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REVIEW ARTICLE

Meal Frequency and Time-Restricted Feeding as Strategies for Reducing Metabolic Risk: a Review

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Abstract

Obesity is a global health concern since it can develop into a clustering of pro-atherosclerotic metabolic abnormalities, including elevated blood pressure, blood glucose, and triglycerides and lower levels of high-density lipoprotein (HDL) cholesterol. Considering the rising prevalence of obesity in developed as also in developing countries, remedial measures are necessary to deter the upsurge of diet-related diseases. Caloric restriction, low carbohydrate, and high protein diet plans are some popular dietary strategies for weight loss and improving metabolic health. Even so, these methods face the problems of weight regain in the long term. Instead of controlling the quantity and nutritional quality of diets, approaches like reducing the number of meals per day or increasing fasting hours between meals, have recently been investigated for their usefulness in decreasing insulin resistance along with weight loss. There are limited intervention trials reporting the impact of meal frequency (MF) and time-restricted feeding (TRF) on weight control and metabolic health markers. Therefore, in this review, we surveyed literature to assess the impact of meal frequency and time-restricted feeding for their effectiveness in achieving weight loss and insulin sensitivity. This review demonstrates the potential of meal frequency and extended fasting hours for achieving weight loss and sound metabolic health. Lower meal frequency of 2 to 3 meals per day with higher protein intakes is a sustainable lifestyle change that can achieve weight loss, reduced adiposity and insulin sensitivity. TRF, with a smaller fasting window (12-14 hours), may be beneficial in achieving weight loss provided there is a compensatory adjustment in total caloric and carbohydrate intake. However, due to the lack of uniformity in study designs, sample sizes, duration, and outcome parameters, currently published data are inadequate to recommend either of these strategies for overcoming the risk of metabolic syndrome.

Keywords: meal frequency, time-restricted feeding, obesity, insulin resistance, weight loss, body fat, HbA1c, metabolic risk, fasting glucose, lipids

Introduction

Worldwide prevalence of obesity has markedly increased in the past few decades[1]. Obesity leads to many metabolic abnormalities such as insulin resistance, hyperlipidemia, and high blood pressure. These, in turn, increase the risk of developing non-communicable diseases, i.e. type 2 diabetes and cardiovascular disease[2]. Multiple factors such as sedentary lifestyle, overconsumption of food or hormonal imbalance may contribute to the rise in the percentage of obese and overweight individuals[3]. Amongst the conventional corrective measures for reducing adiposity, the most predominant are restricting dietary intakes of calories, fats, and sugars, increasing protein intake and physical activity. Several studies have reported that individuals consuming plant-based meals experience improved blood sugar control as well as reduced risk of cardiovascular disease compared to people consuming animal foods 2 to 3 times a day[4]. People consuming plant-based diets have been found to have better insulin sensitivity, lower insulin concentrations and higher insulin-stimulated glucose uptake compared to their omnivorous counterparts[5]. It has also been observed that a high protein (31%), low-carbohydrate plant-based diet has lipid-lowering advantages over a high-carbohydrate, low-fat lacto-ovo-vegetarian weight-loss diet (16% protein) in improving cardiovascular risk[6]. Regular consumption of pulses in an ad-libitum diet is reported to be equally effective in reducing the risk of metabolic syndrome compared to energy restricted diets. Overweight or obese adults consuming five cups of pulses/week for 8 weeks without calorie restriction were equally benefitted with improved blood sugar control and reduced waist circumference as those without legume meals but calorie cutting. The legume group also gained additional benefits of increased HDL and insulin regulation[7].

Caloric restriction combined with exercise or otherwise, results in negative energy balance and thus, results in weight loss. Weight loss induced by negative energy balance is reported to be helpful in improving metabolic risk factors associated with obesity[8]; weight loss also helps in enhancing insulin sensitivity[9]. Weight loss, caloric restriction and increased physical activity are observed to be beneficial in improving insulin sensitivity[10]. However, in a long-term study on women with the intervention of caloric restriction and increased physical activity, the weight loss at the end of 7.5 years was not significantly different between the 'Eat less and move more' group and the control group. Further, the intervention group regained weight after one year of caloric restriction and increased exercise[11],[12]. The reasons for the weight regain despite reducing calorie intake may be the adaptations to calorie restriction. Thus, the calorie intake deficit leads to less energy expenditure and the hormonal signals that stimulate hunger increase[13]. One of the fundamental hormones that regulates energy metabolism and promotes fat accumulation is insulin. High insulin levels cause insulin resistance and in turn, lead to weight gain.

Insulin is a peptide hormone secreted by beta cells of islets of Langerhans, located in the pancreas. Circulating insulin concentrations increase with feeding[14]. The quantity of insulin secreted by beta cells depends on the prevailing circulating blood glucose concentrations, as well as the nature and quantity of food consumed. Dietary carbohydrates trigger an increase in blood glucose levels more than the other two macronutrients, proteins and fat. The rise in blood glucose stimulates insulin release. Insulin binds with its receptor to initiate translocation of glucose receptors (GLUT 4) on the cell surface. This allows entry of glucose inside the cells; glucose can then be used for energy production and/or storage[15].

Insulin has three major target tissues: skeletal muscles, adipocytes, and hepatocytes. Only these three tissues are capable of deposition and storage of glucose. In healthy individuals, blood insulin concentrations increase in response to food from 15 µU/ml to 40 µU/ml, which results in glucose uptake by target cells. As a result of the postprandial insulin surge, blood glucose concentrations return to within 90-120 mg/dl in around 2 hours[16].There are two primary conditions that contribute to the development of insulin resistance: high insulin levels and constant stimulus. When the postprandial increase in circulating insulin is unable to bring the circulating glucose level in the optimum range, beta cells secrete additional insulin to reduce the high circulating blood glucose levels; this state indicates resistance to insulin. The compensatory hyperinsulinemia response prevents frank hyperglycemia but at the same time, increases an individual's risk of developing some degree of glucose intolerance. Hyperinsulinemia also, may result in high circulating levels of triglycerides, a lower concentration of high-density lipoproteins (HDL-C) and also, essential hypertension. These conditions are collectively known as the metabolic syndrome[17].

