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Timing of Eating in Adults Across the Weight Spectrum: Metabolic Factors and Potential Circadian Mechanisms

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Abstract

Timing of eating is recognized as a significant contributor to body weight regulation. Disruption of sleep-wake cycles from a predominantly diurnal (daytime) to a delayed (evening) lifestyle leads to altered circadian rhythms and metabolic dysfunction. This article reviews current evidence for timed and delayed eating in individuals of normal weight and those with overweight or obesity: some findings indicate a benefit of eating earlier in the daytime on weight and/or metabolic outcomes, although the findings have not been uniformly consistent, and more rigorous and longer-duration studies are needed. We also review potential circadian mechanisms resulting from the metabolic- and weight-related impact of changes in timing of eating. Further identification of mechanisms using deep phenotyping is required to determine targets for medical interventions for obesity and for prevention of metabolic syndrome and diabetes, and to inform clinical guidelines regarding eating schedules for management of weight and metabolic disease.

Keywords

delayed eating; adipose; gene expression; weight; metabolism; circadian

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Authorship

Both authors contributed equally to the conception, execution and writing of this review. Both authors have read and approved the final version of this manuscript.

Human Rights and Informed Consent

All reported studies/experiments using human subjects have been previously published and complied with all applicable ethical standards (including obtaining of informed consent, and the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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1. Introduction

Obesity has been increasing since the 1980s worldwide [1, 2], currently affecting at least 35% of the U.S. population [2, 3]. Obesity is formally recognized as an epidemic by the World Health Organization and is related to many serious medical comorbidities, including type 2 diabetes, hypertension, cardiovascular disease, many cancers, musculoskeletal disorders, obstructive sleep apnea, and nonalcoholic fatty liver disease [2, 4–6]. However, approximately 10–30% of persons with obesity remain metabolically healthy [7], characterized by low visceral and liver fat, C-reactive protein, and mean adipocyte size, and high serum adiponectin and adipocyte insulin sensitivity [8]. The other 70–90% of individuals with obesity have metabolic syndrome [7], a cluster of conditions—increased blood pressure, high blood sugar, excess abdominal body fat, and abnormal cholesterol or triglyceride levels—occurring together that increase the risk of cardiovascular disease and diabetes. Behavioral weight loss approaches are effective at aiding individuals in reducing their initial body weight by 5–10% [6], but obesity prevention remains a primary public health goal, along with identifying behavioral strategies to optimize weight loss and maintenance. Of the many factors contributing to the obesity epidemic, the timing of food consumption is recognized as a significant contributor to body weight regulation [9–13].

2. Agenda and method

In this integrated review, we examine the available evidence evaluating the link between the timing of eating with weight and with metabolic outcomes, as well as possible mechanistic pathways (e.g., gene expression) that could underlie such a relationship. We include sections on the relationship between weight and metabolism with circadian rhythms, sleep, and night eating syndrome (NES) to describe the history of our and others' work in these areas, and how this work lays the foundation for the current topic. Notably, this is not a formal systematic review or meta-analysis; in the remaining sections, we review studies available in PubMed using search terms including *timing of eating, delayed eating, night eating, nighttime eating,* and *timed restricted feeding*. We included studies that reported weight and/or metabolic marker outcomes with respect to these terms, and expanded on the details of these studies to highlight their clinical utility and significance.

3. Circadian regulation of feeding and metabolism

The underlying mechanisms governing the circadian rhythms of fundamental processes such as sleeping and eating are well characterized. The circadian system enables organisms to synchronize behaviors, metabolism, and physiological processes to sleep-wake cycles [14,15]. The core clock mechanism is based on a feedback loop involving the transcription factors BMAL1, CLOCK, and NPAS and their targets [14]. Circadian rhythms are ordered hierarchically in mammals with the hypothalamic suprachiasmatic nucleus (SCN) controlling a network of central and peripheral clocks. The SCN responds primarily to light and synchronizes behavioral and physiological rhythms via circadian oscillations in extra-SCN brain circuits and peripheral tissues [14]. When food is abundant and animals remain under normal light-dark (LD) cycles, the photoperiod is the primary "zeitgeber" (time-giver)

for the master clock in the SCN, and produces a near 24-hour rhythm in feeding behavior and metabolism [14].

