Review

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Circadian clock and temporal meal pattern

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Abstract: The central circadian clock in the brain controls the time-of-the-day variations in acute meal responses, with a low glycemic response but a high satiety/thermogenic response to meals consumed at waking compared to other time points. Consistently, studies show that consuming a significant proportion of calories, particularly carbohydrates, in breakfast is beneficial for the chronic management of obesity and its associated metabolic syndrome, compared to consuming identical meals at dinner. Conversely, breakfast skipping or/and late dinner can have unfavorable metabolic outcomes. It remains controversial how meal frequency affects metabolic health. In contrast, irregular meals, especially irregular breakfasts, show consistent adverse metabolic consequences. Time-restricted feeding (TRF), with all calories consumed within less than 12-h per day, can improve metabolism and extend lifespan. A major component of TRF in humans is caloric restriction, which contributes significantly to the beneficial effects of TRF in humans. By comparison, TRF effects in rodents can be independent of caloric restriction and show day/night phase specificity. TRF could alleviate metabolic abnormalities due to circadian disruption, but its effects appear independent of the circadian clock in rodents. Understanding neuroendocrine mechanisms underlying clock-mediated metabolic regulation will shed light on the metabolic effects of temporal meal patterns.

Keywords: cardiometabolic; circadian rhythm; daily variation; diabetes; meal response; suprachiasmatic nuclei.

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Introduction

We are what we eat. In addition to "what we eat", "when we eat" is increasingly recognized as another important factor that determines metabolic health. Since eating is generally a repetitive behavior on a daily basis in humans, it is intrinsically connected to the daily 24-h rhythm of the neuroendocrine system. We will focus on the temporal aspects of meals in this review and will not discuss macronutrient compositions or caloric restriction. Given the vast literature on circadian disruptions and sleep disorders due to changes in light schedules, we will focus on studies on the normal light/dark schedule. For the same reason, we will not discuss genetic mouse models of the circadian clock unless it provides direct insights into the 24-h physiological rhythms under normal light/dark or feeding conditions. Lastly, we will focus on metabolic outcomes related to obesity, diabetes, fatty liver, and other cardiometabolic risk factors.

Circadian clock

The molecular circadian clock generates cue-independent 24-h rhythms in behavior and metabolism physiology. The molecular circadian clock operates in mammalian cells and consists of several interlocked transcriptional-translational feedback loops [1, 2]. Heterodimers of the transcription factors Brain and Muscle ARNT-Like 1 (BMAL1) and CLOCK bind to the E-box elements in the promoter/enhancer regions of the target genes and activate their transcription. Among BMAL1/CLOCK target genes are core clock genes Period (PER) and Cryptochrome (CRY) (Figure 1). PER and CRY proteins form heterodimers that interact with BMAL1/CLOCK and counteract BMAL1/CLOCK-mediated transcription activation. As a result, the levels of PER and CRY transcripts and proteins would decay until the brake on BMAL1/CLOCK is released, followed by another rise of the PER and CRY expression with a 24-h period [1, 2]. The casein kinase controls the rate at which the PER/CRY complex is degraded or enters the nucleus. A loss-of-function mutation in a casein kinase shortens the intrinsic period of the clock in mice and gives rise to sleep phase disorders in humans [3]. Pharmacological modulation of the casein

kinases can alter the period by modulating PER localization and stability [4].

While the PER and CRY constitute the primary negative feedback loop, REV-ERB and retinoic-acid-receptor-related orphan receptors (ROR) constitute a second negative loop within the molecular clock machinery. BMAL1/CLOCK stimulates the transcription of nuclear receptors REV-ERB and ROR (Figure 1). The REV-ERB/ROR proteins compete for the ROR elements in the promoter/enhancer regions of the target genes, such as BMAL1, where REV-ERB proteins inhibit BMAL1 transcription and ROR proteins activate it [1, 2]. The REV-ERB/ROR loop also drives the transcription of nuclear factor, interleukin 3 regulated (NFIL3). NFIL3 binds to D-box elements in the promoter/enhancer regions of REV-ERB and ROR to repress their transcription. BMAL1/CLOCK drives other D-box binding proteins, including albumin D-box binding protein (DBP), thyrotroph embryonic factor (TEF), and human hepatic leukemia factor (HLF), creating another transcription loop [1, 2]. These interlocked transcriptional feedback loops of the clock machinery cooperatively regulate the rhythmic expression of clock-controlled genes that serve as the output pathways of the clock to confer temporal cues to various physiological processes.

The molecular clock machinery is expressed in most tissues and organs in mammals. The central clock refers to the clock in the hypothalamic suprachiasmatic nuclei (SCN), while peripheral clocks refer to those expressed in peripheral tissues and other parts of the central nervous system [5]. The SCN clock is kept in alignment with the external photic cues through the retinohypothalamic tract (RHT) that connects the light-sensing melanopsin-expressing intrinsically photoreceptive retinal ganglion cells (ipRGCs) to the SCN [6]. The RHT releases excitatory glutamate as its primary neurotransmitter to depolarize

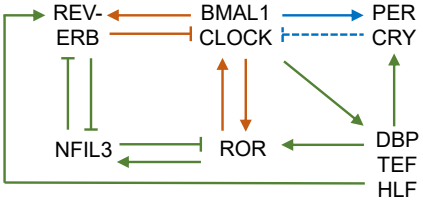

Figure 1: Diagram of the molecular circadian clock machinery. The blue, red, and green depicts the first, second, and third feedback loops, respectively. The solid lines indicate transcriptional regulation, while the dotted line indicates posttranslational regulation. BMAL1, brain and muscle ARNT-like 1; PER, period; CRY, cryptochrome; ROR, retinoic-acid-receptor-related orphan receptors; NFIL3, nuclear factor interleukin 3 regulated; DBP, albumin D-box binding protein; TEF, thyrotroph embryonic factor; HLF, human hepatic leukemia factor.

neurons within the SCN [7]. At the molecular level, glutamate receptor activation leads to a post-synaptic increase of intracellular calcium levels, which activates cAMP-responsive element-binding protein (CREB) and then transactivates clock genes, such as PERs. These mechanisms allow the SCN central clock to be aligned with the external photic cues [8–10].