A constant stimulus for insulin release is the frequent rise in blood glucose due to increased frequency of eating[18]. With three meals per day and no snacks in between, insulin will be released three times; after breakfast in the morning, after lunch at noon, and after dinner at night. This pattern ensures a balanced 10 hours of eating window with fourteen hours of fasting. This creates a balance between periods of high insulin (eating) and decreased insulin (fasting). Varying fasting and eating hours, also called time-restricted feeding (TRF), will affect insulin release. Insulin resistance, which is caused by persistently high insulin levels, can be avoided with this diet pattern. Eating two to three snacks in addition to three meals per day was considered as a strategy to keep blood glucose levels in a moderate range. This reduces the fasting hours, in turn, causing the recurrent release of insulin. This pattern of eating is likely to result in down-regulation of receptors and development of insulin resistance. This further emphasizes the possible role of meal frequency and timing in controlling insulin resistance and in turn, reducing obesity and the metabolic syndrome.

Figure 1 illustrates a probable model for the development of insulin resistance and obesity and depicts how strategies such as caloric restriction, reduced meal frequency and time restricted feeding may be helpful against development of obesity and insulin resistance.

Cross-sectional studies are inconsistent in reporting the beneficial effects of eating frequently per day in controlling obesity in adults[19],[20]. Some prospective studies have shown that frequent snacking leads to weight gain[21],[22]. Other studies have reported meal timing as an important factor in achieving and maintaining weight loss[23]. Other than weight control, the effect of meal frequency on metabolic markers of health, namely, glucose, insulin, and lipid concentrations has been investigated in normal weight adults more than in overweight/obese individuals[24,25]. Many randomized controlled trials have examined the effects of two or three meals vs multiple meals per day in normal and diabetic individuals[26,27]. The objective of the present review was therefore, to evaluate the efficacy of varying patterns of meal frequency and time-restricted feeding in weight control and reducing metabolic risk, as also to provide insight about dietary advice for overweight and obese or diabetic individuals.

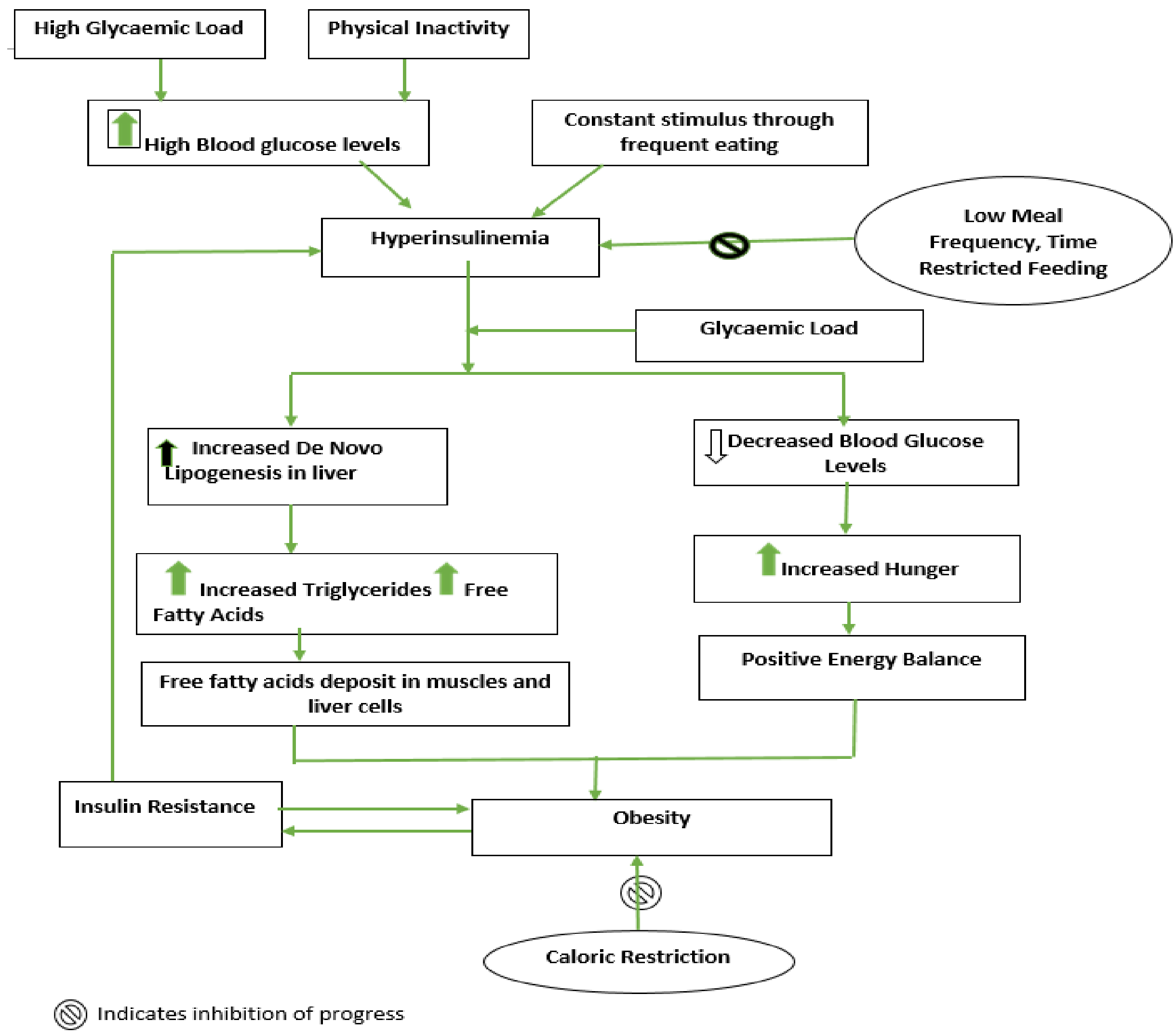

Figure 1: Insulin Resistance and Obesity:

High carbohydrate content of food and sedentary lifestyle cause rise in blood glucose levels, which along with increased frequency of eating result in hyperinsulinemia. Excessive insulin in circulation causes de-novo lipogenesis in the liver, because of which blood glucose levels rapidly fall and result in increased hunger. Increased hunger causes excessive eating leading to positive energy balance. The free fatty acids get deposited in liver and muscle cells. Together, the positive energy balance and fatty acid deposition in muscle and liver cells lead to obesity which, in turn, leads to insulin resistance and hyperglycemia. Conventional weight loss strategies (mainly caloric restriction) cause weight and fat loss which reduces insulin resistance. Reduced meal frequency (RMF) and Time-restricted feeding (TRF) prohibit hyperinsulinemia and hence, may avoid the development of this vicious cycle.

