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Weight loss is superior to exercise in improving the atherogenic lipid profile in a sedentary, overweight population with stable coronary artery disease: A randomized trial

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ABSTRACT

Background: Dyslipidemia and low-grade inflammation are integral in the pathogenesis of atherosclerosis. We aim to compare the effects of a considerable weight loss and intensive exercise training on lipid atherogenicity and low-grade inflammation in a high-risk population with coronary artery disease (CAD).
Methods: 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 85–90% of peak heart rate three times/week or a low energy diet (LED, 800–1000 kcal/day) for 8–10 weeks followed by 2–4 weeks' weight maintenance diet. Lipid profile atherogenicity was described using lipoprotein particle size and density profiling. Low-grade inflammation was evaluated by tumor necrosis factor alpha (TNFα), C-reactive protein, interleukin 6 and soluble urokinase plasminogen activator receptor.
Results: Twenty-six (74%) AIT and 29 (83%) LED participants completed intervention per protocol. AIT and LED decreased total (AIT: −518 {−906;−129},P = 0.011, LED: −767 {−1128:−406},P < 0.001) and low-density lipoprotein (LDL, AIT: −186 {−306;−65},P = 0.004, LED: −277 {−433;−122},P < 0.001) assessed as the area under the density profile curve. LED was superior to AIT in decreasing atherogenicity reflected by increased LDL (between-group: 1.0 Å {0.4; 1.7},P = 0.003) and high-density lipoprotein (between-group: 1.2 Å {0.2; 2.4},P = 0.026) particle size and a decreased proportion of total lipoprotein constituted by the small, dense LDL_5 subfraction (between-group: −5.0% {−8.4;−1.7},P = 0.004). LED decreased TNFα (9.5% {−15.8;−2.6},P = 0.009). No changes were seen following AIT.
Conclusion: LED and AIT decreased total and LDL lipoprotein. LED was superior in decreasing atherogenicity assessed by a shift in density profile and increased particle size. Effect on low-grade inflammation was limited.

1. Introduction

Initiation and progression of atherosclerotic plaque are mediated by deposition of atherogenic lipoproteins in the intima and media of the arterial wall eliciting an inflammatory response. Unstable atherosclerotic plaque prone to rupture is characterized by perivascular inflammation and a lipid-rich core. Plaque rupture is believed to be the cause of 60–70% of myocardial infarctions [1,2]. In clinical practice amounts of low and high-density lipoprotein

Abbreviations: AIT, Aerobic interval training; BMI, Body mass index; CAD, Coronary artery disease; CRP, C-reactive protein; HDL, High density lipoprotein; FFM, Fat free mass; IL6, Interleukin 6; LDL, Low density lipoprotein; LED, Low energy diet; TNFα, Tumor necrosis factor alpha; SuPAR, Soluble urokinase plasminogen activator receptor; TRL, Triglyceride-rich lipoprotein; VO_2peak, Peak aerobic capacity.

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(LDL and HDL) cholesterol in blood are used to monitor lipid-lowering treatment and assess cardiovascular risk [3]. However, measurement of lipoprotein density and particle size could provide a more accurate risk estimation by taking into account the small, dense atherogenic lipoprotein particles with triglyceride-rich, cholesterol-depleted cores [4–8].

The pro-inflammatory cytokines tumor necrosis factor alpha (TNFα) and interleukin 6 (IL6) are believed to be involved in the pathogenesis of atherosclerosis [2]. A meta-analysis comprising 29 studies associated IL6, TNFα and the inflammatory marker C-reactive protein (CRP) to increased cardiovascular risk independent of traditional risk factors in healthy populations [9]. Increased IL6, CRP and TNFα predicts a poor prognosis in stable and unstable CAD [10–12]. Recently, the inflammatory marker soluble urokinase plasminogen activator receptor (suPAR) was linked to atherogenesis, cardiovascular risk in healthy populations and prognosis following ST-elevation myocardial infarction [13–15].

Dyslipidemia and low-grade inflammation are associated with obesity and sedentarism [2,3,16]. The current paper compares the effects of 12 weeks' aerobic interval training (AIT) to those of a rapid weight loss using a low energy diet (LED) on lipid profile atherogenicity and low-grade inflammation. We recently demonstrated that both interventions elicited similar decreases in total cholesterol, triglycerides and nonHDL-cholesterol and reduced visceral abdominal fat; albeit, LED was superior to AIT [17]. Since low-grade inflammation and lipoprotein particle size [18,19] have been associated with visceral adipose tissue we hypothesize a superior effect of LED in terms of decreasing inflammatory response and lipoprotein atherogenicity.