Output of the SCN clock

The SCN central clock relays temporal signals to other regions of the brain, which coordinates the diurnal rhythm of circulating hormone levels or the autonomic nervous system (ANS) [11, 12]. The SCN is primarily composed of neurons using gamma-aminobutyric acid (GABA) as the neurotransmitter [13] and projects to several hypothalamic nuclei that regulate metabolism, including the subparaventricular zone (SPZ), paraventricular nucleus (PVN), arcuate nucleus (ARC), dorsomedial hypothalamic nucleus (DMH), and medial preoptic area (MPOA) [14, 15].

The SPZ is the main efferent target of neural projections from the SCN and an essential relay for the circadian timing system. Early studies have found that electrolytic lesion of the SPZ abolishes the circadian rhythmicity of the eating and drinking behaviors in rats and reduces the amplitude of curling-up behaviors during sleep [16]. Restricted lesion of subregions of SPZ reveals that separate neuronal populations in the SPZ play distinct roles in circadian rhythms of sleep and body temperature. Ventral SPZ lesion causes substantial loss of circadian rhythms of sleep and locomotor activity but has less effect on body temperature. On the contrary, dorsal SPZ lesion reduces the amplitude of the body temperature rhythm but not that of the locomotor activity or sleep [17]. Thus, ventral SPZ regulates the rhythm of the sleep/wake cycle, whereas dorsal SPZ controls body temperature oscillation. The SCN output to the SPZ extends dorsocaudally to the PVN, a pivotal feeding center. The neurocircuit from the SCN to PVN contributes to the light-mediated suppression of feeding behavior [18]. PVN relays the SCN signal to the pineal gland to control the nocturnal secretion of melatonin [19]. PVN also regulates the daily oscillation of adrenocorticotropic hormone (ACTH), glucocorticoid, and oxytocin [11]. The SCN-to-PVN circuit regulates the ANS and hepatic glucose production [20]. Activation of neuronal activity in the PVN induces time-dependent hyperglycemia only during the light cycle, an effect that is abolished in SCN-ablated animals lacking GABAergic input from the SCN to the PVN [21]. Apart from its connection with the SCN, the PVN also has its own circadian oscillator, as specific deletion of BMAL1 in PVN

neurons in mice reduces diurnal rhythmicity in oxygen consumption, feeding, and locomotor activities and promotes diet-induced obesity [22].

The ARC is a hypothalamic nucleus that senses nutrient availability and regulates hunger or satiety [23]. The ARC is located close to the median eminence (ME) that is free of the blood–brain barrier. Therefore, the ARC has access to metabolites and hormones in the circulation [24]. The SCN sends direct projections to ARC neurons expressing α melanocyte-stimulating hormone (αMSH), which influences the ARC neural activity [25]. The bilateral SCN lesion can ablate the nocturnal peak of the ARC neural activity at zeitgeber time ZT22 (ZT0 is when light is on, and ZT12 is when light is off) [25]. Disruption of the SCN-ARC connection in rats results in ARC desynchronization and a loss of rhythmicity in locomotor activity, corticosterone levels, and body temperature without affecting the SCN clock gene expression rhythmicity, suggesting that the neural projection between the SCN and ARC is essential for multiple physiological rhythms [26]. A recent study revealed that SCN input drives the daily regulation of the permeability of the ME-ARC barrier. The SCN enhances the penetrability of glucose from cerebrospinal fluid (CSF) into the ARC by inducing glucose transporter 1 (GLUT1) expression in tanycytes at ZT22 before sleep in rats, which promotes glucose counter-regulation [27].

The SCN projection to the DMH influences various behavioral circadian rhythms [28]. The DMH lesion in rats causes a marked reduction in the circadian rhythms of wakefulness, locomotor activity, feeding, and blood corticosteroid levels [28]. The DMH relays the signals from the SCN to other sleep-regulating regions. For example, the DMH sends GABAergic projections to the ventrolateral preoptic nucleus (VLPO) to inhibit sleep and sends glutamate/thyrotropin-releasing projections to the lateral hypothalamus to promote wakefulness [28]. MPOA also receives projections from the SCN and contributes to the indirect neuronal pathway in circadian control of the sleep/wake cycle [29]. In addition to receiving projections from the SCN, the DMH also sends inhibitory projections to the SCN, which plays a role in food anticipatory activity [30]. The DMH neuronal activity increases while the SCN neuronal activity decreases when animals anticipate food [30].

Daily variations in acute responses to meals

The SCN clock not only controls food eating or food-anticipating behaviors but also regulates responses to meals. The acute glycemic responses to a meal, or glucose tolerance, show a robust diurnal rhythm. In healthy individuals, the same meal at breakfast induces a lower glucose excursion than at dinner in healthy human subjects [31–36] (Table 1). Similarly, mice or rats have the best glucose tolerance at waking or the early active phase compared to the other times of the day, associated with the best systemic insulin sensitivity [37–40]. Insulin is secreted in response to dietary carbohydrates to stimulate glucose uptake from the blood and suppress endogenous glucose production from the liver [41]. Hyperinsulinemic euglycemic clamp analysis demonstrates that the diurnal rhythm of insulin sensitivity is attributable to the heightened sensitivity to insulin-mediated suppression of hepatic glucose production at waking [39, 40]. The SCN lesion abolishes the diurnal rhythm of glucose tolerance, suggesting that the SCN central clock is responsible for these time-of-the-day variations in glycemic responses to meals [42]. Knockout of BMAL1 in mice abolishes the diurnal rhythm in systemic insulin sensitivity, suggesting that the circadian clock is responsible for this temporal pattern [38]. Depletion of REV-ERBα/β in the GABAergic neuron in mice (REV-GABA-KO) abolishes the diurnal neural firing pattern of the SCN^{GABA} neurons and disrupts the diurnal rhythm of glycemic responses to meals [40]. Chemogenetic manipulation of SCN^{GABA} neurons can mimic or abolish the waking-specific glucose intolerance in REV-GABA-KO mice, demonstrating that the SCN clock controls the diurnal rhythm of insulin-mediated suppression of hepatic glucose production [40]. Inducible phase-specific re-expression of REV-ERBα in the SCN^{GABA} neurons in REV-GABA-KO mice can rescue the ZT-dependent glucose intolerance [40]. The SCN might relay the temporal information to the liver through neuronal or endocrine mediators without affecting the overall behavioral rhythm under the normal light-dark cycles [43]. These results suggest that the SCN clock regulates the diurnal rhythm of acute glycemic responses to meals and results in better glycemic control at breakfast in healthy subjects. Thus, it is likely better to consume meals with high glycemic indices at breakfast as compared to consuming the same meal at other times of the day.