Literature search methods

Meal frequency and time restricted feeding as strategies for achieving metabolic health or controlling obesity include a variety of inter-related factors including diet composition, the timing of meals, food order of eating and so on. Relevant studies are also diverse in both outcome measures and study design. Therefore, a non-systematic review method was applied and a comprehensive literature search was carried out with electronic databases Google Scholar and PubMed central using various combinations of keywords: meal frequency, time restricted feeding, body fat, overweight, insulin resistance, hyperlipidemia and impaired glucose. Inclusion criteria were: i) studies published between 2005 till 2018, ii) randomized and nonrandomized control trials, iii) cohort and observational studies, iv) participants above 18 years of age, v) primary outcome measures as body weight, fat mass, relevant cardio-metabolic markers, glucose and insulin levels. Exclusion criteria were: studies reporting the effect of meal frequency on energy expenditure[24], cross-sectional studies without any intervention[20],[28], children and adolescent populations, participants with cardiovascular disorders and type 2 diabetes mellitus. We identified 90 studies through literature search as relevant to the objectives. Of these, we included 18 studies in our analysis as they were the best fit with the selection criteria. Details of 9 meal frequency studies and 9 TRF studies are given in Table 1 and Table 2 respectively.

TABLE 1: Summary of Meal frequency studies

Study	Population	Duration	Study Design	Eating pattern (MF*)	Significant Findings
Arciero et al, 2013[29]	30 adults (45.9 ± 9.4 yr), BMI: 30.3 ± 5.9 kg/m^2	4 weeks	Parallel	3 meals vs 6 meals/day	Change in body weight for 3 m/d -4% vs -2.8% in 6 m/d; percent body fat -5.8% for 3 m/d vs -7.5% for 6 m/d Plasma glucose and insulin showed no significant difference. Macronutrient composition (increased dietary protein), nutrient quality (low glycemic index and unprocessed carbohydrates), and frequency of eating (six times per day) is more important than total energy intake for overweight/obese men and women to reduce abdominal obesity and enhance postprandial thermogenesis.

Cameron, Marie-Jose, & Doucet, 2010[26]	8 men & 8 women (34.6 ± 9.5 yr), BMI: 37.1 ± 4.5 kg/m^2	8 weeks	RCT[#]	3 meals vs 6 meals/day	Though not significant, 3 m/d group showed more reduction in BMI (-5.4%), body fat (-8.1%) than 6 md/ group (-4% in BMI, -6.5% in body fat)
Betts, et al., 2014[30]	21 women and 12 men (21-60 yr), BMI: 22.4 ± 2.2 kg/m^2	6 weeks	RCT	Daily breakfast (≥700 kcal before 1100) vs extended fasting (0 kcal until 1200)	Marginal decreases in BMI in both daily breakfast group (-0.18%) vs extended fasting (no breakfast) group (– 0.6% reduction) and -1.2% reduction in body fat in breakfast group vs 0.39% in fasting group although not significant.
Bachman, J. L., & Raynor, H. A. 2012[31]	51 men & women (51.0 ± 9.9 yr), BMI: 35.5 ± 4.8 kg/m^2	6-months	RCT	3 meals vs 6 meals/day	Both 3 MF and 6 MF groups showed a similar significant reduction in BMI and body fat after 6 months.
Munsters, M. J., & Saris, W. H. 2012[32]	12 men (18-31 yr). BMI: 21.6 ± 0.6 kg/m^2	Two 36 hours' periods. One week apart	Randomized 2-way cross over study	3 meals vs 14 meals/day	Glucose and insulin profiles showed greater fluctuations, but a lower AUC of glucose in the 3MF diet compared with the 14MF diet.
Heden et al, 2013[33]	8 obese women (39 ± 3 yr), BMI 34.5 ± 1.3 kg/m^2	Two 12 hr periods, one month apart	Randomized cross-over study	3 meals vs 6 meals/day	3 meals /d results in higher postprandial insulin concentrations than a 6 meals/d The iAUC[!] for insulin was significantly higher in 3 meals/d pattern indicating higher postprandial insulin concentration with lower meal frequency.
Kanaley, Heden, Liu, & Fairchild, 2014[34]	3 men and 11 women (29-50 years), BMI	3 12-hr study periods, one	Randomized cross over study	3 meals vs 6 meals/day	Postprandial insulin response was significantly higher in 3 meals/d. Insulin total AUC and peak insulin concentrations were

	of 35·5± 3.7 kg/m^2	month apart			significantly higher in lower meal frequency (3 m/d) compared to higher meal frequency (6 m/d) indicating increased postprandial insulin response with a reduction in meal frequency. Meal frequency didn't significantly alter insulin secretion and glucose: insulin ratio
Dixit & Indurkar, 2017[18]	33 prediabetic men and 15 prediabetic women	3 months	Self-controlled intervention trial	2 meals/day	Significant reduction in HbA1c and fasting insulin levels as compared to baseline In prediabetic participants lower meal frequency (2 meals/d) resulted in significant reduction (-13.4%) in HbA1c and fasting insulin levels in a duration of 3 months compared to baseline
State, et al., 2007[25]	15 men and women, (45.0 ± 0.7 yr), BMI: 23.4 ± 0.5 kg/m^2	two 8-wk treatment periods	Randomized Cross Over Study	3 meals vs 1 meal/day	Significant reduction in body weight and body fat mass in 1 meal/day vs 3 meals/d. Compared to HF (3 m/d) LF (1 m/d) resulted in loss body weight by -2.1% and body fat by -13%.