2. Methods

2.1. Study design

Population, study design and intervention of this randomized trial has been described in detail previously [20]. Main inclusion criteria were CAD diagnosed >6 months prior to inclusion, BMI 28–40 kg/m^2, age 45–75 years and no diabetes. Participants were randomized to either 12 weeks' supervised AIT at 85–90% of VO_2peak three times/week or a weight loss program using an LED (800–1000 kcal/day, the Cambridge Weight Plan, Northants, UK) for 8–10 weeks, followed by a 2–4 week weight maintenance diet to ensure a non-catabolic state at follow-up. The AIT group was examined >18 h after the last exercise session [20].

Per protocol adherence to intervention was a priori defined as: ≥5% weight loss in the LED group and training attendance ≥60% overall and ≥50% the last two weeks of the intervention in the AIT group. The aim of the study was a direct comparison of weight loss and exercise training thus the main results are the per protocol analyses. All participants who were examined at 12 weeks entered into the intention-to-treat analyses (Fig. 1).

Written informed consent was obtained from each participant.The study obtained approval from the Danish Dataprotection Agency and the regional ethics committee of the Capital Region of Denmark (H-4-2010-146) and adheres to the Helsinki declaration.

2.2. Body composition and peak aerobic capacity

As previously published [17] body fat mass and fat free mass (FFM) was determined by dual X-ray absorptiometry. Magnetic resonance imaging (MRI) estimated abdominal visceral and subcutaneous fat. For logistic and medical reasons only 33 participants underwent MRI at both baseline and follow-up. A bicycle ergometer and breath-by-breath gas exchange measurements determined peak aerobic capacity (VO_2peak). To account for changes in body composition VO_2peak was expressed as mL/kg FFM$^{0.67}$/min.

2.3. Blood samples: collection and analyses

All blood samples were drawn from an intravenous cannula in an antecubital vein in the morning after a 10-h overnight fast. Samples were centrifuged for 10 min at 3500 rpm (Universal 320R, Hettich Centrifugen, Tuttlingen, Germany) and plasma was stored at −80 °C.

2.3.1. Density profiling

Density profiling was carried out using ultracentrifugation [21,22] with a bismuth sodium ethylenediaminetetraacetic acid (NaBiEDTA, TCI America, Portland, OR) gradient solution and lipoproteins pre-stained with the lipophilic fluorescent probe NBD C6 (ceramide (6-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)hexanoyl)sphingosine, Invitrogen, Carlsbad, CA). Each sample was centrifuged in an ultracentrifuge tube (Beckman Coulter Inc., Palo Alto, CA) at 120,000 rpm, for 6 h using an Optima TLX ultracentrifuge and a TLA 120.2 fixed-angle rotor (Beckman–Coulter, Palo Alto, CA). An image of tube was obtained and analyzed using a digital OptronicsMicrofireCamera (S99808, Goleta, CA) with a Fiber-Lite MH-100 Illuminator as a light source (MH100A, Edmund Industrial Optics, Barrington, NJ). A digital color microscope camera (S99808, Optronics, Goleta, CA) was used to record the image. The image was converted to a density profile using a commercially available software program (OriginPro 7.5, Microcal Software Inc., Northampton, MA) depicting fluorescence emission in pixels at any given point versus tube coordinate (6–33 mm length). For a more detailed description of the method and an example of the density profile curve see online appendix B.

The lipoproteins were divided into subfractions based on density. The amount of each subfraction was determined as the area under the density profile curve which is determined as the total amount of pixels per defined subfraction as indicated by the length along the tube. Lipoprotein density is inversely related to lipoprotein particle size (Table 2) [4]. Average particle size was calculated using the percentage each subfraction constituted of total LDL or HDL.

2.3.2. Inflammatory markers

TNFα was determined using an enzyme-linked immunosorbent assay (ELISA, DRG instruments Marburg, Germany). SuPAR was analyzed using suPARnostic® ELISA (ViroGates, Copenhagen, Denmark). CRP was determined using a high sensitivity assay ELISA with a lower detection limit of 0.2 mg/L. The ELISA used for IL6 had a lower detection level of 2 pg/mL (Immulite 2000, Siemens Healthcare diagnostics, LA, CA). All kits were used according to the manufacturer instructions. The intra-assay variation was 3.2%, 3.3–4.5%, 2.8–8.7% and 3.3–4.9% whereas inter-assay variation was 5.4%, 6.3–6.6%, 3.1–8.7% and 4.6–7.2% for suPAR, TNFα, CRP and IL6, respectively. Baseline and 12-week samples were analyzed using the same assay.

2.4. Statistics

Sample size calculation was published earlier and was based on the primary endpoint of the study, coronary flow reserve [20,23]. Categorical data, including IL6 dichotomized at 2 ng/mL, are presented as number (percentage) and compared using χ^2 or Fischer's exact test. McNemar's test was used for within-group comparison of IL6. Continuous data are presented as mean (SD) or median (Q1, Q3) if not normally distributed. An appropriate t-test was used for comparisons of paired (within-group) and unpaired (between-group) continuous data. Logarithmic transformation (log10) was