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Randomized Control Trials

The impact of rate of weight loss on body composition and compensatory mechanisms during weight reduction: A randomized control trial

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SUMMARY

Background & aims: Rapid weight loss (WL) has been associated with a larger loss of fat free mass and a disproportional reduction in resting metabolic rate (RMR), but the evidence is inconclusive. We aimed to evaluate the impact of WL rate on body composition and compensatory mechanisms activated with WL (reduced RMR, increased exercise efficiency (ExEff) and appetite), both during negative and neutral energy balance (EB).

Methods: Thirty-five participants with obesity were randomized to lose a similar weight rapidly (4 weeks) or gradually (8 weeks), and afterwards to maintain it (4 weeks). Body weight and composition, RMR, ExEff (10, 25 and 50 W), appetite feelings and appetite-regulating hormones (active ghrelin, cholecystokinin, total peptide YY (PYY), active glucagon-like peptide-1 and insulin), in fasting and every 30 min up to 2.5 h, were measured at baseline and after each phase.

Results: Changes in body weight (≈9%) and composition were similar in both groups. With WL, RMR decreased and ExEff at 10 W increased significantly in the rapid WL group only. However, fasting hunger increased significantly with gradual WL only, while fasting and postprandial prospective food consumption, and postprandial hunger decreased (and postprandial fullness increased) significantly with rapid WL only. Basal total PYY, and basal and postprandial insulin decreased significantly, and similarly in both groups. After weight stabilization and no ketosis no differences between groups were found.

Conclusions: Despite differences while under negative EB, WL rate does not seem to have a significant impact on body composition or on compensatory mechanisms, once EB is reestablished.

Clinical trial registration number: NCT01912742 (the study was registered in clinicaltrial.gov).

1. Introduction

The worldwide prevalence of obesity has nearly doubled between 1980 and 2008 [1]. Although significant weight loss (WL) can be achieved by a combination of dietary restriction and increased physical activity (PA) [2], only approximately 15% of individuals with obesity succeed in maintaining WL in the long-term [3].

The problem of weight relapse is likely to be due, among other factors, to the activation of compensatory metabolic responses triggered by WL [4,5]. These include a reduction in both resting and non-resting energy expenditure [6]. The latter is thought to be driven mainly by an increase in exercise efficiency (ExEff) [7]. Moreover, an increase in the drive to eat has also been reported with WL [5]. The increased hunger and decreased fullness observed after WL are driven, at least partially, by changes in the plasma concentrations of appetite-regulating hormones [8]. It has been

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demonstrated that concentrations of anorexigenic hormones such as cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and insulin decrease with WL, whereas the concentration of the orexigenic hormone ghrelin increase [9,10].

International guidelines regarding obesity management recommend gradual WL (0.5–1 kg/week) [2]. There is a common belief that losing weight rapidly is associated with poorer outcomes, namely a greater loss of fat free mass (FFM) [11], a reduction in RMR greater than predicted [12], and more weight regain in the long-term [13]. However, these assumptions suffer from several methodological limitations, such as lack of randomization and/or not controlling for magnitude of WL [14,15]. In fact, the potential advantage of losing weight gradually has been recently questioned [16], and losing weight fast, with very low calorie diets (VLCD), has been associated with better [17] or similar [18,19] WL maintenance in the long-term. Moreover, no studies have evaluated if WL rate has an impact on the strength of compensatory mechanisms activated with WL, so more studies are required.

This study aimed to explore the impact of WL rate (rapid *vs* gradual) on body composition and compensatory mechanisms (RMR, ExEff and appetite).

2. Materials and methods

2.1. Participants

Adults (18–65 years old) with obesity (30 < BMI<45 kg/m^2) were recruited. The study was approved by the local Regional Ethics Committee (Midt-Norway, Trondheim, Norway). All participants provided written informed consent before enrolling in the study. The study was registered in clinicaltrial.gov (NCT01912742).

Participants had to be weight stable over the past 3 months (±2 kg) and have a sedentary lifestyle. Women were required to have a regular menstrual cycle (28 ± 2 days). Persons with clinical significant illness, including diabetes, with previous WL surgery and/or those taking medication known to affect appetite or induce WL were excluded.