Macronutrients (i.e., glucose, fatty acids, and amino acids) and nutrient-sensing molecules (e.g., AMPK, SIRT1, mTOR, and CRTC2) entrain central and peripheral clocks, changing the timing and amplitude of gene expression rhythms and metabolic pathways [14]. However, a disruption in the timing of food availability induces another regulator—the "food entrainable oscillator" [16–18]. Unlike the SCN, peripheral clocks in the liver, other organs, and the gut microbiome respond to the timing of feeding [15]. Rodent studies have demonstrated that eating out of phase promotes obesity, insulin resistance, fat storage, and inflammation [e.g., 19–21], highlighting the need for examination of the impact of the timing of eating on these parameters in humans.

4. Transcriptomics (gene expression)

Transcriptomics or expression profiling is the study of the complete set of RNA transcripts produced by the genome (transcriptome), under specific circumstances or in a specific cell, using high-throughput methods such as microarray analysis or short-read high-throughput sequencing (RNASeq). Comparison of transcriptomes allows for the identification of genes that are differentially expressed in distinct cell populations or in response to different conditions [22]. In this section, we discuss the links between the white adipose tissue transcriptome and obesity, circadian rhythms and timed/delayed eating in humans, and the blood transcriptome and these same topics.

4.1. White adipose tissue transcriptome and obesity

Persons with obesity have an excess amount of white adipose tissue fat, a major site of energy storage that plays a role in the regulation of metabolism through the release of adipokines. Adipose tissue dysregulation contributes to the development of obesity-related co-morbidities [23–25]. Adipose tissue constitutes an important source of circulating RNAs, which can regulate gene expression. Such adipose tissue gene expression is differentially altered during various dietary weight loss interventions in obese persons [26–32] and in short- and long-term overfeeding [33, 34]. Adipose tissue gene expression distinguishes metabolically healthy obese persons [35, 36] and associates with insulin sensitivity and plasma lipid and glucose levels in this population [27, 37].

4.2. White adipose tissue transcriptome and circadian rhythms

Adipose tissue is a peripheral oscillator capable of modulating central core clock genes [38]. Moreover, clock genes are expressed in both visceral and subcutaneous adipose tissue depots, and are associated with a number of metabolic syndrome parameters in individuals with obesity [39]. Clock genes control some adipokines, and their expression in adipose tissue exhibits diurnal variation in persons with obesity [40–42]. In addition, ex vivo explants demonstrate the presence of peripheral circadian oscillators in human adipose tissue that can function independently of the central (SCN) circadian mechanism [43]. Adiponectin-related [44], cortisol metabolism-related [45] and leptin and leptin receptor-related gene expression [46] all show circadian rhythmicity, with different circadian patterns

between visceral and subcutaneous white adipose tissue depots. In addition, adipose tissue from persons with obesity shows a robust insulin signaling circadian rhythm [47].

4.3. White adipose tissue transcriptome and timed/delayed eating

Diet and various dietary interventions affect adipose tissue gene expression [48–50]. In addition, timed or delayed eating impact circadian rhythms [14,20]. Given these effects, and the fact that adipose tissue shows circadian rhythms in gene expression, timing of eating should affect adipose tissue gene expression. One study in mice examined this question. Hatori et al. [21] investigated mice who received *ad lib* or time-restricted feeding of a high-fat diet for 8 hours per day and consumed equivalent calories; those on the time-restricted feeding showed improvements in adipose tissue gene expression. One recent human study has also addressed this important issue. Wehrens et al. [51] studied 10 healthy men, providing three isocaloric meals at 5-hour intervals starting at 0.5 hours from awakening (for 4 days) followed by 5.5 hours from awakening (for 6 days), with 37-hour constant routine assessments following each condition. They sampled adipose tissue during the constant routine assessments following the early and late eating schedules. They demonstrated that *PER2* mRNA rhythms were delayed by 1 hour in the later eating condition, suggesting a possible mechanism for the glucose delay that was also observed. Much more research on how delayed timed eating affects adipose tissue gene expression in humans is needed, particularly in studies of longer duration.

