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Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials

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A B S T R A C T

Energy restriction induces physiological effects that hinder further weight loss. Thus, deliberate periods of energy balance during weight loss interventions may attenuate these adaptive responses to energy restriction and thereby increase the efficiency of weight loss (i.e. the amount of weight or fat lost per unit of energy deficit). To address this possibility, we systematically searched MEDLINE, PreMEDLINE, PubMed and Cinahl and reviewed adaptive responses to energy restriction in 40 publications involving humans of any age or body mass index that had undergone a diet involving intermittent energy restriction, 12 with direct comparison to continuous energy restriction. Included publications needed to measure one or more of body weight, body mass index, or body composition before and at the end of energy restriction. 31 of the 40 publications involved 'intermittent fasting' of 1–7-day periods of severe energy restriction. While intermittent fasting appears to produce similar effects to continuous energy restriction to reduce body weight, fat mass, fat-free mass and improve glucose homeostasis, and may reduce appetite, it does not appear to attenuate other adaptive responses to energy restriction or improve weight loss efficiency, albeit most of the reviewed publications were not powered to assess these outcomes. Intermittent fasting thus represents a valid – albeit apparently not superior – option to continuous energy restriction for weight loss.

1. Introduction

Recent years have seen a surge in popularity of eating patterns involving intermittent energy restriction (IER). Such eating patterns involve restricting energy intake by varying degrees for a predefined period of time, and eating *ad libitum* (i.e. to satisfy appetite) – or at least more than during the energy-restricted period – at all other times. The most common form of IER is 'intermittent fasting', where energy intake is severely restricted for short periods (typically 1–4 days per week). During periods of greater energy intake, there may or may not be restrictions placed on the types and amounts of foods and beverages consumed.

While IER in varying forms has been used for health and religious reasons for thousands of years (Faris et al., 2012; Sweileh

Abbreviations: ADF, alternate day fasting; BMI, body mass index; CER, continuous energy restriction; DHEAS, dehydroepiandrosterone sulphate; 24-hour EE, 24-hour Energy expenditure; EI, energy intake; ER, energy restriction; EX, exercise; FFM, fat-free mass; %FM, percent fat mass; FM, fat mass; HbA_{1C}, glycated hemoglobin; Hip, hip circumference; HOMA-IR, homeostatic model assessment–[Insulin Resistance]; IER, intermittent energy restriction; IGF-1, insulin-like growth factor-1; REE, resting energy expenditure; T3, triiodothyronine or 3,3′,5-triiodothyronine; T4, thyroxine or 3,5,3′,5′- tetraiodothyronine; TSH, thyroid stimulating hormone; Waist, waist circumference.

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et al., 1992), it has more recently been popularised in a weight management context through various forms of the media. IER contrasts with the conventional approach to weight management, or continuous energy restriction (CER). The latter entails continuously trying to restrict energy intake to below weight maintenance requirements for an extended and often open-ended period of time, and usually also involves restrictions on the types of foods consumed (e.g. limiting the intake of energy-dense, nutrient-poor foods).

A question that has not been extensively addressed is whether or not IER provides *physiological* benefits over CER for weight management. For instance, is there a 'metabolic advantage' associated with IER? Specifically, does energy restriction achieved via IER result in greater weight or fat loss than the same overall amount of energy restriction achieved by CER? Or, do people who follow IER lose the same amount of weight or fat per unit of energy restriction, on average, as those on CER? IER might be expected to result in more efficient weight loss than CER, because of the known effects of energy restriction to induce physiological responses that oppose ongoing weight loss, and because of emerging evidence that these adaptive responses can be normalised or at least attenuated by a period of energy balance (i.e. where energy intake is matched to energy requirements and weight remains constant) or by *ad libitum* food intake. These considerations will be briefly reviewed in the next paragraph.

