Clinical Nutrition 37 (2018) 815–823

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized Control Trials

Compensatory mechanisms activated with intermittent energy restriction: A randomized control trial

Sílvia Ribeiro Coutinho [a,*], Eline Holli Halset [a], Sigrid Gåsbakk [a], Jens F. Rehfeld [b], Bård Kulseng [a,c], Helen Truby [d], Cátia Martins [a,c]

[a] Obesity Research Group, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[b] Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[c] Centre for Obesity, Department of Surgery, St. Olav Hospital, Trondheim University Hospital, Trondheim, Norway
[d] Department of Food, Nutrition and Dietetics, Monash University, Melbourne, Australia

ARTICLE INFO

Article history:
Received 25 December 2016
Accepted 3 April 2017

Keywords:
Intermittent energy restriction
Continuous energy restriction
Body composition
Energy expenditure
Appetite
Weight loss

SUMMARY

Background & aims: Strong compensatory responses, with reduced resting metabolic rate (RMR), increased exercise efficiency (ExEff) and appetite, are activated when weight loss (WL) is achieved with continuous energy restriction (CER), which try to restore energy balance. Intermittent energy restriction (IER), where short spells of energy restriction are interspaced by periods of habitual energy intake, may offer some protection in minimizing those responses. We aimed to compare the effect of IER versus CER on body composition and the compensatory responses induced by WL.
Methods: 35 adults (age: 39 ± 9 y) with obesity (BMI: 36 ± 4 kg/m^2) were randomized to lose a similar weight with an IER (N = 18) or a CER (N = 17) diet over a 12 week period. Macronutrient composition and overall energy restriction (33% reduction) were similar between groups. Body weight/composition, RMR, fasting respiratory quotient (RQ), ExEff (10, 25, and 50 W), subjective appetite ratings (hunger, fullness, desire to eat, and prospective food consumption (PFC)), and appetite-regulating hormones (active ghrelin (AG), cholecystokinin (CCK), total peptide YY (PYY), active glucagon-like peptide-1 (GLP-1), and insulin) were measured before and after WL.
Results: Changes in body weight (≈12.5% WL) and composition were similar in both groups. Fasting RQ and ExEff at 10 W increased in both groups. Losing weight, either by IER or CER dieting, did not induce significant changes in subjective appetite ratings. RMR decreased and ExEff at 25 and 50 W increased ($P < 0.001$ for all) in IER group only. Basal and postprandial AG increased ($P < 0.05$) in IER group, whereas basal active GLP-1 decreased ($P = 0.033$) in CER group only. Postprandial CCK decreased in both groups ($P = 0.0012$ and $P = 0.009$ for IER and CER groups, respectively). No between group differences were apparent for any of the outcomes.
Conclusions: The technique used to achieve energy restriction, whether it is continuous or intermittent, does not appear to modulate the compensatory mechanisms activated by weight loss.
Clinical Trial Registration number: NCT02169778 (the study was registered in clinicaltrial.gov).

1. Introduction

The prevalence of obesity has increased to epidemic proportions worldwide [1]. Energy restricted diets remain the major tool for obesity management which assist individuals to lose weight. Most recommendations support the use of continuous energy restriction (CER) with a consistent daily reduction in energy intake [2].

Intermittent energy restriction (IER), characterized by short spells of severe energy restriction interspaced by periods of habitual energy intake, have become a popular method of weight loss (WL) [3]. This form of IER, referred to as alternate day fasting, involves a 'fast day', where food intake is either completely or partially restricted over 24 h period, alternated with a 'feed day', where food is consumed *ad libitum* over a 24 h. The fasting days vary between 2 and 4 days/week [4].

* Corresponding author. Obesity Research Group, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Forsyningssenteret, Prinsesse Kristinas Gate 5, 7030 Trondheim, Norway. Fax: +47 72571463.
E-mail address: silvia.coutinho@ntnu.no (S.R. Coutinho).

http://dx.doi.org/10.1016/j.clnu.2017.04.002

Few studies have compared the effects of IER with CER on body weight and composition in individuals with obesity. A recent study led by Catenacci et al. (2016) concluded that IER is a safe and tolerable approach to WL, producing similar changes in body weight and composition when compared with a CER diet [5]. However, that study is limited by the fact that physical activity (PA) levels were not measured, and as a result we do not know if differential changes in PA levels in the two intervention groups could have affected the outcome variables. A review by Varady et al. (2011) which compared independent studies that were done either IER or CER diets, with no direct comparisons between the two, showed that intermittent diets are equally effective in decreasing body weight and fat mass, although IER may be more effective in minimizing the loss of FFM [4]. However, in a 6 months RCT (comparing IER with CER) conducted by Harvie et al. (2011) was shown no differences between groups in the body composition changes [3]. More research comparing protocols of IER with CER diets is needed, given the few available studies, methodological limitations such as lack of a comparison group and/or not controlling for PA, and conflicting results. Furthermore, what has yet to be determined is whether IER offers some protection in terms of minimizing some of the compensatory mechanisms known to be activated during WL [6–9]. Deliberate periods of energy balance during WL – as in IER – could attenuate or deactivate various adaptive responses to energy restriction, and thereby reduce the risk of weight regain [58].