*MF: meal frequency,!RCT: Randomised Controlled Trial, !iAUC: incremental area under the curve, NS: Not Significant.

Table 2: Summary of Time-restricted feeding studies

Study	Population	Duration	Study Design	Eating pattern (TRF*)	Significant Findings
Norouzy, et al., 2013[35]	158 men and 82 women (40.1± 0.7), BMI: (M) 26.4± 0.5 and (F) 27.7 ± 0.8 kg/m^2	1 month	Prospective observational study	No Restriction	Ramadan fasting resulted in reduced body weight (-2.2% in males and – 1.3%); fat mass (-4.3% in males and -2.0% in females)) in ≤ 35 years group and ((-1.6% in males and -1.0% in females), (-2.4% in males and + 0.8% in females) in 36-70 years group respectively.
Al-Hourani & Atoum, 2007[36]	57 women (21.6 ±4.1 yr), BMI: 22.2 ± 3.2 kg/m^2	1 month	Prospective Observational Study	No Restriction	Ramadan fasting resulted in significant reduction in body weight (-1.0%).
Lamri-Senhadji, Kebir, & J Belleville, 2009[37]	22 men and 24 women (24±3 yr), BMI: 22 – 25 kg/m^2	1 month	Prospective Observational Study	2 meals during Ramadan compared to 5 meals in usual months	Ramadan fasting resulted in a decrease in body weight (-1.9% in women and 0% in men) the change was NS for both groups.
Ajabnoor, et al., 2014[38]	18 males and 5 females (23.16±1.2 yr)	1 month	Prospective Observational Study	No restriction	No significant change in body weight, BMI and % body fat during the study period. A significant increase in HOMA IR; during Ramadan fasting, the HOMA IR value changed from 1.98 ± 0.24 to 4.51± 1.04 in the morning and 4.94 ± 0.8 to 12.01 ± 1.53 in the evening.
Harder-Lauridsen N. M., et al., 2017[39]	10 healthy lean men aged 18 – 35 years BMI: 22.5 kg/m^2	8 weeks	Non-randomized cross over intervention study	4 weeks control period followed by 4 weeks of 14 hr/d fasting	TRF showed significant reduction in BMI as compared to control period (-0.3 kg/m^2 vs + 0.2 kg/m^2), total fat mass (-0.1 vs +0.1%) and HbA1c (-0.8 vs -1.1).

Sutton, et al., 2018[40]	8 pre-diabetic men (56 ± 7 yr), BMI: 32.2 ± 4.4 kg/m^2	5 weeks	Randomized Cross Over Study	6 hours (TRF) vs 12 hrs (control) Time-Restricted Feeding	TRF regime showed a significant decrease in fasting insulin by 3.4 ± 1.6 mU/L, mean and peak insulin values by 26 ± 9 mU/L and 35 ± 13 mU/L respectively; leading to a reduction in insulin resistance (3 hr increment ratio) by 36 ± 10 U/mg.
Tinsley, et al., 2016[41]	28 healthy, recreationally active men (22.5±4.1 yr), overweight and obese	8 weeks	RCT	4 hr eating window after 4 pm.	TRF group showed -1.14% change in body weight, -0.33% change in lean tissue and -3.37% change in fat mass, although not statistically significant from the control group.
Gabel, et al., 2018[42]	23 participants (50±2 yr); BMI: 35 ± 1 kg/m^2, with historic controls (48± 2 yr) and BMI 34± 1kg/m^2	12 weeks	Pilot Study	8 hr eating window between 10.00 to 18.00 hr	TRF group showed a significant decrease (-3.1%) in body weight, -4.8% in fat mass as compared to 0% change in the control group.
Antoni, Robertson, Robertson, & Johnston, 2018[43]	16 healthy men and women (47 ± 3 years and BMI 29 ± 1.7 kg/m^2)	12 weeks	Pilot Study	Feeding window reduced by 3 hr	TRF group showed a reduction (-0.8%) in body weight although NS from the control group (-0.6%). TRF group showed significant (-1.9 ± 0.3 %) reduction in body fat compared to control group (0%).

TRF: extended Time-restricted feeding

Results and Discussion:

Meal frequency

Daily energy intake depends on the total intake of food per day, the energy density of food consumed and feeding frequency[44]. Several cross-sectional studies have reported an inverse relationship between eating frequency and body weight[45, 46, 28]. It has been postulated that increased meal frequency causes a reduction in hunger and cravings, increase in metabolism, improvement in glycaemic control and reduction in body weight and % body fat[47]. Moreover, it has been reported that people who maintain their weight in a healthy range (BMI 19 -24.9 Kg/M^2) with/without weight loss, tend to eat more frequently (3 meals + 2 snacks) compared to people who are unable to maintain their weight[48].

However, an opposite trend was reported by randomized controlled trials. A reduction in body weight was observed to be more (-4%) in 3 MF than 6 MF (-2.8%), but the percent body fat was reduced more in 6 MF in a study by Arceiro et al, 2013 (Table 1)[29]. Cameron et al, 2010 on the other hand, found a higher reduction in BMI as also body fat in adult men and women consuming 3 MF than those consuming 6 MF[26]. In a 6 months' intervention of 3 MF vs 6 MF, both the groups showed a significant reduction in energy intake, BMI and percent body fat ($p<0.01$). However, percent reduction in BMI (16.5% vs 13.7%) or body fat (21.8% vs 17.6%) were slightly more in 3 MF than 6 MF though not statistically significant[31]. Further, the belief that breakfast is an important meal of the day was tested in an RCT where one group was given breakfast and the other had no breakfast with remaining meals being the same. Results indicated no significant difference between the two groups with respect to BMI and body fat. Fasting plasma glucose and serum insulin concentrations were unaffected by 6 wk of either daily breakfast or extended morning fasting[30]. Nonetheless, regular daily breakfast maintained more stable glucose responses during the afternoon and evening. With no breakfast, in a self-controlled intervention trial for 3 months, 2 meals/day with 45 min walking/day resulted in a significant reduction in body weight, HbA1c and waist circumference[18]. In a randomized crossover design with two 8-wk treatment periods of 3 vs 1 meal/day, normal weight adults on 1 meal/day showed weight loss and a decrease in fat mass[25]. In most of these studies, duration was 4 weeks to 6 months.