4.4. Blood transcriptome and obesity

Given the limited accessibility and subject burden involved in obtaining adipose tissue biopsies, alternative tissues are needed. As a result, a number of blood transcriptome studies have been conducted, as the collection of peripheral blood is minimally invasive and easily accessible. Moreover, the peripheral blood transcriptome is remarkably consistent within samples from a single person but differs across persons [52]. It also dynamically reflects systemwide biology across different tissue types [53], although there are some tissue-specific differences in gene expression levels [54–58] and in circadian phasing [59].

Peripheral blood gene expression profiling in persons with obesity has identified distinct biological pathways associated with obesity [60–62] and body mass index (BMI) [63]. Differential peripheral gene expression, including in genes related to metabolism, signaling and cellular function, distinguish persons with and without obesity [64–66]. In addition, food intake, dietary patterns including breakfast skipping, dietary challenges and high fat diets all alter blood gene expression, including circadian genes [48, 49, 67–71].

In a study of men of normal weight, the expression of two clock genes, *PER1* and *PER2*, was associated with waist circumference, a marker of abdominal fat accumulation, and plasma glucose concentration, respectively [72]; moreover, *BMAL1* and *CLOCK* gene expression were associated with susceptibility to obesity. Similarly, *PER1*, *PER2*, *BMAL1*, and *CRY1* gene expression were correlated with visceral fat adiposity in participants with BMIs of 25 kg/m^2 or greater [73,74].

4.5. Blood transcriptome and circadian rhythms

Transcriptomic studies using peripheral blood show daily variation in a number of clock genes including *PER1*, *PER2*, *PER3*, *DEC1*, *BMAL1* and *CLOCK* [75–79]. In addition, gene expression and rhythmicity were affected by desynchrony between sleep and circadian phase (i.e., mistimed sleep), constant routines, and sleep loss, whereby the number and/or amplitude of genes exhibiting circadian rhythmicity is altered [22, 80–89]. These studies highlight the gene expression interrelationships between circadian rhythmicity and sleep homeostasis in blood.

4.6. Blood transcriptome and timed/delayed eating

Because timed or delayed eating impact circadian rhythms (see sections 5.3 and 5.4), and blood shows circadian rhythms in gene expression, the timing of eating should affect blood gene expression. However, Wehrens et al. [51], as described above, did not find any changes in clock gene expression in peripheral blood. Much more research examining how delayed timed eating affects blood gene expression in humans is needed.

5. Normal, delayed, and timed eating in humans

5.1. “Normal” eating in humans

While a common assumption is that most people eat breakfast, lunch, and dinner and a couple of snacks as discrete eating episodes, Gill and Panda [90] described the eating habits of a sample of 156 adults, mean age 27.6 years, mean BMI 24.7 kg/m^2, quite differently. Using an app that allowed pictures of food consumed and time stamps of these eating events, they showed that the number of caloric eating events varied from 3 to 11 per day, with 25% of intake occurring before noon, and 35% of intake occurring after 1800h. Half of the sample ate over a period of 14.75 hours, and the timing of this eating period frequently shifted on the weekends, suggesting that “social jetlag” (misalignment of biological and social time) was common [90]. Gupta and colleagues [91] similarly described the eating habits of a sample of 93 healthy Indian adults. Their data illustrated an unstructured pattern of eating such that the average number of eating episodes was 8.5 per day. Additionally, and similar to the findings of Gill and Panda [90], 60% of their sample ate at least 15h per day, with greater than a third of all intake occurring after 1800h. Later eating was not significantly correlated with BMI; no metabolic outcomes were measured, and weight change within a specific time frame was also not assessed between early versus later eaters. Further, a study of 432 older South Asian adults living in Canada (mean age 65 years), characterized participants’ dinner times as early (before 1800h, 19% of the sample), average (1800h–2000h, 44% of the sample) or late (after 2000h, 37% of the sample). The time of dinner was not related to hemoglobin A1c (HbA1c), apolipoprotein, diastolic blood pressure, or higher BMI [92]. More work clearly is needed to characterize “normal” eating behavior in today’s society, how dinnertime relates to time of sleep onset, and the implications of those eating schedules on weight and metabolism.

5.2. Delayed eating in humans with shifted or restricted sleep

Despite these null findings in general community samples for those who report eating on a later schedule, circadian misalignment resulting from shift work, has been shown to alter the circadian rhythms of leptin, cortisol, glucose, and insulin in a carefully controlled 10-day laboratory study [93]. This misalignment from shift work as well as “social jetlag” have been related to metabolic complications such as diabetes, cardiovascular disease, and risk for the development of overweight and obesity [94–100].