The main challenge in obesity management is that WL is usually not sustained in the long-term [6,9,10], and the majority experience weight regain over time [11]. Even though reduced motivation and compliance with the intervention are likely also to be involved in weight regain [12,13], diet-induced WL is known to activate metabolic adaptations [10,14], which increase the risk of relapse. These include a reduction in total energy expenditure [15], driven by a reduction in both resting and non-resting metabolic rate [15,16]. The mechanism responsible is likely to be a combination of both - an increase in exercise efficiency (ExEff) [17] plus a reduction in PA [18]. Moreover, WL is also known to be associated with a reduction in fat oxidation [19], and an increase in the drive to eat [10,20]. Changes in appetite-regulating hormones favoring increased hunger and reduced fullness have been described with WL [21,22], including an increase in the concentrations of the orexigenic hormone ghrelin [23], and a reduction in the concentrations of anorexigenic hormones such cholecystokinin (CCK), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1) [24–26].

No randomized control trials to date have examined the effects of IER on the type or strength of compensatory mechanisms activated during WL. Therefore, this experimental study aimed to explore the impact of IER versus CER, inducing a similar WL, on body composition and compensatory responses (resting metabolic rate (RMR), ExEff, respiratory quotient (RQ) and appetite) in adults with obesity.

2. Materials and methods

2.1. Participants

Adults (18–65 years of age, both genders) with obesity ($30 < BMI < 40$ kg/m^2) were recruited through advertisement posted in the local newspaper and surrounding community in Trondheim, Norway.

The study was approved by the local Regional Ethics Committee (Midt-Norway, Trondheim, Norway), and conducted according to the guidelines laid down in the Declaration of Helsinki. All participants provided written informed consent before enrolling in the study. The study was registered in clinicaltrial.gov under the number NCT02169778.

Inclusion criteria included weight stability (no large weight fluctuations during the previous 3 months (±2 kg)) and having a sedentary lifestyle (not engaged in strenuous work or in regular brisk leisure time exercise more than once a week or in light exercise for more than 20 min/day in more than 3 times/week). Women were required to have a regular menstrual cycle (28 ± 2 days). Those with clinical significant illness, including diabetes, or those who had WL surgery and/or those taking medication known to affect appetite or induce WL, and milk intolerance were excluded.

2.2. Sample size estimation

Twelve participants would be needed to detect a difference of 4 pM × h/L in the area under the curve (AUC) for GLP-1 between the two groups, assuming a standard deviation of 2 pM × h/L, at a power of 80%, and a significance level of 5%. To allow for a dropout rate of 25%, a minimum of 15 participants/group was deemed necessary.

2.3. Study design

Participants were randomized, using simple randomization, to one of two intervention groups: [1] an IER or [2] a CER diet over 12 weeks WL, with the sequence determined using a web-based randomization system (WebCRF). Both interventions aimed at the same overall energy restriction (33% reduction of the estimated energy needs; measured RMR × PAL (1.4)), and macronutrient composition (20% protein, 30% fat, and 50% carbohydrate). Participants were asked not to change their PA levels throughout the study.

2.4. Detailed protocol

The IER group underwent 3 non-consecutive days of partial fasting per week. During those 3 days, participants followed a commercial very low calorie diet (VLCD) (550 and 660 kcal/day for women and men, respectively) (Allévo, Karo Pharma AB, Sweden), plus were allowed to have low-starch vegetables (maximum 2 cups/day). For the feeding days, a diet matching energy needs was prescribed, using conventional food.

The CER group followed a low calorie diet (LCD) using conventional food every day. In both groups, the participants were encouraged to consume at least 2.5 L of non-caloric liquids/day. For more details regarding the dietary plan of both groups see Tables S1, S2 and S3 in Supplementary tables.

Energy prescription was reviewed throughout the trial (weeks 4 and 8) to account for changes in weight and RMR, in order to maintain a 33% energy restriction below estimated requirements for weight maintenance.

2.5. Compliance

Diet: All participants kept daily food records and were scheduled for weekly visits for weight monitoring and diet counseling with a trained dietitian. Food diaries for weeks 1, 4, 8 and 12 were analyzed for nutrient content in both groups using Mat på data version 5.1 (Mattilsynet og Helsedirektoratet, Norway).

Physical activity: All participants were asked to use armbands (SenseWear, Body Media, Pittsburg, USA) for one week, at baseline and again at weeks 6 and 12. For data to be considered valid, participants needed to wear the armbands for ≥4 days, including at least 1 weekend day, and more than 95% of data needed to be