Some studies have reported the effect of ingestion of a varying number of meals in two periods of 12 hrs or 36 hrs. Short term study (36 hr) of the response of glucose and insulin to low meal frequency (3MF) was found to be lower though not stable as compared to 14 MF in normal healthy men[32]. Other short term studies (12 hr) in obese women and men demonstrated higher insulin response with 3 MF than 6 MF[33, 34].

Thus, these studies indicate no significant difference in weight loss as a result of low (3 or fewer meals/day) or high (6 or more meals/day) meal frequency [30, 31, 49]. Nevertheless, compared to low meal frequency, high meal frequency does offer a significant reduction in hunger[31] along with reduced protein oxidation, stable blood glucose and insulin (lower peaks, higher troughs, and values during the course of the day), which indicates improvement in glycaemic control[32]. The lower protein oxidation in high meal frequency can be a useful dietary strategy when increased daily protein uptake is a treatment goal. The benefits of increased meal frequency in reducing metabolic fluctuations are translated better in overweight and obese populations compared to normal weight and/or normoglycemic population[50]. Consuming increased protein (by 35%) more frequently (6 meals/d) decreased total and abdominal body fat, increased lean mass over three meals/day in overweight individuals during both energy balance and negative energy balance states[29]. These observations suggest that increasing meal frequency is helpful in preventing metabolic fluctuations and preserving lean tissue.

On the other hand, improved glycaemic control as a result of increasing meal frequency may not result in weight loss for several reasons. Firstly, the stable and high circulating insulin in the high-frequency diet is not sufficient to inhibit oxidation of dietary fatty acids. Secondly, low-frequency diet can improve the feeling of satiety by inhibition of ghrelin to a greater degree compared to high-frequency diet and thus, provide improved appetite control. Lastly, since snacks are typically high carbohydrate and high-fat calorie dense foods, they increase the total daily caloric intake[32].

Low meal frequency offers improvement in metabolic profile by reducing the circulating concentrations of triacylglycerol (TAG). It has been proposed that the lower TAG concentrations in three meals/day dietary pattern are because of higher postprandial insulin concentration compared to six meals/day dietary pattern. In obese women, higher postprandial insulin concentration (significantly high insulin iAUC) and lower postprandial TAG concentration (15% vs 22% above the baseline) in lower meal frequency was observed as compared to higher meal frequency. The higher insulin concentration causes uptake of free fatty acids into adipocytes by the action of insulin-sensitive lipoprotein lipase[33]. This gives rise to a question; 'Will reducing meal frequency even further, help with weight loss and improvement in metabolic profile?' Few studies have reported the effects of meal frequency of fewer than 3 meals per day. In a randomized cross-over study with normal weight women, it was observed that reducing meal frequency from three to two meals per day had no significant effect on 24-hr energy expenditure, diet-induced thermogenesis (DIT), activity-induced energy expenditure and sleeping metabolic rate (SMR)[24]. The satiety was reported to be higher in 3 meals/day compared to 2 meals/day whereas, the fat oxidation was reported to be higher with increased inter-meal intervals. The observation that two meals per day result in higher dietary fat oxidation suggests that meal frequency plays a role in differential utilization of substrate.

In the self-controlled trial with prediabetic men and women, two meals/day dietary pattern brought significant reduction in HbA1c and fasting insulin levels compared to baseline within three months[18]. In a randomized cross-over study of eight-week duration in normal-weight men and women, compared to three meals, one meal per day dietary pattern resulted in an increase in total, LDL and HDL cholesterol and a decrease in triacylglycerol and cortisol concentrations with no significant difference in circulating glucose concentration[25]. These studies indicate a promising trend of reduction in meal frequency (less than 3 meals/d) for weight loss and improved glycaemic control. However, more studies with varied study populations and longer study duration are required to advocate lower (< 3 meals/day) meal frequency for better metabolic health.

To summarise, high meal frequency (6 or more meals/day) imparts improvement in glycaemic control and macronutrient partition. However, improved glycaemic control with higher meal frequency doesn't ensure weight loss. In contrast, low meal frequency (3 meals/day) is a promising strategy for weight loss and loss of body fat with modest or even absence of caloric restriction. Reducing the meal frequency even further may be beneficial in potentiating the weight and fat loss benefits.

Time-restricted feeding

Both feeding/fasting methods impact circadian rhythm, our body's internal clock. The circadian rhythm is mainly controlled by light and dark stimuli in an area of the brain's hypothalamus called the SCN, suprachiasmatic nucleus. In agreement with the body clock, the concept of time restricted feeding encourages eating only within a defined time interval, usually an 8-hour window each day, and can be thought of as extending the normal overnight fast that occurs naturally with sleep. Time-restricted feeding refers to restricting the timing of food intake to certain hours per day without an overt attempt to reduce caloric intake[51]. The feeding window may be anywhere between 3 to 12 hours per day followed by a fast of 21 to 12 hours respectively[52].