Short sleep duration (i.e., sleeping less than 6 hours per night), in which sleep is curtailed but not misaligned, has been consistently associated with increased appetite and caloric intake, changes in appetite regulating hormones, eating late at night, weight gain, and obesity [101–108].

Although these findings indicate that disrupting normally-timed sleep-wake cycles either by misalignment or by sleep restriction impacts weight, adiposity, and metabolism, it is unclear whether meal timing independently plays a causal role in metabolic dysregulation when sleep-wake cycles are held constant among persons with obesity.

5.3. Human phenotype of delayed/nighttime eating – Night Eating Syndrome (NES)

The human phenotype of a delayed pattern of eating is consistent with NES, defined by evening hyperphagia (i.e., consumption of greater than 25% of daily caloric intake after dinner) and/or nocturnal ingestions (i.e., waking during the sleep period to eat) at least twice per week [109]. NES is positively related to BMI [110, 111] in some epidemiological [112–114] and clinical [115–118] studies, but not in others [119,120], particularly those that included higher proportions of young adults. One population-based study examining the relationship between NES and weight identified a U-shaped curve, suggesting that night eating was significantly positively associated with BMI between 31–60 years old, but was not correlated in younger and older adults outside of this age range [121].

While lower sleep efficiency (i.e., the ratio of the total time spent asleep compared to the total amount of time spent in bed) occurs in NES [122], sleep onset and offset are similar to those observed in control participants in inpatient [122] and outpatient [123] settings, even with increased caloric intake [124]. Despite the lack of delayed sleep, persons with NES showed blunted peaks and troughs of the circadian rhythms of food intake, cortisol, ghrelin, and insulin, but increased thyroid stimulating hormone (TSH) amplitude during a 24-hour blood draw with ad lib food access [125]. Those with NES also showed circadian phase delays of leptin, cortisol, insulin, and melatonin, with a circadian phase inversion of glucose and a phase advance in ghrelin. The phase advance of ghrelin was unexpected, but likely related to the ad lib food access allowing for nocturnal ingestions, which limited the overnight fasting period [125]. Additionally, eating habitually during the night may re-program the stomach and gastrointestinal track to release ghrelin before a person’s usual time for nocturnal ingestions.

5.4. Nighttime eating in other populations

Results from other populations also strongly suggest that nighttime eating may contribute to weight gain or maintenance of higher weight. Gluck et al. [126] provided food *ad libitum* to participants during a 3-day inpatient stay and found that those who ate between 2300h–0500h had higher 24-hour respiratory quotients and carbohydrate oxidation rates, and lower fat oxidation rates than those who did not eat between 2300h–0500h, suggesting a phenotype of increased energy intake and weight. Moreover, among a sample of adults from the Quebec Family Study, the presence of morning anorexia, a symptom related to nighttime eating given eating during the night typically reduces appetite for breakfast, was associated with the presence of metabolic syndrome. Additionally, higher scores on the Night Eating Questionnaire, a screening questionnaire containing items related to the criteria for NES including morning appetite, timing of eating and nocturnal ingestions, insomnia, and mood, were related to higher blood pressure among women, and higher waist circumference and triglycerides among men [127].

Collectively, these aforementioned studies (sections 5.2, 5.3 and 5.4) demonstrate the link between night eating behaviors and increased weight and metabolic dysfunction. Therefore, it is critical to understand the impact of the timing of eating on weight and energy metabolism, independent of interrupted or phase-shifted sleep or psychiatric distress (e.g., in NES). One theory suggests that high nocturnal core body temperature may disturb sleep and increase late-night eating, and thereby increase weight and metabolic dysfunction [128]. An alternative explanation may be that nocturnal eating produces a thermic effect, thereby increasing core body temperature as a result, instead of a cause, of night eating. Most studies have not measured body temperature, but if abnormal core body temperature does play a role, it is likely one of a number of mechanistic factors at play.