The adaptive responses to energy restriction in individuals that are overweight or obese are numerous and have been reviewed elsewhere (Sainsbury A, Seimon RV, Hills AP, Wood RE, King NA, Gibson AA, Byrne NM, submitted manuscript; Sainsbury and Zhang, 2012; King et al., 2012; Melanson et al., 2013; Leibel et al., 2015; MacLean et al., 2015; Rosenbaum et al., 2010; Maclean et al., 2011; Sumithran and Proietto, 2013; Sainsbury and Zhang, 2010). They include increased appetite (Mason et al., 2015; Purcell et al., 2014; Sumithran et al., 2011, 2013), reduced physical activity (Hunter et al., 2015; Camps et al., 2013) or the energy cost of physical activity (Hunter et al., 2015; Martin et al., 2011; Rosenbaum et al., 2003; Novak and Levine, 2007; Bonomi et al., 2013), reduced energy expenditure greater than that expected from the reduction in body mass (Knuth et al., 2014; McNeil et al., 2015), and hormonal effects that can adversely affect body composition by promoting the accumulation of adipose tissue (particularly central adiposity) and stimulating the loss of lean tissues (Sainsbury and Zhang, 2012; Stolzenberg-Solomon et al., 2012; Carpenter et al., 2012; Seimon et al., 2013; Wright et al., 2013). Indeed, studies in lean animals and humans clearly show that negative energy balance markedly inhibits activity of the hypothalamo-pituitary-thyroid (de Vries et al., 2015), -gonadotropic and -somatotropic axes (or reduces circulating insulin-like growth factor-1 [IGF-1] levels) (Steyn et al., 2011), while concomitantly activating the hypothalamo-pituitary-adrenal axis (Sainsbury and Zhang, 2012; Seimon et al., 2013). There is little information available as to the effects of weight loss in people that are overweight or obese on the circulating concentrations of effector hormones of these neuroendocrine axes (notably thyroid hormones, sex hormones, IGF-1 and cortisol), but available evidence suggests that similar changes to those occurring during energy deficit in lean animals and humans may also occur in overweight and obese people during weight loss interventions (Sainsbury and Zhang, 2012; Stolzenberg-Solomon et al., 2012; Carpenter et al., 2012; Seimon et al., 2013; Wright et al., 2013). Such changes could conceivably hamper outcomes from weight loss interventions, by fostering a hormonal milieu known to promote accretion of adipose tissue (particularly central adiposity) while simultaneously promoting loss of lean tissues (Sainsbury and Zhang, 2012). Some research suggests that the greater the deficit between energy requirements and intake, the greater the magnitude of these adaptive responses (Knuth et al., 2014; McNeil et al., 2015; Williams et al., 2015; Bailey et al., 2008; Sweeney et al., 1993). Interestingly, several lines of evidence from lean (Dulloo and Jacquet, 1998; Friedl et al., 2000) and overweight or obese (Camps et al., 2013; Stolzenberg-Solomon et al., 2012; Leibel et al., 1995; Rosenbaum et al., 1997; Westerterp-Plantenga et al., 2004; de Jonge et al., 2012; Belza et al., 2009) humans suggest that some adaptive responses to energy restriction may be deactivated or partially deactivated by well-controlled restoration of energy balance and weight maintenance at the reduced body weight, at least in some individuals. This phenomenon appears to be dependent upon restoration of true energy balance or even positive energy balance (not continued energy restriction) (Stolzenberg-Solomon et al., 2012), although positive energy balance was not a panacea for all aspects of the adaptive response to energy restriction (Purcell et al., 2014; Sumithran et al., 2011), as reviewed elsewhere (Sainsbury A, Seimon RV, Hills AP, Wood RE, King NA, Gibson AA, Byrne NM, submitted manuscript). Deactivation of adaptive responses to energy restriction may also occur more effectively when exercise is incorporated into the weight management regime (Sainsbury A, Seimon RV, Hills AP, Wood RE, King NA, Gibson AA, Byrne NM, submitted manuscript; Hunter et al., 2015; Weinsier et al., 2001; Foright, 2014; MacLean et al., 2009; Steig et al., 2011). Taken together, this literature would suggest that deliberate periods of energy balance during weight loss interventions – as in IER – could attenuate or deactivate various adaptive responses to energy restriction and thereby increase the efficiency of weight loss. But what is the evidence for this in humans?

To this end, we conducted a systematic review of original human clinical trials involving IER. We included studies with humans of any age or body mass index (BMI) incorporating a diet involving IER, with or without comparison to CER or a control arm, in order to assess any evidence that IER may reduce or fail to induce adaptive responses to energy restriction, or improve the efficiency of weight loss. To be included in the review, publications needed to measure body weight, BMI or body composition both before commencement of the intermittent diet, as well as upon completion of the diet.

2. Methods for the systematic review of intermittent energy restriction

2.1. Inclusion and exclusion criteria

Study designs included in this review were human clinical trials (randomized controlled trials and pilot studies). Only original research studies were included; review articles, case studies, surveys, as well as abstracts and conference papers, were excluded. To be included in this systematic review, publications needed to have investigated humans of any age or BMI that had undergone a diet involving IER. Ramadan fasting as a form of IER was excluded due to the pattern of eating not matching that of common forms of intermittent diets, but Sunnah fasting (nil by mouth, sunrise to sunset, typically 2 days per week) was included, as it is of a similar format to other forms of IER. Studies that did and did not include a comparator group on CER or control conditions were included, to give a broad perspective of the wide variety of ways in which IER is being investigated.

No limit was placed on the duration of IER. Studies were excluded if participants had undergone bariatric surgery, were diagnosed with cancer, Crohn's disease or were taking medications designed to induce weight loss. Any non-surgical, non-cancer or non-medication arms of any of the above such studies could, however, be included if they met the inclusion criteria.