Commonly reported evidence of time restricted feeding is from Ramadan studies. Ramadan fasting takes place during daylight hours from sunrise to sunset. There is seasonal variation between the duration of fast with longest fast being ~ 14 hours[39]. Studies have reported mixed effects of Ramadan fasting in terms of weight loss and/or other study parameters (Table 2). This may be due to the variation in dietary intake as a result of cultural influences. With similar dietary intake before and during observing Ramadan, the effect of TRF on weight and fat loss is reported to vary among age groups. A significant reduction was reported in weight loss, waist and hip circumference, %body fat in young men below 35 years of age, while no reduction in waist, hip and fat mass in 36-70 yr old women[35]. Another study in young women (18-29 years) with similar caloric and macronutrient content of diet pre and during Ramadan showed a significant decrease in body weight and %body fat[36]. The study based on Ramadan model of fasting (14 hr fasting/day) in ten lean, healthy men reported a significant reduction in BMI as a result of fasting for four weeks[39]. With significant alteration in caloric and macronutrient intake during Ramadan fasting in healthy, young Algerian adults (21-27 years), no significant change in body weight and improvement in cardiovascular risk parameters (reduction in LDL concentration and increase in LDL concentration) has also been documented[41]. Lastly, a study conducted in young (22-24 years) healthy Saudi Arabians, reported that fasting resulted in an alteration in adipokine pattern indicating a state of insulin resistance and hence, increased cardio-metabolic disease risk. Authors proposed disruption in circadian rhythm as the probable cause of exacerbation of metabolic risk parameters[42]. One of the reasons for diverse results in these studies is an alteration in lifestyles including changes in regular meal pattern with increased total energy and carbohydrate intake, different sleep cycle, etc. Ramadan studies indicate that in order to be beneficial TRF need to be designed with controlled caloric and micronutrient intake appropriate for individual's health maintenance. Despite this, the effects of TRF on body weight and % body fat are influenced by an individual's age and gender. These results are important as guidelines for designing a format of TRF giving due consideration to confounding factors such as age, gender, circadian rhythm, and individual meal composition,

In other studies on TRF, feeding time varied from 4 hr to 8 hr. The main focus in TRF is on restricting the time and not the caloric intake[53]. Without limiting the consumption of any food, the time restriction alone is expected to show a significant reduction in caloric intake and ultimately weight loss. It has been reported that a feeding window restricted to 4 hours/day resulted in a caloric deficit of 650 kcal[41] and feeding window restricted to 8 hours per day resulted in a caloric deficit of 341 ± 53 kcal/day[42]. The most notable aspect is that, in both cases, in spite of caloric deficit there was no significant reduction in lean tissue. The deficit of 650 kcal didn't result in significant weight and/or fat loss in young, healthy and recreationally active men. This suggests that there may be a compensatory reduction in energy expenditure as a result of TRF. However, the small size of the intervention group (10 participants), self-reported dietary intake of the participants and relatively limited duration (8 weeks) of study may have masked the effects of TRF on weight loss[41]. Recently, Gabel et al, 2018 found that a caloric deficit of ~ 350 kcal/day resulted in significant weight loss (-2.6%) in 23 obese participants in a duration of 12 weeks[42]. However, the weight loss was not accompanied by a subsequent change in fat mass, visceral fat mass, lean tissue mass, circulating triglycerides, fasting glucose and insulin concentration, indicating lack of improvement in cardio-metabolic disease risk.

Sutton et al, 2018 conducted the first supervised controlled feeding trial to test whether early time-restricted feeding (eTRF) has benefits independent of weight loss by feeding participants enough food to maintain their weight[40]. eTRF implies time-restricted feeding in alignment with circadian rhythms with early dinner in the mid-afternoon and 6 hr daily eating period. The 5 weeks of eTRF improved insulin levels, insulin sensitivity, β cell responsiveness, blood pressure and oxidative stress levels in men with prediabetes-even though food intake was matched with the control group and no weight loss occurred.

Although TRF was or wasn't able to achieve weight loss, the studies have reported a reduction in adiposity[43] and improvement in insulin sensitivity[40] with the increased fasting window (16-18 hours of fasting). In a pilot study by Antoni et al, 2018, 16 hours fasting for the duration of 10 weeks, was able to produce a significant reduction in % body fat with no change in body weight in 13 overweight participants. This suggests a compensatory increase in lean tissue mass during the intervention[43].

Together the data from TRF studies indicate that fasting duration (~ 16 hours or more) is critical in achieving weight loss and improvement in cardio-metabolic risk markers. The fasting window of 16 hours or more results in the caloric deficit that translates into weight loss. In TRF, the caloric deficit does not seem to have a negative effect on lean tissue mass. It is important to take into consideration the limitation of most of the TRF studies that they are pilot studies with limited duration and small sample sizes. Moreover, adopting TRF as a change in lifestyle may be a difficult challenge. Long-term studies with larger sample sizes and fasting duration in line with circadian rhythm need to be conducted to elucidate the appropriateness of TRF as a dietary strategy for achieving metabolic health.

Conclusions

The present review highlights the fact that frequency and timing of meals and time restricted feeding have potential as strategies for achieving health benefits. Lower meal frequency of 2 to 3 meals per day is a sustainable lifestyle change that can achieve weight loss, reduce adiposity and insulin sensitivity without restricting daily caloric intake. However, considering the possible increased protein oxidation, meals need to be designed with compensatory protein intakes.

TRF, with a smaller fasting window (12-14 hours) may be beneficial in achieving weight loss provided there is a compensatory adjustment in total caloric and carbohydrate intake. The longer fasting window (>16 hr) can improve metabolic health and achieve weight loss with an ad-libitum diet without any apparent restriction in terms of daily caloric or carbohydrate intake. However, TRF has not yet been reported as a feasible long term solution.

Current literature on MF and TRF lacks uniformity in study designs, effective sample sizes, duration of intervention and participant characteristics. Further research on optimal meal frequency, timing and fasting hours are necessary to develop strategies for a healthy lifestyle for populations and for offering therapeutic dietary advice.

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References:

1. Stevens GA, Singh GM, Lu Y, et al. National, regional, and global trends in adult overweight and obesity prevalences. *Popul Health Metr*. 2012;10(22):1-16. doi:10.1186/1478-7954-10-22

2. Hutchison AT, Heilbronn LK. Metabolic impacts of altering meal frequency and timing - Does when we eat matter? *Biochimie*. 2016;124:187-197. doi:10.1016/j.biochi.2015.07.025

3. Del Corral P, Chandler-Laney P, Casazza K, Gower B HG. Effect of Dietary Adherence with or without Exercise Weight Loss: A Mechanistic Approach to a Global Problem. *J Clin Endocrinol Metab*. 2009;94(5):1602-1607. 10.1210/jc.2008-1057.