In addition to glycemic responses to meals, triglycerides (TG) levels also respond differently to identical meals at different times of the day, although the difference is less well characterized compared to glycemic responses (Table 1). In healthy men, identical meals at noon result in higher postprandial blood TG levels than breakfast [31] or dinner [44]. The difference between noon and dinner was not observed in women [44]. However, the oral fat challenge in rats at the beginning of the active cycle (equivalent to breakfast) results in lower blood TG levels compared to the early sleep

Table 1: The effects of temporal meal patterns on metabolism.

Test subjects	Groups	Duration	Outcomes	Reference, PMID
Intrinsic acute responses to meals				
Humans: healthy men	Identical meal at breakfast vs. noon (n = 6)	Acute	Less postprandial glucose and insulin levels, higher postprandial TG levels	Burdge 2003 [31] 14647218
Human: healthy adults	Isoenergetic big meals at breakfast vs. dinner (n = 6)	Acute	Lower postprandial glucose and better insulin sensitivity indices	Morgan 2012 [32] 22176632
Human: healthy adults	Identical meals at 8am vs. 8pm (n = 20)	Acute	Lower postprandial glucose, insulin, and FFAs levels; higher postprandial metabolic rate	Bo 2015 [33] 26219416
Human: healthy adults	Breakfast vs. dinner (n = 14)	Acute	Lower postprandial glucose levels	Morris 2015 [34] 25870289
Human: healthy men	Meal at morning (9am) vs. evening 5pm) (n = 19)	Acute	Lower postprandial glucose and GIP levels, higher AUC of 5 glycolysis, TCA, and nucleotide-related metabolites, and 18 amino acid-related metabolites	Takahashi 2018 [35] 30441841
Humans: meta-analysis	Identical meal during the day (7am-4pm) vs. night (8pm-4am)	Acute	Lower postprandial glucose levels after identical meals preceded by at least 3 h fast	Leung 2020 [36] 31782659
Rat	6 time-points (ZT2, 8, 11, 14, 18, 22)	Acute	Lowest meal-induced glucose and insulin increase at ZT14	Fleur 2001 [37] 11375322
Mouse	4 time-points (ZT1, 7, 13, 19)	Acute	Highest insulin sensitivity at waking (ZT13) by insulin clamp	Shi 2013 [38] 23434278
Mouse	Active phase (ZT18) vs. sleep (ZT6)	Acute	Higher insulin sensitivity by insulin clamp	Coomans 2013 [39] 23303208
Mouse	Waking (ZT12) vs. sleep (ZT6) or before sleep (ZT0)	Acute	Higher insulin sensitivity by insulin clamp	Ding 2021 [40] 33762728
Humans: healthy adults	Identical meal at noon vs. midnight (n = 25)	Acute	Lower postprandial blood TG levels in men, no difference in women	Sopowski 2001 [44] 11407787
Rat	Oral fat challenge at the beginning of the active phase vs. rest phase	Acute	Lower plasma TG; higher TG uptake in muscle and brown adipose; no differences in the rate of intestinal TG secretion, abolished by SCN lesion	Moran-Ramos 2017 [45] 29113012
Mouse: effect of fish oil on top of a high-sucrose diet	Fish oil at around the activity onset (breakfast) vs. offset (dinner)	Acute	Lower plasma and liver TG and total cholesterol; higher plasma PUFAs	Oishi 2018 [46] 29149647
Human: healthy adults	Identical meals at 8am vs. 8pm (n = 20)	Acute	Higher postprandial epinephrine/norepinephrine and lower acylated ghrelin	Bo 2017 [47] 29255175
Human: healthy adults	Breakfast vs. dinner (n = 13)	Acute	Higher diet-induced thermogenesis	Morris 2015 [48] 26414564
Human: overweight adults	Post-breakfast vs. post-lunch or post-dinner (n = 14)	Acute	Higher thermogenic effects of the meal	Ruddick-Collins 2022 [49] 34473293
Big breakfast				
Human: adults	High-carb intake in the morning vs. control (n = 1488)	Observational correlation	Lower incidence of metabolic syndrome using multivariate nutrient density logistic models	Almoosawi 2013 [50] 22777542
Human: adolescents	Morning snacking (n = 180) vs. evening snacking (n = 28)	Cross-sectional observation	Smaller chance of overweight	Bo 2014 [51] 24897170
Human: non-obese adults	Early high-carbohydrate (<1:30 pm), late high-fat (4:30–10:00 pm) vs. inverse order (n = 29)	4 weeks	Lower whole-day glucose levels in subjects with impaired glucose tolerance	Kessler 2017 [52] 28272464

Table 1: (continued)

