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A randomized trial of cold-exposure on energy expenditure and supraclavicular brown adipose tissue volume in humans

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ABSTRACT

Objective. To study if repeated cold-exposure increases metabolic rate and/or brown adipose tissue (BAT) volume in humans when compared with avoiding to freeze.

Design. Randomized, open, parallel-group trial.

Methods. Healthy non-selected participants were randomized to achieve cold-exposure 1 hour/day, or to avoid any sense of feeling cold, for 6 weeks. Metabolic rate (MR) was measured by indirect calorimetry before and after acute cold-exposure with cold vests and ingestion of cold water. The BAT volumes in the supraclavicular region were measured with magnetic resonance imaging (MRI).

Results. Twenty-eight participants were recruited, 12 were allocated to controls and 16 to cold-exposure. Two participants in the cold group dropped out and one was excluded. Both the non-stimulated and the cold-stimulated MR were lowered within the group randomized to avoid cold (MR at room temperature from 1841 ± 199 kCal/24 h to 1795 ± 213 kCal/24 h, $p = 0.047$ cold-activated MR from 1900 ± 150 kCal/24 h to 1793 ± 215 kCal/24 h, $p = 0.028$). There was a trend towards increased MR at room temperature following the intervention in the cold-group ($p = 0.052$). The difference between MR changes by the interventions between groups was statistically significant ($p = 0.008$ at room temperature, $p = 0.032$ after cold-activation). In an on-treatment analysis after exclusion of two participants that reported ≥8 days without cold-exposure, supraclavicular BAT volume had increased in the cold-exposure group (from 0.0175 ± 0.015 l to 0.0216 ± 0.014 l, $p = 0.049$).

Conclusions. We found evidence for plasticity in metabolic rate by avoiding to freeze compared with cold-exposure in a randomized setting in non-selected humans.

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1. Introduction

Brown adipose tissue (BAT) can activate non-shivering thermogenesis which turns glucose and fatty acids into heat. In rodents the volume and activity of BAT increase following prolonged stimulation by cold [1]. In humans it has been demonstrated that there is a tendency for obese people to have less activity in BAT and also that high age is related to lower non-shivering thermogenesis activity after stimulation [2–4]. However, most studies on BAT activity in humans have relied on radioactive markers such as fluorodeoxyglucose-PET with or without concomitant computer tomography (CT) [3–6]. Both these imaging techniques subject the participants to radiation, which limits the use of such investigations in healthy subjects. Magnetic resonance imaging (MRI) is an imaging technique which is devoid of radiation. BAT has a water content of about 50% which is intermediate compared with that of fat with has 10% water and muscle tissue having about 90% of water. This makes it plausible to use MRI to study BAT volume in humans [7–11] based on water content. The iron content of a particular tissue is also detectable by MRI, which has been the basis for functional magnetic resonance imaging (fMRI) as a means to detect and measure regional blood flow in tissues such as the human brain [12]. Similar techniques could potentially also be used for non-invasive and non-radioactive detection of blood flow and hence the activation of human BAT.

Since there is an inverse relationship between BAT activity and measures of obesity [13], and since activation of BAT can increase the energy expenditure, there is a great interest in how to increase BAT in order to lose body weight [13–16]. However, almost all trials on this theme have been conducted in animals, and little is known about plasticity of human BAT regarding both volume and activity. Data from observational studies in humans are suggestive of changes in BAT activity. Saito et al. demonstrated that BAT activity determined by PET CT was higher during periods of low outdoor temperatures compared with warm periods [4]. More specifically, a recent study by Yoneshiro et al. demonstrated that in young men who had been selected for little or no BAT activity, cold stimulation for 2 h a day at 17 °C during 6 weeks promoted development of visible BAT activity in all these subjects and that this also resulted in increased cold-induced activation of BAT [17].

We aimed to study whether basal metabolic rate, with or without acute cold-stimulation, could be affected by repeated cold exposure for 6 weeks in a randomized study in non-selected healthy men and women. We also aimed to see whether such stimulation would affect BAT volume and activation when assessed by MRI-based techniques which also gave information about potential changes in subcutaneous and visceral fat depots.

2. Methods

2.1. Recruitment and Intervention

The participants were recruited by local advertising at the University of Linköping. The subjects had to be free from known significant diseases as judged by medical check-up and history. Subjects were randomly assigned to either the cold (intervention) or warm group (controls) by drawing ballots. Since a higher drop-out rate was anticipated in the intervention group, 16 subjects were randomized to the cold-intervention and 12 to become controls. The study was conducted from February to April 2013 in Linköping, Sweden. Thus the study start was during the coldest time of the year in Sweden, at late winter, and progressed through very early spring. Participants randomized to the cold group were instructed to stay cool but to avoid shivering, for at least one hour a day every day for the study duration of six weeks. Examples of how this could be done were provided. For instance to sit by an open window or on a balcony with light clothing. Prolonged cold showers or baths were also suggested. The subjects in the cold group were asked to keep a diary on how they accomplished the cold-exposure, and also to grade how cold they had felt on these occasions. Participants of the control group were conversely instructed to stay warm for the duration of the study and to not, at any time, feel cold. They were encouraged to use long-johns and caps.

2.2. Metabolic Rate

Blood samples and measurements of metabolic rate were obtained at baseline and at the end of the study in the fasting state in the morning. A ventilated hood technique (Quark RMR, Cosmed, Finland) was used to measure metabolic rate, as based on oxygen inhalation and carbon dioxide exhalation i.e. indirect measurement of metabolic rate. The registration started with the subject being warm, wearing only underwear but covered with a blanket in a room with a temperature of about 21 °C. After 8–14 min, depending on when the metabolic rate had individually stabilized, the subject drank a glass of ice cold water (3 dl) and a cold vest, that had previously been fitted, was activated by starting the internal flow of cold tap-water. The total duration of the registration, including the acute cold stimulation, varied between 18 and 28 min. The mean values of the last five minute-based readings of metabolic rates during regular body temperature (before acute cold stimulation) were calculated and also the corresponding readings during acute cold exposure (but without shivering) after drinking the chilled water.

2.3. Laboratory Tests

Blood was drawn in the morning after a 10 h over-night fast. Standard laboratory tests such as plasma glucose, thyroid hormones, apolipoproteins and insulin were analyzed according to routines at Department of Clinical Chemistry at the Linköping University Hospital. The Milliplex® MAP Gut Hormone Panel (Merck Millipore, Billerica, MA) designed for analysis with Luminex®-technique (Luminex, Austin, TX) was used for analysis of leptin, in concordance with the accompanying instructions. Total coefficient of variation (intra + inter assay) for leptin was 11%.

2.4. Magnetic Resonance Imaging

Muscle, visceral fat and total fat volumes were quantified based on water-fat whole-body MRI, acquired on a 3.0 T