4. Trapp CP and Barnard ND. Usefulness of vegetarian and vegan diets in treating type 2 diabetes. *CurrDiab Rep*. 2010;10(2):152-158. 10.1007/s11892-010-0093-7 LK.

5. Gojda J, Patková J, Jaček M, et al. Higher insulin sensitivity in vegans is not associated with higher mitochondrial density. *Eur J Clin Nutr*. 2013;67(12):1310-1315. doi:10.1038/ejcn.2013.202

6. Jenkins DJA, Wong JMW, Kendall CWC, et al. The effect of a plant-based low-carbohydrate ("eco-atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. *Arch Intern Med*. 2009;169(11):1046-1054. doi:10.1001/archinternmed.2009.115

7. Mollard RC, Luhovyy BL, Panahi S, Nunez M, Hanley A, Anderson GH. Regular consumption of pulses for 8 weeks reduces metabolic syndrome risk factors in overweight and obese adults. *Br J Nutr*. 2012;108:S111-122. doi:10.1017/S0007114512000712

8. Ogden, CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ FK. Prevalence of overweight and

obesity in the United States, 1999-2004. *J Am Med Assoc*. 2006;295(13):1549-1555. 10.1001/jama.295.13.1549%0A[Indexed for MEDLINE].

9. Muscelli E, Mingrone G, Camastra S, et al. Differential effect of weight loss on insulin resistance in surgically treated obese patients. 2005;118:51-57. doi:10.1016/j.amjmed.2004.08.017

10. Mlinar B, Marc J, Jane A, Pfeifer M. Molecular mechanisms of insulin resistance and associated diseases. 2007;375:20-35. doi:10.1016/j.cca.2006.07.005

11. Howard B V, Manson JE, Stefanick ML, et al. Low-Fat Dietary Pattern and Weight Change Over 7 Years The Women ' s Health Initiative Dietary Modification Trial. 2006;295(1):39-49.

12. Rosenbaum M, Hirsch J, Gallagher DA, Leibel RL. Long-term persistence of adaptive thermogenesis in subjects who have maintained reduced body weight. *Am J Clin Nutr*. 2008. doi:10.1093/ajcn/88.4.906

13. Sumithran, Priya, Prendergast Luke A. DE et al. Long-Term Persistence of Hormonal Adaptations to Weight Loss. *N Engl J Med*. 2011;365:1597-1604. 10.1056/NEJMoa1105816.

14. Neil A. Schwarz, B. Rhett Rigby, Paul La Bounty, Brian Shelmadine & RGB. A Review of Weight Control Strategies and Their Effects on the Regulation of Hormonal Balance. *J Nutr Metab*. 2011:1-15. 10.1155/2011/237932.

15. Kahn, S. E., Hull, R. L., & Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006;444:840-846.

16. Bhattacharya S, Dey D RS. Molecular mechanism of insulin resistance. *J Biosci*. 2007;32.2:405-413.

17. Reaven GM. THE INSULIN RESISTANCE SYNDROME: Definition and Dietary Approaches to Treatment. *Annu Rev Nutr*. 2005;25(1):391-406. 10.1146/annurev.nutr.24.012003.132155.

18. Dixit J V., Indurkar S. Effect of eating frequency on prediabetes status: a self-controlled preventive trial. *Int J Clin Trials*. 2017. doi:10.18203/2349-3259.ijct20174118

19. Holmbäck I, Ericson U, Gullberg B WE. A high eating frequency is associated with an overall healthy lifestyle in middle-aged men and women and a reduced likelihood of general and central obesity in men. *Br J Nutr*. 2010;104(7):1065-1073. 10.1017/S0007114510001753.

20. Kahleova H, Lloren JI, Mashchak A, Hill M, Fraser GE. Meal Frequency and Timing Are Associated with Changes in Body Mass Index in Adventist Health Study 2. *J Nutr*. 2017:jn244749. doi:10.3945/jn.116.244749

21. Heijden, Amber A.W.A van der et al. A Prospective Study of Breakfast Consumption and Weight Gain among U.S. Men. *Obesity*. 2007;15(10):2463-2469.

22. Howarth NC1, Huang TT, Roberts SB, Lin BH MM. Eating patterns and dietary composition in relation to BMI in younger and older adults. *Int J Obes*. 2007;31(4):675-684.

10.1038/sj.ijo.0803456.

23. Jakubowicz D, Froy O, Weinstein J, Boaz M. Meal timing and composition influence ghrelin levels, appetite scores and weight loss maintenance in overweight and obese adults. In: *Steroids*. ; 2012. doi:10.1016/j.chieco.2012.09.003

24. Smeets AJ, Westerterp-Plantenga MS. Acute effects on metabolism and appetite profile of one meal difference in the lower range of meal frequency. *Br J Nutr*. 2008;99(6):1316-1321. doi:10.1017/S0007114507877646

25. Stote KS, Baer DJ, Spears K, et al. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. *Am J Clin Nutr*. 2007;85(4):981-988. doi:85/4/981 [pii]

26. Cameron JD, Cyr MJ, Doucet É. Increased meal frequency does not promote greater weight loss in subjects who were prescribed an 8-week equi-energetic energy-restricted diet. *Br J Nutr*. 2010. doi:10.1017/S0007114509992984

27. Kahleova H, Belinova L, Malinska H, et al. Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: A randomized crossover study. *Diabetologia*. 2014;57(8):1552-1560. doi:10.1007/s00125-014-3253-5

28. Jung CH, Lee JS, Ahn HJ, et al. Association of meal frequency with metabolic syndrome in Korean adults: From the Korea National Health and Nutrition Examination Survey (KNHANES). *Diabetol Metab Syndr*. 2017. doi:10.1186/s13098-017-0277-2