Test subjects	Groups	Duration	Outcomes	Reference, PMID
Human: overweight or obese women	Big breakfast vs. big dinner (n = 36–38 in each group)	12 weeks of weight loss program	Greater reduction in weight, waist circumference, blood glucose, insulin, TG levels, HOMA-IR, and glucose tolerance; equal calorie intake	Jakubowicz 2013 [53] 23512957
Human: women with PCOS	Big breakfast vs. big dinner (n = about 30 each group)	12 weeks of weight loss program	Greater reduction in blood glucose, testosterone, and HOMA-IR; higher ovulation rate, despite equal total calorie intake	Jakubowicz 2013 [54] 23688334
Human: adults with type 2 diabetes	Big breakfast vs. big dinner (n = about 20–30 each group)	12 weeks of weight loss program	Greater reductions in HbA1c, glucose levels, blood pressure, and hunger scores; equal body weight and calorie intake	Rabinovitz 2014 [55] 24311451
Human: obese adults	Big vs. normal breakfast on top of the Mediterranean diet (n = 18)	12 weeks	Lower body weight, glucose, and lipid levels despite equal total calorie	Lombardo 2014 [56] 24809437
Human: adults with type 2 diabetes	Metformin with big breakfast vs. metformin with big dinner (n = 22)	7 days	Greater improvement in glucose tolerance, greater increase in insulin secretion, equal total calorie intake	Jakubowicz 2015 [57] 25724569
Human: adults with type 2 diabetes	Low-carb high-fat breakfast vs. normal breakfast (n = 23)	24 h	Lower glucose levels and glucose variability as measured by CGM	Chang 2019 [58] 30968140
Breakfast skipping and late dinner				
Human: men	Breakfast skipping vs. normal 3 meals (n = 29,206)	Observational correlation	Higher risk of type 2 diabetes	Mekary 2012 [60] 22456660
Human: non-shift-working type 2 diabetes patients	Breakfast skipping vs. normal (n = 194)	Observational correlation	Higher HbA1c levels even after adjusting multiple factors	Reutrakul 2014 [61] 24094031
Human: adults with type 2 diabetes	Skip breakfast vs. non-skipping (n = 22)	Acute	Higher postprandial glucose levels after lunch/dinner, lower insulin secretion	Jakubowicz 2015 [62] 26220945
Human: healthy adults	Skip breakfast vs. skip dinner (n = 17)	24-h	Higher insulin levels and fat oxidation, equal total calorie intake	Nas 2017 [63] 28490511
Human: healthy men	Skip breakfast vs. normal 3 meals (n = 10)	6 days	Higher mean glucose levels and glycemic variability, no change in energy expenditure	Ogata 2019 [64] 31095288
Human: healthy adults	Skip breakfast vs. normal eating	6 weeks	No difference in body weight or indexes of cardiovascular health, less glycemic variability	Betts 2014 [65] 24898233
Human: healthy adults	Skip breakfast vs. normal breakfast (n = about 15)	6 weeks	Same response to food in appetite, glucose, insulin, and thermogenesis	Chowdhury 2018 [66] 29378040
Human: healthy adults	Late dinner vs. early dinner vs. (n = 6)	3 days	higher RER after breakfast, higher glucose variability	Nakamura 2021 [67] 34371933
Human: overweight/obese women	Late dinner (11pm) vs. early dinner (8 pm) (n = 40)	acute	Impaired glucose tolerance in MTNR1B risk carriers and not in the non-risk carriers.	Lopez-Minguez 2018 [68] 28455106
Human: overweight or obese women	Late eater (lunch after 3 pm) vs. early eater (lunch before 3 pm) (n = about 200)	20 weeks of weight loss program	Lose less weight; no change in energy intake, diet composition, energy expenditure, appetite hormones, or sleep duration	Garaulet 2013 [69] 23357955
Human: healthy men	Late meals vs. early meals (n = 10)	13 days	Lower average glucose levels; no change in subjective hunger, sleepiness, or clock markers	Wehrens 2017 [70] 28578930
Human: type 2 diabetes patients	Early dinner before 6pm or skipping dinner vs. habitual eating (n = 20)	3 days	More nocturnal hypoglycemia incidences	King 2015 [71] 25370327
Human	Self-reported meal timing (n = 133)	Correlation	No correlation with BMI	Marinac 2019 [72] 30798690

Table 1: (continued)

Test subjects	Groups	Duration	Outcomes	Reference, PMID
Rat	Skip breakfast or dinner vs. no skip	5 weeks	Lower blood TG, cholesterol, and glucose in the active phase	Wu 2011 [73] 22080734
Human: adults with type 2 diabetes	Night eating vs. non-night eating (n = 194)	Correlation	Poorer glycemic control and depressive symptoms	Hood 2014 [75] 24751916
Human: Pregnant women	Night-eating vs. non-night eating (n = 148)	Correlation	Higher indices of insulin resistance and HbA1c level	Deniz 2019 [76] 31360584
Human: overweight or obese adults	Night-eating vs. non-night eating (n = 615)	Correlation	Higher BMI; higher blood pressure in women; higher waist circumference and blood TG in men	Gallant 2014 [77] 24854802
Human: overweight or obese adults	Night-eating vs. non-night eating (n = 388 total)	Correlation follow-up	Bodyweight gain in non-obese subjects; reduced bodyweight in severely obese subjects	Gallant 2015 [78] 25797608
Human: adults with type 2 diabetes.	Night eaters vs. non-night eater (n = 85)	Correlation	Lower heart rate variability in the low and very-low-frequency bands, and poorer sleep quality	Bermúdez-Millán 2022 [79] 35534102
Human: adults	Dinner immediately before bed or/and snacks after dinner vs. control (n = 8,153)	Correlation	Higher chances of obesity in both sexes, higher chances of metabolic syndrome in women	Yoshida 2018 [80] 30537972
Human: healthy adult participants	Night eating vs. non-night eating (n = 7,771 total)	Correlation	Positive correlation with arterial stiffness in women, but not in men	Zhang 2020 [81] 32954888
Human: adults with type 1 diabetes	Late-night snacking vs. control (n = 148 total)	Correlation	No change in glycemic control in subjects with continuous subcutaneous insulin infusion	Matejko 2015 [83] 26221525
Meal frequency				
Human: healthy adults	Meal frequency correlation with BMI (n > 10,000)	Correlation	Eating less frequently and big breakfasts are correlated with lower long-term weight gain	Kahleova 2017 [84] 28701389
Human: type 2 diabetes adult patients	2 meals (breakfast and lunch) vs. 6 smaller meals (n = 27 each)	12 weeks on top of oral hypoglycemic agents	Greater reduction in body weight, hepatic lipid content, fasting glucose, C-peptide, glucagon, and insulin resistance; equal caloric intake	Kahleova 2014 [85] 24838678
Human: type 2 diabetes adult patients	2 meals (breakfast and lunch) vs. 6 smaller meals (n = 27 each)	12 weeks on top of oral hypoglycemic agents	Higher fasting ghrelin levels despite similar postprandial responses of leptin, GIP, and other appetite hormones and equal total caloric intake	Belinova 2017 [86] 28369078
Human: adults with type 2 diabetes	3 meals per day vs. 6 meals per day (n = about 14)	12 weeks	Greater reduction in body weight, HbA1c, appetite, glucose, and insulin; equal total calorie intake	Jakubowicz 2019 [87] 31548244
Human: obese adults	3 vs. 6 meals per day (n = 13)	3 days	No change in glucose total AUC; increased postprandial insulin responses	Kanaley 2014 [88] 25231499
Human: healthy adults	1 vs. 3 meals per day (n = 15)	8 weeks	Higher fasting glucose levels, impaired morning glucose tolerance, delayed insulin response	Carlson 2007 [89] 17998028
Human: adults with impaired glucose tolerance	3 vs. 6 eucaloric meals per day (n = 47)	12 weeks	Less glucose tolerance, same total calorie intake	Papakonstantinou 2018 [90] 29680359
Human: women with PCOS	3 vs. 6 isocaloric meals per day (n = 24)	24 weeks	Less post-OGTT insulin sensitivity (Matsuda index), same total calorie intake	Papakonstantinou 2016 [91] 26862008
Meal regularity				
Human: overweight or obese adults	High vs. low daily variability in breakfast timing (n = 73 total)	Observational correlation	High body weight and HbA1c levels	Zhao 2021 [94] 34348822

