Homeostatic Model Assessment; ISR, Insulin secretion rate; LED, Low energy diet; NEFA, Non-esterified fatty acids; OGTT, Oral glucose tolerance test; T2D, Type 2 diabetes; 2hPG, 2-h plasma glucose.

Clinical Trial Registration: NCT01724567.

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1. Introduction

Physical inactivity and overweight, especially with abdominal distribution, are common denominators in coronary artery disease (CAD), type 2 diabetes (T2D) and prediabetes (i.e. impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)) [1–4]. The T2D diagnosis is based on the glucose levels at which retinopathy occurs; nevertheless, macrovascular changes develop at glucose levels below the diabetic threshold and cardiovascular risk increases [4–6]. CAD, T2D and prediabetes are increasingly common co-morbidities with a large proportion of CAD patients exhibiting abnormal glucose metabolism which predicts poor prognosis [7,8].

Consequently, targeting disturbances in glucose metabolism in CAD is pivotal. Life style interventions comprising weight loss and physical activity have prevented T2D [9] and decreased cardiovascular mortality [10] in populations with IGT. Effects of exercise and weight loss, induced by caloric restriction on glucose metabolism have been compared in healthy overweight populations [11,12]; however, the two intervention modalities have not yet been compared in a high-risk population of overweight, prediabetic CAD patients.

The CUT-IT trial was designed to compare the effect of aerobic interval training (AIT) with limited weight loss and a considerable weight loss following a low energy diet (LED) as secondary prevention in CAD [13]. We previously reported that the interventions were feasible and caused the desired improvements in physical fitness and body weight [14]. This paper addresses the effect on insulin action, β-cell responsiveness and suppression of lipolysis during an oral glucose challenge. Abdominal obesity and visceral adipose tissue are central in the complex interplay between CAD and defects in insulin action [15]. Since LED was superior to AIT in reducing waist circumference and abdominal visceral fat [14] we hypothesize that LED will be superior to AIT in improving glucose metabolism, insulin sensitivity and β-cell function.

2. Methods

2.1. Population

Population, design and intervention in this randomized trial were described previously [13]. In short, the main inclusion criteria were CAD diagnosed more than 6 months prior to inclusion, body mass index (BMI) 28–40 m/kg^2, age 45–75 years and no diabetes. The participants were randomized en bloc (1:1) to either 12 weeks' supervised AIT three times a week or weight loss induced by an LED described in detail in Section 2.2. The trial was conducted at the Department of Cardiology, Bispebjerg University Hospital. Approval was obtained from the ethics committee of the Capital Region of Denmark (H-4-2010-146) and the study adheres to the Helsinki declaration.

2.2. Intervention

As described previously [13] the total duration of the AIT protocol was 38 min. It was initiated by a 10-min warm-up on a staircase or an exercise bike followed by high intensity interval training on an exercise bike. The intervals were 1–4 min (85%–90% of peak aerobic capacity (VO_2peak) and Borg scale 17–18, total of 16 min) separated by active pauses of 1–3 min (65%–70% of VO_2peak). The estimated energy expenditure for each session can be calculated based on the energy equivalent of oxygen (4.825 kcal/L O_2) [16], mean baseline VO_2peak of 1988 L/min and a mean intensity of 85% of VO_2peak during the intervals and 75% of VO_2peak during the active pause and the warm-up. Thus, the energy expenditure is calculated as: (0.85 × 1.988 L/min × 16 min × 4.825 kcal/L) + 0.75 × 1.988 L/min × 22 min × 4.825 kcal/L) = 288 kcal. The sessions were supervised by physiotherapists with experience in cardiac rehabilitation and all participants were monitored using heart rate monitors and the Borg scale [17]. The AIT group was examined at least 18 h after the last exercise session.

Experienced clinical dieticians instructed the participants to follow the LED (800–1000 kcal/day, the Cambridge Weight Plan, Northants, UK) for 8–10 weeks followed by 2–4 weeks' transition to a weight maintenance diet to ensure that the LED group was examined during a non-catabolic phase. The LED consisted of soups, shakes, porridge and bars four times a day supplemented by a few additional vegetables, yoghurt and one liter of skimmed milk. The diet was designed to provide the participants with all necessary micro- and macronutrients. The weight maintenance diet was a high protein/low glycemic index diet modified from the DiOGenes study [18]. Considering that the participants had CAD the high protein diet was adapted to resemble the Mediterranean diet, which is recommended to heart patients [19], thus the protein sources were mainly fish, poultry, egg, dairy and vegetables. After the 12-week intervention the participants consulted the dieticians once a month for another 40 weeks to sustain the obtained weight loss.

Neither group was given activity or dietary advice outside the specific LED and AIT protocol. However, 45 (82%) participants had attended an organized cardiac rehabilitation program >3 months prior to enrolment.

2.3. 3-h Oral Glucose Tolerance Test

After an overnight 10-h fast the participants underwent a three-hour oral glucose tolerance test (OGTT). Blood samples were drawn using a polyethylene cannula in an antecubital vein at −10, 0, 10, 20, 30, 45, 60, 75, 90, 105, 120, 150 and 180 min. Directly after time 0 min a standard 75-g glucose solution was ingested within 3–5 min. Glucose blood samples were immediately cooled on ice and centrifuged within 15 min whereas samples for hormone analyses rested for 30–45 min before centrifugation. All samples were centrifuged for 10 min (3500 rpm, Universal 320R, Hettich Centrifugen, Tuttlingen, Germany). Plasma was stored at −80 °C. Glucose analyses were performed using an YSI 2300 STAT Plus Glucose and Lactate Analyzer (YSI, Yellow Springs, OH, USA). Enzyme-linked immunosorbent assay (ELISA) was used to determine C-peptide and insulin (pmol/l, Immulite 2000, Siemens Healthcare Diagnostics, LA, CA, USA) whereas an enzymatic test was used to determine non-esterified fatty