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Review

Metabolic impacts of altering meal frequency and timing – Does when we eat matter?

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ABSTRACT

Obesity prevalence continues to rise throughout the developed world, as a result of positive energy balance and reduced physical activity. At present, there is still a perception within the general community, and amongst some nutritionists, that eating multiple small meals spaced throughout the day is beneficial for weight control and metabolic health. However, intervention trials do not generally support the epidemiological evidence, and data is emerging to suggest that increasing the fasting period between meals may beneficially impact body weight and metabolic health. To date, this evidence is of short term duration, and it is becoming increasingly apparent that meal timing must also be considered if we are to ensure optimal health benefits in response to this dietary pattern. The purpose of this review is to summate the existing human literature on modifying meal frequency and timing on body weight control, appetite regulation, energy expenditure, and metabolic health under conditions of energy balance, restriction and surplus.

1. Introduction

Obesity and overweight is a serious medical condition, and the prevalence of this continues to rise in developed nations, now affecting up to 60% of individuals. Worldwide in 2014, 39% of adults were overweight, and 13% were obese [1]. If the current rates of obesity continue, projections predict that by 2030, around 1.9 billion adults will be overweight or obese [2]. Obesity is associated with multiple metabolic abnormalities including low grade inflammation, hepatic steatosis, and insulin resistance that markedly increase the risk of developing type 2 diabetes, cardiovascular disease, infertility, and some types of cancers.

Identifying nutritional strategies that help regulate appetite and limit energy intake is a key goal of many researchers, and the consumption of small, regular meals has frequently been touted as a dietary approach that may limit weight gain [3–5]. The original concept for this approach was based on epidemiological evidence that shows an inverse relationship between adiposity, metabolic health and meal frequency [6–8]. Increased meal frequency has also been advocated as a dietary strategy to promote weight loss by enhancing satiety and reducing hunger [9], increasing energy expenditure [10], and improving metabolic health [11,12]. However, the evidence arising from intervention studies that have examined "nibbling" vs. "gorging" eating patterns in energy balance or under hypocaloric conditions shows limited benefit [13–21]. Furthermore, prescribing for increased eating opportunities must be carefully considered in today's obesogenic environment, since this may inadvertently result in over-consumption and weight gain [22–25]. This is especially important in light of recent evidence that shows that overconsumption of energy-dense foods with increased frequency results in poorer metabolic health [26].

Attention has turned to reduced meal frequency regimens, which prolong the fasting period between meals, and improve a number of health parameters including glycaemic control [27], lipid profiles [28,29], oxidative stress, inflammation [29,30], and body composition. Two modified meal patterns are of particular interest: 1) intermittent or alternate day fasting (ADF), or 2) time-restricted feeding (TRF). ADF is a dietary approach where food is

Abbreviations: ADF, alternate day fasting; AUC, area under the curve; DIT, diet induced thermogenesis; EE, energy expenditure; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; OGTT, oral glucose tolerance test; RMR, resting metabolic rate; RQ, respiratory quotient; TRF, time restricted feeding; VAS, visual analogue scale.

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either withheld, or minimal calories are consumed typically at 1 meal, for 2–3 non-consecutive days per week followed by *ad-libitum* consumption for 4–5 days per week. TRF is a dietary pattern whereby food intake is restricted to short windows of time, ranging from 4 to 13 h. In this review, the evidence for modified meal frequency and timing on appetite regulation, body weight, energy metabolism, and metabolic health parameters, including glycaemic control and lipid profiles will be compared. We will also examine the role that circadian rhythms may play in mediating the physiological responses to a meal.

2. The effects of increased meal frequency on the energy balance equation

Over 50 years ago, it was reported that lower meal frequency was associated with increased body weight [6]. Since then, a number of observational studies have supported this notion [7,8,31]. However, as recently reviewed [32], these data should be interpreted with caution. Most of these studies have relied solely on self-reported diet records or 24-h recollections. Self-report is prone to under-reporting of both caloric intake and meal frequency, especially in overweight, obese and diet-restrained individuals [33–35]. When under-reporting was accounted for, McCrory et al. observed that greater eating frequency was associated with positive energy balance [32]. This highlights the need for controlled intervention studies to delineate these effects. However, a paucity of high quality studies exist. Most of these are acute studies of small sample sizes [9,10,14,27,36–47], a handful are of short term duration [19,28,47–50], and few have examined effects over a longer term [51–54].