Table 1: (continued)

Test subjects	Groups	Duration	Outcomes	Reference, PMID
Human: school children	Irregular vs. regular meal pattern (n = 604)	Observational correlation	Higher BMI, although breakfast was the only single meal associated with BMI.	Lehto 2011 [95] 21129237
Human: adults	Irregular vs. regular meal pattern (n = about 1400)	Observational, 10 and 17 year follow-up, correlation	Higher BMI, TG, blood pressure, especially with irregular breakfast or lunch	Pot 2016 [96] 26548599
Human: adults	Irregular vs. regular meal pattern (n = 1768)	Observational correlation	Higher BMI and metabolic syndrome risk with irregular breakfast	Pot 2014 [97] 24675713
Human: adolescent	Irregular vs. regular meal pattern (n = 889)	27 years follow-up	Higher prevalence of BMI and metabolic syndrome in later life, only with irregular breakfast	Wennberg 2015 [98] 25936413
Human: healthy adult women	Variable meal frequency (3–9 meals/day) vs. 6 regular meals per day (n = 11 total)	2 weeks	Higher postprandial insulin and fasting total/LDL cholesterol; lower postprandial energy expenditure and thermogenesis; no change in total calorie intake	Farshchi 2004–2005 [99–101] 15220950 15085170 15640455
Human: normal-weight adult women	Variable meal frequency (3–9 meals/day) vs. 6 regular meals (n = 11)	2 weeks	Less thermic effect of food, higher glucose AUC, no difference in gut hormones	Alhussain 2016 [102] 27305952
Time-restricted feeding (TRF)				
Human: healthy young men	TRF (11 h) vs. baseline (n = 27)	2 weeks	Lower body weight	LeCheminant 2013 [106] 23702187
Human: overweight or obese adults	TRF (10 h) vs. baseline (before TRF) (n = 8)	16 weeks	Lower calorie intake, lower body weight, improved sleep	Gill 2015 [107] 26411343
Human: Strength-trained men	TRF (8 h) vs. control (n = 17 per group)	8 weeks	Lower fat mass, glucose, insulin, TG, and leptin levels	Moro 2016 [108] 27737674
Human: men with prediabetes	Early TRF (6 h, dinner before 3 pm) vs. habitual (n = 8)	5 weeks	Better insulin sensitivity, lower blood pressure, less oxidative stress, no weight loss	Sutton 2018 [109] 29754952
Human: healthy adults (mostly females)	TRF (delay breakfast and advance dinner by 1.5 h each) vs. habitual (n = 6–7)	10 weeks	Reduced total calorie intake, reduced adiposity and fasting glucose levels	Antoni 2018 [110] doi.org/10.1017/jns.2018.13
Human: obese adults	TRF (8 h) vs. baseline (before TRF) (n = 23)	12 weeks	Reduced blood pressure; no change in body weight, glucose, insulin, or lipid levels	Gabel K 2018 [111] 29951594
Human: obese adults	TRF (8 h) vs. baseline (before TRF) (n = 40)	12 weeks	Lower body weight and HbA1c	Kesztyus 2019 [112] 31766465
Human: overweight older subjects	TRF (8 h) vs. baseline (before TRF)	4 weeks	Reduced body weight	Anton 2019 [113] 31262054
Human: overweight adults	TRF (8 h) vs. control habitual eating (n = about 10)	12 weeks	Lower body weight and fat mass, no change in physical activity, glucose, or lipid levels	Chow 2020 [114] 32270927
Human: adults with metabolic disorder	TRF (10 h) vs. before TRF (n = 19)	12 weeks	Lower body weight, total cholesterol, and blood pressure	Wilkinson 2020 [115] 31813824
Human: healthy young adults	TRF (8 h) vs. baseline (before TRF) (n = 33)	4 weeks	Lower body weight, insulin levels, no difference in sleep	Park 2021 [116] 34202475
Human: healthy runners	TRF (8 h) vs. habitual eating (n = 7–10)	8 weeks	Lower body mass and energy intake, no change in endurance performance or metabolism	Brady 2021 [117] 32796255
Human: obese adults	TRF (4 h or 6 h) vs. habitual (n = 20/group)	8 weeks	Lower body weight, reduced energy intake	Cienfuegos 2020 [118] 32673591
Human: healthy, physically active men	TRF (8 h) vs. isocaloric control (n = 22)	4 weeks	Lower body weight, fat mass, and blood pressure; no change in glucose, insulin, or lipids	McAllister 2020 [119] 31955013

Table 1: (continued)