5.5. Delayed eating in population-based and healthy, normal weight samples

Some observational studies suggest that total daily caloric intake is negatively related to breakfast intake, but positively related to the proportion of food consumed at night, defined as after 2200h [129], or “after dinner” [130]. However, other epidemiological studies have not found a relationship between BMI and evening eating, the latter of which has been defined with varying clock hours, including after 1700h [131, 132], and after 1800h [133, 134]. Given that dinner time varies within individuals and also cross-culturally, differences in the times used to denote evening or late night eating in each study may explain the mixed nature of these results; those studies using later clock times may be more likely to detect positive relationships.

Several experimental studies have demonstrated improvements in metabolic function with a daytime compared to a delayed eating schedule using different paradigms among healthy adults of normal weight, but with mixed results among these studies [51, 135–140] (Table 1). Five studies (one with two samples) using randomized crossover designs, representing a mix of manipulations including single meals, snacks, and total daily energy intake are detailed here [135–139], along with two additional experimental studies [51, 140]. LeCheminant et al. [135] examined 27 men in a randomized crossover design who were prohibited from eating between 1900h–0600h for two weeks, or ate as per their usual

schedule for two weeks, with a 1-week intervening washout period; no food was provided. Compliance was high at 94% on the restricted eating condition. Participants consumed 2420 kcals in the restricted eating condition as compared to 2664 kcals in the usual eating condition, with weight changes of −0.4 kg and +0.6 kg, respectively. Thus, the short-term evening food restriction resulted in a small, but likely clinically relevant reduction of calories and weight. Given the design of the study, the weight change was probably related to the relative differences in energy intake; it is unclear what role the timing of eating played.

Hibi et al. [136] studied the effect of the timing of a snack. Participants included 11 women who ate a ~200 kcal snack either in the morning (1000h) or the evening (2300h) in addition to their three usual meals (food not provided) for a period of 13 days each. Compliance was excellent at 100% for the daytime and 98% for the nighttime snack conditions. The evening, compared to the daytime snack condition, decreased fat oxidation and increased total and LDL cholesterol, but glucose and insulin levels did not differ between conditions [136]. The decreased fat oxidation finding replicates results from Gluck et al. [126] who also showed decreased fat oxidation among persons who ate after 2300h during their inpatient *ad lib* eating study.

Similar to Hibi et al. [136], Bo and colleagues [137] were interested in isolating the effect of a single meal as opposed to the timing of a person's 24-hour intake. They assigned 20 participants to receive an identical meal either at 0800h or at 2000h, one week apart. A standard meal was provided 8h prior to the test meal, followed by a fast in each condition. However, unlike Hibi et al. [136], resting metabolic rate was increased after the morning compared to the evening meal, and glucose, insulin, and free fatty acid responses were reduced after the morning meal relative to the evening meal condition, showing a significant benefit to consuming the meal early in the day. Bandín et al. [138] also manipulated one meal, assigning women to an early (1300h) compared to a late (1600h) lunch for one week each, keeping breakfast and dinner times fixed and providing food for these meals. Two samples were run through this protocol (N=22 women and N = 10 women), each using different assessments to arrive at the following results. The late-lunch condition was associated with decreased resting energy expenditure, fasting carbohydrate oxidation, glucose tolerance, and thermal effect of food, and a blunted daily cortisol profile. These findings also replicate aspects of both Hibi et al. [136] and Bo et al.'s [137] studies.

Examining a shift in total daily intake, Qin et al. [139] assessed seven students assigned in a crossover design to a typical daytime versus a delayed eating schedule for three weeks each. After the delayed condition, melatonin and leptin peaks were attenuated, glucose increases were maintained across the early morning hours, and insulin secretion decreased, as compared to the changes observed after the daytime condition, suggesting impaired insulin sensitivity when eating occurs later in the day. These results are similar to Bandín et al.'s findings [138], as well as findings reported with NES patients [125]. However, sleep was not held constant, food was not provided, and the meal structure differed in the two conditions, so these and other factors could have affected Qin et al.'s [139] results.

Yoshizaki et al. [140] used a between subjects randomized design and assigned 14 men who were habitual breakfast skippers to three meals at either a) 0800h, 1300h, and 1800h, or b) 1300h, 1800h, and 2300h for two weeks. Food was provided and sleep was held constant from 2400h to 0600h. The early, daytime eating schedule lowered triglycerides and total and LDL cholesterol, but did not affect blood glucose, non-esterified fatty acids (NEFAs), insulin, or homeostatic model assessment of insulin resistance (HOMA-IR) compared to the later schedule.