29. Arciero PJ, Ormsbee MJ, Gentile CL, Nindl BC, Brestoff JR, Ruby M. Increased protein intake and meal frequency reduces abdominal fat during energy balance and energy deficit. *Obesity*. 2013;21(7):1357-1366. doi:10.1002/oby.20296

30. Betts JA, Richardson JD, Chowdhury EA, Holman GD, Tsintzas K, Thompson D. The causal role of breakfast in energy balance and health: A randomized controlled trial in lean adults. *Am J Clin Nutr*. 2014. doi:10.3945/ajcn.114.083402

31. Bachman JL, Raynor HA. Effects of manipulating eating frequency during a behavioral weight loss intervention: A pilot randomized controlled trial. *Obesity*. 2012. doi:10.1038/oby.2011.360

32. Munsters MJM, Saris WHM. Effects of meal frequency on metabolic profiles and substrate partitioning in lean healthy males. *PLoS One*. 2012. doi:10.1371/journal.pone.0038632

33. Heden TD, Liu Y, Sims LJ, et al. Meal frequency differentially alters postprandial triacylglycerol and insulin concentrations in obese women. *Obesity*. 2013. doi:10.1002/oby.20247

34. Kanaley JA, Heden TD, Liu Y, Fairchild TJ. Alteration of postprandial glucose and insulin concentrations with meal frequency and composition. *Br J Nutr*. 2014. doi:10.1017/S0007114514002128

35. Norouzy A, Salehi M, Philippou E, Arabi H, Shiva F, Mehrnoosh S, Mohajeri SM, Mohajeri SA, Motaghedi Larijani A NM. Effect of fasting in Ramadan on body composition and nutritional intake: a prospective study. *J Hum Nutr Diet*. 2013;26(1):97-104. 10.1111/jhn.12042.

36. Al-Hourani HM AM. Body composition, nutrient intake and physical activity patterns in young women during Ramadan. *Singapore Med J 4*. 2007;2007(10):906-910.

37. Lamri-Senhadji MY, El Kebir B, Belleville J BM. Assessment of dietary consumption and time-course of changes in serum lipids and lipoproteins before, during and after Ramadan in young Algerian adults. *Singapore Med J*. 2009;50(3):288-294.

38. Ajabnoor Ghada M., Suhad Bahijri, Anwar Borai, Altaf A. Abdulkhaliq, Jumana Y. Al-Aama and GPC. Health Impact of Fasting in Saudi Arabia during Ramadan: Association with Disturbed Circadian Rhythm and Metabolic and Sleeping Patterns. *PLoS One*. 2014;9(5):e96500. 10.1371/journal.pone.0096500.

39. Harder-Lauridsen NM, Rosenberg A, Benatti FB, et al. Ramadan model of intermittent fasting for 28 d had no major effect on body composition, glucose metabolism, or cognitive functions in healthy lean men. *Nutrition*. 2017. doi:10.1016/j.nut.2016.12.015

40. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab*. 2018. doi:10.1016/j.cmet.2018.04.010

41. Tinsley GM, Forsse JS, Butler NK, et al. Time-restricted feeding in young men performing resistance training: A randomized controlled trial†. *Eur J Sport Sci*. 2017. doi:10.1080/17461391.2016.1223173

42. Gabel K, Hoddy KK, Haggerty N, et al. Effects of 8-hour time-restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study. *Nutr Heal Aging*. 2018;4(4):345-353. doi:10.3233/NHA-170036

43. Antoni R, Robertson TM, Robertson MD, Johnston JD. A pilot feasibility study exploring the effects of a moderate time-restricted feeding intervention on energy intake, adiposity and metabolic physiology in free-living human subjects. *Journal of Nutritional Science*. 2018.

44. TP Solomon, Chambers ES, Jeukendrup A and TA. The effect of feeding frequency on insulin and ghrelin responses in human subjects. *Br J Nutr*. 2008;100(4):810-819. 10.1017/S000711450896757X.

45. Drummond SE, Crombie NE, Cursiter MC, Kirk TR. Evidence that eating frequency is inversely related to body weight status in male, but not female, non-obese adults reporting valid dietary intakes. *Int J Obes*. 1998. doi:10.1038/sj.ijo.0800552

46. Ruidavets, JB, Vincent Bataille, Bongard V GP. Eating frequency and body fatness in middle-aged men. *Int J Obes*. 2002;26(11):1476-1483. 10.1038/sj.ijo.0802143.

47. Leidy HJ and WWC. The Effect of Eating Frequency on Appetite Control and Food Intake: Brief

Synopsis of Controlled Feeding Studies. *J Nutr*. 2011;141(1):154-157. 10.3945/jn.109.114389.

48. Bachman JL, Phelan S, Wing RR, Raynor HA. Eating frequency is higher in weight loss maintainers and normal-weight individuals than in overweight individuals. *J Am Diet Assoc*. 2011. doi:10.1016/j.jada.2011.08.006

49. Kazunori Ohkawara, Marc-Andre Cornier WMK, and ELM. Effects of Increased Meal Frequency on Fat Oxidation and Perceived Hunger. *Obes Biol Integr Physiol*. 2013;21:336-343. 10.1002/oby.20032.

50. Kulovitz MG, Kravitz LR, Mermier C, et al. Potential role of meal frequency as a strategy for weight loss and health in overweight or obese adults. *Nutrition*. 2014. doi:10.1016/j.nut.2013.08.009

51. Longo V and PS. Fasting, Circadian Rhythms, and Time-Restricted Feeding in Healthy Lifespan. *Cell Metab*. 2016;23(6):1048-1059. 10.1016/j.cmet.2016.06.001.

52. Rothschild J, Hoddy KK, Jambazian P, Varady KA. Time-restricted feeding and risk of metabolic disease: A review of human and animal studies. *Nutr Rev*. 2014;72(5):308-318. doi:10.1111/nure.12104

53. Moro, T., Tinsley, G., Bianco, A., Marcolin, G., Pacelli, Q. F., Battaglia, G., Antonio Palma, Paulo Gentil, Marco Neri AP. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males.". *J Transl Med*. 2016;14(1):290. 10.1186/s12967-016-1044-0.