Test subjects	Groups	Duration	Outcomes	Reference, PMID
Human: obese adults	TRF (10 h) vs. TRF (12 h) (n = 39)	8 weeks	Lower body weight and glucose levels	Peeke PM 2021 [120] 33446635
Human: healthy adults	early TRF (early part of the day) vs. mid-day TRF (n = 82)	5 weeks	More effective at improving insulin sensitivity; lower glucose, adiposity, and inflammation	Xie 2022 [121] 35194047
Human: overweight adults	early TRF (8 h) vs. habitual eating (n = 11)	4 days	Lower mean 24 h glucose levels	Jameshed 2019 [122] 31151228
Human: overweight adults	early TRF (8am – 2pm) vs. control (8am – 8pm) (n = about 10)	4 days	increase protein oxidation, decreased indices of appetite, equal energy expenditure	Ravussin E. 2019 [123] 31339000
Human: obese men	early TRF (8am–5pm) or late TRF (12–9pm) vs. baseline (n = 15)	7 days	Lower body weight and mean glucose levels in both early TRF and delayed TRF	Hutchison 2019 [124] 31002478
Human: overweight/ obese adults	TRF (8 h) vs. habitual eating (n = 11)	5 days	Lower nocturnal mean glucose levels	Parr 2020 [125] 32079327 Jamshed 2022 [126] 35939311
Human: Strength-trained men	TRF vs. habitual (n = 9 per group)	8 weeks	No change in lean mass retention or muscle function; reduced energy intake	Tinsley 2017 [127] 27550719
Human: healthy men	TRF vs. habitual (n = 10–20 per group)	12 weeks	No change in body composition or muscle function, decreased hematocrit, white blood cells, lymphocytes, and neutrophils	Gasmi 2018 [128] 29571007
Human: resistance-trained women	TRF (12–8pm) vs. habitual (n = 17)	8 weeks	No effects on training-induced muscle hypertrophy or muscular performance improvements	Tinsley 2019 [129] 31268131
Human: healthy adults	TRF (8 h) vs. habitual (n = 22)	6 weeks	No change in body weight, cardiovascular functions, glucose	Martens 2020 [130] 31975053
Human: type 2 diabetes	TRF (9 h) vs. habitual (n = 19)	4 weeks	No change in HbA1c or body weight; reduced calorie intake	Parr 2020 [131] 33105701
Human: adults with metabolic disorder	TRF (12 h) vs. standard dietary advice (n = 54)	6 months	Equal reduction in body weight	Phillips 2021 [132] 33807102
Human: obese adults	TRF 8 h (8am-4pm) vs. equal CR (25%) without TRF (n = 70)	1 year	Equally effective in reducing body weight, body fat, blood pressure, glucose, dyslipidemia	Liu 2022 [133] 35443107
Human: overweight or adult adults	TRF (2–8pm) vs. 3 structured meals (n = about 60)	12 weeks	No effects on body weight, fat mass, insulin, glucose, HbA1c levels, or energy expenditure	Lowe 2020 [134] 32986097
Human: obese men without diabetes	TRF (10 h) vs. CR without TRF (n = 15)	8 weeks	No change in glycemic responses to meals	Zhao 2022 [135] 35150947
Human: at risk of type 2 diabetes	TRF (10 h) vs. habitual eating	12 weeks	Ongoing	Quist 2020 [136] 32847912
Human: firefighters on a diet program	TRF (10 h) vs. habitual (n = about 75)	1 year	Ongoing	Manoogian 2021 [137] 34135038
Human: Metabolic syndrome patients	TRF (10 h) vs. habitual	12 weeks	Ongoing	Świątkiewicz 2021 [138] 33498955
Mouse: high-fat diet	TRF (8 h of the active cycle) vs. *ad libitum*	20 weeks	Reduced obesity, insulin, hepatic steatosis and inflammation; improved motor coordination; equal total calorie intake	Hatori 2012 [139] 22608008
Mouse: high-fat diet	TRF (4 h in the sleep cycle) vs. *ad libitum*	18 weeks	Lower body weight, cholesterol, and TNFα levels; improved insulin sensitivity; lower total calorie intake	Sherman 2012 [140] 22593546

Table 1: (continued)

Test subjects	Groups	Duration	Outcomes	Reference, PMID
Mouse: various diets	TRF (8–9 h) vs. *ad libitum*	24 weeks	Attenuated or reverse metabolic diseases on different obesogenic diets, even after temporarily interruptions	Chaix 2014 [141] 25470547
Mouse: high-fat diet	TRF (8–12 h) vs. *ad libitum*	9 weeks	Reduce obesity and inflammatory cytokines	Sundaram 2016 [142] 27188906
Mice: high-fat diet	TRF (10 h of the active cycle) vs. *ad libitum*	8 weeks	Lower body weight, lower pro-inflammatory genes expression in white adipose tissue	Lee 2021 [143] 34836036
Mice: high-fat diet	TRF (9 h) vs. *ad libitum*	12 weeks	Reduce fatty liver and glucose intolerance in both sexes; lower body weight only in males	Chaix 2021 [144] 34407415
Mouse: high-fat diet	Feed in the active vs. sleep cycle	6 weeks	Less body weight gain	Arble 2009 [145] 19730426
Mouse: high-fat diet	Feed at the early vs. late phase of the active cycle	12 weeks	Less weight gain, glucose intolerance, insulin, TG, and leptin levels; equal total calories	Bray 2010 [146] 20351731
Mouse: high-fat high-sucrose diet	TRF in the active vs. sleep cycles	1 week	Lower blood insulin and leptin levels, lower liver lipid contents, but higher glucose levels	Yasumoto 2016 [147] 27085778
Rat	TRF (12 h in the active cycle) vs. TRF (12 h during sleep)	8 weeks	Smaller adipose tissue, more total food intake, altered gene expression in multiple tissues	Opperhuizen 2016 [148] 27562056
Rat	TRF (10 h in the active cycle) vs. TRF (10 h during sleep)	4 weeks	Improved glucose tolerance, equal body weight and total calorie intake	De Goede 2019 [149] 31496992
Mouse	TRF (12 h in the active cycle) vs. TRF (12 h during sleep)	>3 years	Better longevity-promoting effects	Acosta-Rodriguez 2022 [150] 35511946
Rat: shiftwork model (sleep deprivation for 8 h in the sleep cycle)	TRF (12 h in the active cycle) vs. TRF (12 h in sleep) or *ad libitum*	4 weeks	Less obesity, better metabolic profiles, equal total calorie intake	Salgado-Delgado 2010 [153] 20080873
Mouse: shift work (6 h advance twice weekly)	TRF (fixed 12 h period every 24 h) vs. *ad libitum*.	14 weeks	Lower body weight gain, improved glucose tolerance, equal total calorie intake	Oike 2015 [154] 26297949
Mouse: Lacking the circadian clock	TRF (10 h) vs. *ad libitum*	12 weeks	Prevents obesity and metabolic disorders in mice with whole-body Cry1/2 KO or liver-specific Bmal1 or Rev-erbα/β KO	Chaix 2019 [155] 30174302
Mouse: SCN clock deficient mice	TRF (12 h) vs. *ad libitum* on SCN-BMAL1 KO mouse	10 weeks in constant darkness	Normalize glucose intolerance and weight gain in SCN-Bmal1 KO mice	Kolbe 2019 [156] 31767165

TG, triglycerides; FFAs, free fatty acids; GIP, gastric inhibitory peptide; AUC, area under the curve; TCA, tricarboxylic acid cycle; ZT, Zeitgeber time; PUFA, polyunsaturated fatty acids; OGTT, oral glucose tolerance test; HOMA-IR, homeostatic model assessment for insulin resistance; HbA1c, hemoglobin A1C; CGM, continuous glucose monitoring; RER, respiratory exchange ratio; BMI, body mass index; CR, caloric restriction; KO, knockout.

phase [45]. Consistent with the rat study, mice showed lower blood and lipid TG levels after the fish oil challenge at the activity onset (breakfast) compared to activity offset (dinner) [46]. These results suggest different phases between humans and rodents in TG responses to meals.