Finally, in a non-randomized experimental design, Wehrens et al. [51] studied 10 healthy men, providing three isocaloric meals at 5-hour intervals starting at 0.5 hours from awakening for 4 days, followed by meal initiation at 5.5 hours from awakening for 6 days, with 37-hour constant routine assessments following each condition. While they did not demonstrate differences during constant routine assessments in the timing of sleep, subjective hunger, plasma melatonin or cortisol (markers of the SCN or central biological clock), or triglycerides, they did demonstrate an average 5.7 hour delay in the glucose acrophase in the later eating condition.

Overall, these human studies suggest that delayed eating produces metabolic dysfunction, while daytime eating generally improves these parameters or produces no changes. However, only three of these studies controlled for, or carefully monitored, calories, macronutrient content, activity levels, or timing of sleep-wake cycles. In addition, most of these studies used small sample sizes, and all studies were of short duration (3 weeks maximum) and either did not report their impact on weight, or did not find any significant changes. Moreover, most of these studies did not examine the mechanisms underlying these observed differences.

5.6. Timed eating in persons with obesity or overweight, including metabolic syndrome, and in bariatric populations

In a weight loss paradigm, a study of 420 Spaniards seeking weight loss with a Mediterranean diet found that “late eaters” (eating the midday meal after 1500h), compared to “early eaters” (eating the midday meal before 1500h), lost significantly less weight during the 5-month study, despite similar self-reported energy intake, sleep duration, macronutrient content, estimated energy expenditure, and appetitive hormone profiles [141]. Ruiz-Lozano et al. [142] used the same paradigm of examining the impact of timing of the main meal of the day among Spanish bariatric patients as described above by Garaulet and colleagues [141]. They found that those bariatric patients who were considered poor weight loss responders to surgery were more likely to consume their main meal of the day after 1500h, with 70% of this group fitting this description, compared with persons who were considered good responders to surgery, with only 37% of this group eating their main meal after 1500h.

Additionally, one observational study showed that among 110 participants of varying body mass status, those with overweight or obesity consumed a higher proportion of their total daily calories closer to melatonin onset, a circadian phase marker, than individuals of a healthy weight [143]. This finding suggests that an individual’s chronotype is an important factor when prescribing optimal eating times, because these times will likely vary for “night owls” compared to “morning larks.”

Jakubowicz et al. [144] tested the timing of calorie distribution during a 12-week weight loss intervention, providing the largest meal of the day (700 kcals out of 1400 daily kcals) either at breakfast or dinner among participants with a BMI greater than 25 kg/m^2 and metabolic syndrome. Lunch was held constant at 500 kcals and the remaining meal was held constant at 200 kcals. The largest meal breakfast group showed greater weight loss and improvements in fasting glucose, insulin, ghrelin, and triglycerides than the group that ate their largest meal at dinner. An oral glucose tolerance test also showed greater decreases in glucose and insulin for the largest meal breakfast group. Similarly, Versteeg and colleagues [145] assigned 25 men with obesity to a hypocaloric diet to be consumed as follows: a) 50% of total caloric intake at breakfast, followed by 35% at lunch and 15% at dinner; or the opposite: b) 15% of total intake at breakfast, 35% at lunch and 50% at dinner. Weight reduction occurred in both groups, but showed no significant differences, and there were no differences between the groups for changes in leptin, ghrelin, and ratings of hunger and appetite. Using single photon emission computed tomography (SPECT) imaging scans taken before and after each condition, they showed that the large breakfast group had increased thalamic serotonin transporter (SERT) binding and striatal dopamine transporter (DAT) binding, but the large dinner group showed decreased binding in these areas. This suggests that the reinforcing value of food may be diminished due to greater activation of these circuits when eating more calories earlier in the day [145], which could play a role in longer-term weight maintenance.

These studies among persons with overweight and obesity focus on the timing of the main meal of the day and suggest that loading calories in the beginning of the day may be beneficial for weight and metabolism, including glucose regulation, although the results are not uniform. The bariatric results are similar to those found among persons consuming their main meal of the day before 1500h who were following a Mediterranean diet program [141], suggesting that both surgical and behavioral modes of weight management may be affected by the timing of intake over the 24-h period. Studies examining melatonin onset suggest that the absolute prescription times for eating may be influenced by chronotype [143].