2.1. Does increased meal frequency alter appetite regulation or energy expenditure acutely?

The division of a meal into 4–5 smaller portions significantly reduced subsequent energy intake in lean men [9], although perceived hunger and satiety were not different between meal conditions. This response was not observed consistently [36] or in obese men [37,44], and still yet other studies have reported reduced feelings of fullness [40] and increased feelings of hunger in response to increased meal frequency [27,41]. Of note, studies are of small sample size (Table 1) and have not examined energy intake at dinner, or subsequent meals. A study that was conducted for 6-days inside a metabolic chamber showed that altering meal frequency by delivering meals two or six times per day did not influence additional snacking on foods that were provided *ad libitum* [14]. Mechanistically, increased meal frequency may modulate the pattern of release of the orexigenic hormone ghrelin [36,37,43]. However, total area under the curve (AUC) for ghrelin release was not different between meal frequencies in lean [36,43] or overweight or obese [37,40] individuals acutely, or following an 8 week hypocaloric intervention [19]. Thus, based on the available data, following a “nibbling” meal pattern does not have superior effects on appetite control, subsequent energy intake, or the modulation of ghrelin release, at least acutely.

It was originally postulated that increasing meal frequency would enhance energy expenditure through an increase in diet-induced thermogenesis (DIT) [55]. DIT was doubled in dogs that were fed 4 small meals as compared with the same number of calories consumed as a single meal [55]. However, studies in humans have generally failed to detect differences in DIT in response to increased meal frequency [39,45] (Table 1). Similarly, studies that have examined energy expenditure over 24-h in metabolic chambers, have not detected any effect of consuming 6 vs. 3 meals/d [41] or 3–5 meals/d vs. 1–2 meals/d [14,42,47]. It should be noted that whilst these studies were well controlled, they have been performed in small cohorts.

2.2. Does increasing meal frequency impact body weight management or preserve lean mass?

In humans, body weight was not altered in lean individuals who were instructed to alter meal frequency by consuming 3 or 6 [56,57], 2, 3 or 9 [58], or 1, 3 or 6 meals/d over 5–8 weeks [59] (Table 2). Similarly, body weight was not altered in men who reduced habitual meal frequency from 4 to 3 meals/d or increased habitual meal frequency from 3 to 4 meals/d for 4 weeks, although fat mass was increased by 360 g when meal frequency was reduced [50]. This study is in contrast to rats that gained more weight when allowed to nibble continuously, or fed 12 meals/d, as compared to rats that were fed 2 meals/d either *ad libitum* or at 1.25× energy requirements [60]. Of note, increased meal frequency did not differentially affect weight, body composition or energy expenditure after 131 days of consuming a 20% energy restricted diet in rats [61]. Similarly, Bortz et al. reported no effects of increased meal frequency on weight loss following a 600 kcal/d diet in obese women [62]. The rate of weight loss, fat loss and fat free mass loss was also not different in overweight women who were prescribed a 1000 kcal/d energy restricted diet as either 2 or 3–5 meals daily for 4 weeks [47]. There was also no difference in weight loss in obese men and women who were randomised to consume 3 meals, or 3 meals +3 snacks for 12 months [52]. Similar findings have been reported in other studies that have been conducted for between 4 and 26 weeks in obese individuals [19,53,63], supporting the conclusion that there is little benefit to increasing meal frequency of hypocaloric diets, at least in terms of total weight loss.

Increased meal frequency may also promote fat mass loss and preserve lean mass under hypocaloric conditions [64]. Lean mass was preserved in obese women who consumed a hypocaloric diet as 6 vs. 3 meals/d over 14 days, although differences in the macronutrient composition may have impacted this outcome [48]. Three groups of obese patients were fed very low calorie diets on a metabolic ward to alter the protein content of the diet ($n = 10$), meal frequency ($n = 14$) or both ($n = 14$) in a crossover design for 1 week each. Nitrogen loss was greater when obese individuals were fed 1 vs. 5 meals/d and when fed 10% vs. 15% protein. Of note, these effects were additive [65]. Similar trends were observed in a subsequent study by Arciero et al. [66]. These studies suggest that manipulating both protein and meal frequency are important to minimise lean mass loss under hypocaloric conditions. Further, a meta-analysis examining the effects of increased meal frequency on body composition in 15 studies [64] reported that increased meal frequency was linked with greater fat loss, and preservation of lean mass. However, the authors conceded that a single study may have influenced this result. When this study, which was conducted in amateur but “well-trained” boxers [67], was removed from the analysis these relationships were lost. Collectively, the available data suggests that increasing meal frequency does not confer additional benefits for appetite regulation, energy expenditure, or body weight, and limited data supports the hypothesis that this may spare lean mass under hypocaloric conditions.

2.3. Does increased meal frequency improve glycaemic control and cardiovascular risk?

Epidemiological research shows more frequent meal intakes are associated with lower fasting blood glucose and insulin, cholesterol and triglycerides, and a reduced risk of developing type 2 diabetes and coronary heart disease [12,68]. Acute intervention studies have partially supported these findings (Table 1), showing that division