In addition to TG responses to meals, the satiety and thermogenic effects of the meals also show diurnal rhythms. Identical meals consumed at breakfast produce more postprandial epinephrine and norepinephrine, less acylated ghrelin, and higher diet-induced thermogenesis than the meal consumed at dinner time in healthy human subjects [47–49] (Table 1). These results suggest that consuming a large proportion of calories at breakfast could be better than at dinner if one aims to control body weight by reducing calorie intake or increasing energy expenditure. In the following sections, we will review human and animal studies that examine the chronic effects of different temporal meal patterns on metabolic health.

Big breakfast

A higher proportion of carbohydrate intake in the morning is associated with a reduced incidence of metabolic syndrome in adults [50, 51] (Table 1). Consistently, morning snacking is associated with smaller chances of being overweight in school adolescents compared to evening snacking [51]. Particularly, the high-carbohydrate breakfast, high-fat dinner meal pattern has a better overall glucose profile than the high-fat breakfast, high-carbohydrate dinner meal pattern in non-obese subjects with impaired glucose tolerance [52]. In patients with metabolic disorders such as obesity, diabetes, or polycystic ovary syndrome (PCOS), dietary intervention with high caloric breakfast and low caloric dinner promoted more robust weight loss compared to low caloric breakfast and high caloric dinner, with a more significant reduction in blood glucose, HbA1c, insulin levels, and insulin resistance indices, without changing the total daily calorie intake [53–56] (Table 1). Big breakfasts also resulted in greater improvement in glucose tolerance than big dinners in combination with metformin therapy, despite equal total caloric intake [57]. Another study suggests that low-carbohydrate, high-fat breakfast lowered glucose levels and glucose variability in patients with type 2 diabetes [58]. In summary, the current evidence suggests that consuming a significant proportion of calories, particularly carbohydrates, in breakfast is beneficial for the chronic management of obesity and its associated metabolic syndrome compared to consuming the same amount of calories or carbohydrates at dinner.

Breakfast skipping and late dinner

Compared to altering calorie or macronutrient distributions among different meals, skipping some meals altogether is a more drastic change in temporal meal pattern [59]. Breakfast skipping is associated with a higher risk of type 2 diabetes in the general population [60] and with higher HbA1C levels among type 2 diabetes patients [61]. Breakfast skipping elevates postprandial or mean glucose levels, increases glycemic variability, and lowers insulin secretion in humans in some studies [62–64] (Table 1). Other studies did not observe changes in glucose/insulin levels or even observed less glycemic variability after breakfast skipping [65, 66].

Breakfast skipping is usually associated with a later chronotype, which contributes to late dinner. Late dinner leads to higher glycemic variability [67] and impaired glucose tolerance in subjects that are genetically predisposed to diabetes [68]. In a 20-week weight-loss trial, overweight women grouped in the late lunch eaters lost less weight and had a slower weight loss rate than early eaters despite similar energy intake, dietary composition, energy expenditure, appetite hormones, and sleep duration [69]. However, healthy men who eat identical meals 5 h later have decreased average glucose than those of an earlier schedule in another study [70]. Early dinner or dinner skipping was found to increase nocturnal hypoglycemia incidences [71] (Table 1). No correlation was found between the early or late meal timing with BMI [72]. Rats that skip the first or the last meal in the active cycle show similar levels of reduction in blood levels of glucose, TG, and cholesterol [73]. Meal skipping on top of the 3-meal/day pattern in small rodents could involve energy imbalance due to their high baseline metabolic rate. Therefore, rodent models are not particularly helpful in addressing the controversy. The results overall suggest that breakfast skipping or/and late dinner can have unfavorable metabolic outcomes.

An extreme case of delayed eating behaviors is night eating syndrome (NES) [74]. The NES is characterized by consuming > 25% of the total daily calorie after the last meal and/or at least two episodes of nocturnal awakening per week with food ingestion, morning anorexia, a strong urge to eat after supper and before initiation of the sleep or upon awakening from the sleep, insomnia, depression [74]. Patients with NES showed phase delay or amplitude reduction of oscillatory hormones involved in appetite regulation and nutrient metabolism, including insulin, ghrelin, leptin, melatonin, and glucocorticoid. Positive correlations were found between NES and poor glycemic control, higher HbA1c, and higher indices of insulin resistance [75, 76] (Table 1). NES was also shown to be correlated with poor cardiometabolic parameters, including high BMI, higher blood pressure, higher blood TG levels, and arterial stiffness [77–81]. The correlations appear more robust in women than men [80, 81]. However, the relationship between NES and BMI is mixed [82], and some studies did not find a correlation between late-night snacking and glycemic control [83].

Meal frequency and regularity

In addition to the phase of the meals (early vs. late), another aspect of the temporal pattern is the frequency. Shall we eat multiple smaller meals or fewer bigger meals? The frequency and phase are two independent questions theoretically but are intrinsically intertwined in reality

because less frequent meals need to be usually eaten at a specific phase, either early or late. In a population-wide observational correlation study, eating less frequently with big breakfasts is associated with lower long-term body weight [84]. Interventional studies on human subjects with type 2 diabetes show that 2–3 meals per day for 12 weeks can cause a greater reduction in body weight, blood glucose and HbA1c levels, and insulin resistance compared to 6 meals per day without affecting total caloric intake [85–87] (Table 1). However, several studies found no change or even higher glucose levels and less glucose tolerance after reducing meal frequency as compared to 6 meals per day, with equal total caloric intake [88–91] (Table 1). A meta-analysis found that higher meal frequency may lower total cholesterol and LDL cholesterol levels without affecting glycemic control [92]. The controversy about the effects of altering meal frequency may be attributable to the fact that 'less meal frequency' is a mixed entity and involves many variables that need to be carefully controlled during studies.