5.7. Time-restricted feeding and intermittent fasting

Time-restricted feeding is defined as the consumption of as much food as desired by a person or animal during a specific time period (e.g., 0800h–1600h), followed by complete absence of food intake during the subsequent period (e.g., 1600h–0800h). In humans, food is limited typically to the daytime, and in rodents it is limited to the nighttime, during their respective usual active phases [146, 147]. In rodents, time-restricted feeding reduced body weight, total cholesterol, and triglycerides, glucose, insulin, interleukin 6, and tumor necrosis factor-α, and improved insulin sensitivity [146, 147], with one recent study showing a more beneficial effect among adolescent than adult rats, suggesting that time-restricted feeding may be a more effective strategy for weight gain prevention than a treatment [148].

Similarly, in humans, time-restricted feeding decreased body weight (though not consistently), lowered triglycerides, glucose, and low-density lipoprotein cholesterol, increased high-density lipoprotein cholesterol, and improved insulin sensitivity [147].

Gill and Panda [90] instructed 8 participants from their descriptive study who had obesity and who typically ate for 14h or greater each day to choose a 10-h eating period to consume all of their energy for a period of 16 weeks. No further instructions were provided for nutrition or caloric recommendations, and no specific consumption start or end time was specified. After 16 weeks, participants had lost 3.8% of their body weight, and they maintained a loss of 3.4% at the 1-year time point. Participants reduced their caloric intake, likely because of the truncated feeding time window (there was an average reduction in the feeding window of 4h and 35 mins). They also reported improved sleep, and they reduced the delay in their weekend eating by one hour.

Time-restricted feeding, while promising, is derived from rodent models [146, 149] and requires more research to conclude definitively that it has positive weight and metabolic benefits in humans [9, 147], particularly among persons with obesity.

6. Conclusion and Future Research

The literature detailing the impact of the timing of eating is in its early stages, but suggests such timing impacts weight and metabolic functioning, with potential circadian mechanisms. However, most studies have been conducted with rodents or persons of normal weight. More work is needed, including extending these studies to metabolically healthy persons with obesity who remain at risk of developing the metabolic syndrome and diabetes. Further, studies that determine causality between meal timing and health outcomes are few, and those that have been published have been short in duration and have used small sample sizes. Finally, there are even fewer studies testing whether there is an additive benefit to weight loss by limiting eating times in addition to reducing calorie intake. As such, intervention studies using meal timing as part, or the main feature, of a weight management approach are also sparse, representing a critical need for more studies. Other potential areas of future research include consideration of gene expression and insulin sensitivity studies to identify what processes may underlie the metabolic changes observed when eating according to these different schedules, as well as potential sex differences.

The current paper did not include a systematic review of the literature or a method for objectively evaluating, via a meta-analysis, the strength of the evidence presented in each study and for each proposed meal timing intervention and/or timeframe. Despite these limitations, the available literature reviewed here suggests that changing the timing of eating may serve as an additional or adjunctive treatment option to other established treatments such as diet, exercise, pharmacotherapy, and surgery for obesity and metabolic dysfunction [5, 6]. In addition, identification of mechanisms underlying the timing of eating would identify targets for medical interventions for obesity and for prevention of the metabolic syndrome and diabetes. They would also inform clinical treatment guidelines regarding behavioral strategies that could be recommended by public health platforms and by medical personnel to modify the timing of eating for management of weight and metabolic disease. Altered genes, including circadian genes, in response to the timing of eating may also serve as therapeutic, pharmacological targets [150] and biomarkers for obesity-related complications.

In summary, the body of work examining the impact of the timing of eating on weight and metabolic health is nascent, with a need for a) more experimental studies in both calorie sustaining and weight management settings; b) studies of longer durations; and c) studies in more diverse populations to confirm the early findings that have largely shown that eating earlier in the day confers important health benefits.

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Highlights

- Timing of food consumption is a significant contributor to body weight regulation
- Delayed or nighttime eating may adversely affect weight, adiposity and metabolism
- Circadian mechanisms underlie metabolic changes resulting from timed eating
- Adipose and blood transcriptomes link to circadian rhythms and delayed eating

Table 1

Summary of experimental studies manipulating timing of eating among participants of normal weight.