2.2. Sample size estimation

Sixteen participants would be needed to detect a difference of 6.5 pM × h/L in the area under the curve (AUC) for GLP-1 between the two groups, assuming a standard deviation of 6.2 pM × h/L, at a power of 80%, and a significance level of 5%.

2.3. Study design

Participants were randomized to one of two intervention groups: (1) rapid or (2) gradual WL with the sequence determined using a web-based randomization system (WebCRF). Allocation concealment was enforced. Both interventions were designed to achieve a similar WL (9–10% WL). Participants were asked not to change their PA levels throughout the study.

2.4. Detailed protocol

- Weight loss phase

The rapid WL group was provided with a commercial VLCD (550 and 660 kcal/day for women and men, respectively) (Allévo, Karo Pharma AB, Sweden) for 4 weeks.

The gradual WL group was provided with a low calorie diet (LCD) (1200 and 1500 kcal/day for women and men, respectively) using meal replacements (Allévo, Karo Pharma AB, Sweden) plus conventional foods for 8 weeks (see Tables S1 and S2 in Supplementary Tables). The macronutrient composition of the diets was matched (% energy provided by each macronutrient): 38.9% protein, 16.4% fat, 40.0% carbohydrates (CHO), 5.9% fiber (VLCD 550 kcal/day: 54 g protein, 10 g fat, 55 g CHO, 16 g fiber; VLCD 660 kcal/day: 64 g protein, 12 g fat, 66 g CHO, 20 g fiber, and LCD 1200 kcal/day: 117 g protein, 22 g fat, 120 g CHO, 35 g fiber; LCD 1500 kcal/day: 146 g protein, 27 g fat, 150 g CHO, 44 g fiber).

- Weight loss maintenance phase

After WL, participants were prescribed an individual diet plan by a dietitian based on their energy requirements (measured, RMR × PAL (1.4)), with a macronutrient composition of 15–20% protein, 20–30% fat, 50–60% CHO, aiming at weight stabilization for 1 month.

2.5. Compliance

Diet: All participants kept daily food records and were monitored weekly by a dietitian. Food diaries were analyzed using Mat på data version 5.1 (Mattilsynet og Helsedirektoratet, Norway). Urine acetoacetic acid concentration was measured weekly, using Ketostix reagent strips, as a measure of compliance in the rapid WL group.

Physical Activity: SenseWear (Body Media, Pittsburg, USA) devices were worn for one week, at baseline, weeks 2 + 4 and 4 + 8 for the rapid and gradual WL groups, respectively, and again (for both groups) at the last week of the WL maintenance. Data was considered valid if participants wear the armbands for ≥4 days, including at least 1 weekend day, on more than 95% of the time [20].

2.6. Data collection

Testing was performed at baseline, after WL (weeks 5 and 9 for rapid and gradual WL groups, respectively), and after WL maintenance (weeks 9 and 13 for rapid and gradual WL groups, respectively).

2.6.1. Body weight and composition

Air displacement plethysmography (Bod Pod Life Measurement, Inc., Concord, CA, USA) was used.

2.6.2. RMR

RMR was measured using indirect calorimetry (Vmax Encore 29, Care Fusion, Germany) using standard reference method procedures [21].

2.6.3. Exercise efficiency

ExEff was measured by graded cycle ergometry, immediately after blood sampling. Participants pedaled at 60 rpm against graded resistance to generate 10, 25 and 50 W of power in successive 4 min intervals. Gas exchange was measured continuously using a metabolic cart (Monark, Eromedic 839E, GIH, Sweden). ExEff was expressed as net efficiency (NE) [7].

2.6.4. Appetite measurements

In fasting and every 30 min after a standard breakfast, for a period of 2.5 h, appetite feelings (hunger, fullness, desire to eat, and prospective food consumption (PFC)) were measured using a validated 10 cm visual analog scale [22], and blood samples were collected. A standard breakfast containing 600 kcal (17% protein, 35% fat, 48% CHO) was consumed within 20 min. Plasma samples were analyzed for active ghrelin (AG), total PYY, active GLP-1, and insulin, using an Human Metabolic Hormone Magnetic Bead Panel