Authors [ref]	Sample	Design	BMI/Weight	Other Outcomes
LeCheminant et al. [135]	N=27 men (completers) 20.9 years, BMI 24.4 kg/m^2	Randomized crossover design: 2 wks with no EI between 1900h–0600h, 2 wks eat as usual. 1 wk washout between conditions; food not provided	−0.4 kg with nighttime restriction; +0.6 kg with usual intake	During nighttime restriction, consumed 244 fewer kcals and had greater morning hunger than during usual eating.
Hibi et al. [136]	N=11 women, 23 years, BMI 20.6 kg/m^2	Randomized cross-over design, 13d with snack (192 kcal) at 1000h and 13d with same snack at 2300h, plus usual meals (not provided); assessed with respiratory chamber and oral glucose challenge test	No significant difference	Nighttime snack decreased fat oxidation, increased total and LDL cholesterol vs daytime. No differences in glucose and insulin response or energy expenditure.
Bo et al. [137]	N=20 (10 men), ages 27.6 years, BMI 23.4 kg/m^2	Randomized crossover design - Single meal manipulation - ate either at 0800h or at 2000h each for 1d, 1 wk apart	Not reported	Glucose, insulin, and free fatty acid response were lower, and resting metabolic rate was higher after morning meal vs evening meal.
Bandín et al. [138]	N=22 women, 26 years, BMI 23.2 kg/m^2 (Cohort 1)	Randomized crossover design - EE early eating (lunch at 1300h) and LE (lunch at 1630h) for 1 wk each; three meals provided; 1 wk washout between conditions	Not reported	Lower pre-meal resting energy expenditure, fasting carbohydrate oxidation, and glucose tolerance in LE vs EE; no difference in postprandial energy expenditure.
Bandín et al. [138]	N=10 women, 26 years, BMI 22.5 kg/m^2 (Cohort 2)	Randomized crossover design - EE early eating (lunch at 1300h) and LE (lunch at 1630h) for 1 wk each; three meals provided; 1 wk washout between conditions	Not reported	Decreased thermal effect of food and blunted cortisol profile in LE vs EE.
Qin et al. [139]	N=7 (6 men), age 21.7 years, BMI 22.9 kg/m^2	Randomized crossover design for 13d to *diurnal* - ate at 0700h, 1300h, 1900h with 2230h–0630h sleep-wake cycle, and *nocturnal* - ate at 1300h, 1900h, and *ad lib* snacking at night with 0130h–0830h sleep-wake cycle; no food provided, intake estimate of 2,200 - 2,600 kcals	No significant difference	Reduced peaks for melatonin and leptin, and lowered glucose and insulin response to meals in nocturnal vs diurnal eating condition.
Yoshizaki et al. [140]	N=14 men, age 21.4 years, BMI 23.1 kg/m^2 controls, 21.9 kg/m^2 early meal group	All were habitual breakfast skippers - randomized for 2 wks to receive 3 isocaloric meals (provided) either at their usual time: 1300h, 1800h, 2300h or at earlier times: 0800h, 1300h, 1800h	Not reported	Triglycerides, insulin, total and LDL cholesterol decreased in early condition; remained unchanged in usual condition. No difference in glucose, NEFAs, HDL cholesterol, HOMA-IR.
Wehrens et al. [51]	N=10 men, age 22.9 years, BMI 23.1 kg/m^2	Within subjects, inpatient study; all received 3 isocaloric meals at 5-h intervals: 1. starting at 0.5h from wake time for 4d, then 2. starting at 5.5h from wake time for 6d, with 37h constant routine assessments after each	Not reported	Delay in mean acrophase of glucose and decreased mean glucose levels in late meals vs early; no differences for timing of sleep, subjective hunger, plasma melatonin, or cortisol.

Notes: Ages and BMI values are presented as means. BMI - body mass index; wk - week; EI - energy intake; h - hour; d - day; LDL- low-density lipoprotein; EE - early eating; LE - late eating; NEFA - non-esterified fatty acids; HDL - high-density lipoprotein; HOMA-IR - homeostatic model assessment of insulin resistance