Compared to meal frequency, more consistent results were reported about meal regularity. Consuming meals irregularly is correlated with higher cardiometabolic risks [93]. Higher daily meal variability is associated with higher BMI, HbA1c, TG, cholesterol, glucose, blood pressure, and thermogenic effects in multiple observational studies in both adults and adolescents [94–98] (Table 1). Interventional studies also showed that variable meal frequency with 3–9 meals per day for 2 weeks increases cholesterol, glucose, insulin, and lower thermic effects of food as compared to regular 6 meals per day in healthy adults [99–102] (Table 1). In many studies, the effects of meal irregularity are the most robust or only observed for irregular breakfasts [95–98] (Table 1). Therefore, irregular meals, especially irregular breakfasts, have adverse metabolic outcomes.

Time-restricted feeding

Time-restricted feeding (TRF) is a dietary intervention limiting daily food intake to a finite time window of 12-h or less every day [103, 104]. By comparison, intermittent fasting (IF) refers to fasting for a more extended period, usually 16–48 h, with intervening periods of normal food intake, on a recurring basis. Periodic fasting (PF) refers to an even longer time scale with fasting or a 'fasting-mimicking diet' lasting more than 2 days. IF and PF involves calorie restriction (CR) while TRF may not because more than 8 h of access to food every day is enough for mice to eat the same calorie as *ad libitum* feeding [105], although TRF in humans tends to lead to reduced caloric intake. As a study tool in animals, TRF can be used to dissect the role of meal timing or misalignment between the central clock and peripheral clocks without the confounding effects of calorie restriction in rodent models. As a therapeutic intervention in humans, TRF also has better patient compliance than IF or PF.

Daily TRF within 6–11 h for 2–12 weeks can reduce caloric intake and lower body weight, glucose levels, and blood lipid levels compared to habitual eating patterns without TRF in human subjects [106–121] (Table 1). The reduction in body fat, glucose, and lipids can be independent of the total caloric intake [119]. TRF within 10 h was shown to have a more robust reduction in body weight and glucose levels compared to TRF of 12-h [120]. Even 4–7 days of TRF, especially early TRF that restricts eating in the morning and early afternoon, can lower body weight, glucose levels, blood pressure and HbA1c levels in obese human subjects [121–126] (Table 1). Several studies did not observe TRF-mediated changes in body composition, body weight, or blood metabolites compared to the habitual eating pattern in healthy subjects [127–131] (Table 1). TRF also did not show superior benefit to caloric restriction or standard dietary guidelines in patients with diabetes or weight or obesity [132–135], but did show more robust effects in lowering body weight in a recent study [126] (Table 1). Several ongoing studies aim to provide more conclusive evidence about the health outcome of long-term TRF [136–138] (Table 1). In summary, the current data suggest that a major component of TRF in humans is caloric restriction, which contributes significantly to the beneficial effects of TRF in human subjects.

In contrast to humans, TRF in rodent models can occur without altering the total caloric intake. TRF on obese mice reduces obesity, insulin resistance, glucose levels, liver lipid content, and inflammatory markers compared to *ad libitum* without altering the total caloric intake [139–144] (Table 1). When compared to TRF in the sleep cycle, TRF in the active cycle showed better metabolic outcomes, including lower weight gain, fat mass, glucose, and TG levels in mice or rats [145–150] (Table 1), demonstrating that the phase of TRF matters. In particular, TRF with 35% caloric restriction within the active cycle prolonged lifespan more profoundly than the same degree of caloric restriction spread out in the day or within the sleep cycle in mice, which was associated with the restoration of the liver gene expression rhythm that was dampened by aging. These results demonstrate the phase-specific TRF effect in rodent animals [150]. In support of this notion, 30% calorie

restriction by dietary dilution, in which mice ate all day to compensate for the low energy density of the diet, had no beneficial effects on lifespan [151] even though dietary dilution was shown to be slightly more effective in reducing body fat than calorie restriction [152] (Table 1). In addition to combating overnutrition, TRF was also efficacious in correcting the metabolic disruptions due to circadian disruption. TRF in the active cycle or in the fixed time in mice or rats on top of the shiftwork models can reduce obesity and improve glucose tolerance [153, 154]. TRF in genetic mouse models lacking core clock genes can also reduce body weight gain or improve glucose tolerance [155, 156]. These results suggest that TRF could be a dietary intervention for circadian disruption. However, the results also demonstrate that the effects of TRF in rodent species were independent of the presence of the intact circadian clock. The available animal studies provide limited information regarding whether or which hypothalamic nuclei are involved in the metabolic regulatory effects of TRF.

Conclusions

The central clock relays the temporal cues through neural or endocrine systems to metabolic organs throughout the body. The central clock controls the time-of-the-day variations in meal-induced responses, with a low glycemic response but a high satiety response to meals consumed at waking compared to that before sleep. These physiologic rhythms of acute meal responses suggest that the best time to consume meals, especially those high in calories or carbohydrates, is at the early phase of the wake cycle, *i.e.*, breakfast. Consistently, the current studies on humans support that consuming a significant proportion of calories, particularly carbohydrates, in breakfast is beneficial for the chronic management of obesity and its associated metabolic syndrome compared to consuming the same amount of calories or carbohydrates at dinner. Conversely, breakfast skipping or/and late dinner can have unfavorable metabolic outcomes. Night eating syndrome, a more severe form of late eating, is found by some studies to be correlated with adiposity, especially in women. It remains controversial how altering meal frequency affects metabolic health, probably because 'less meal frequency' is a mixed entity and involves many variables that need to be carefully controlled during studies. In contrast, irregular meals, especially irregular breakfasts, show consistent adverse metabolic outcomes. TRF can improve systemic metabolism and extend lifespan. The current data suggest that a major component of TRF in humans is caloric restriction, which contributes significantly to the beneficial effects of TRF in human subjects. In contrast, TRF effects in rodent models can be separated from caloric restriction and show day/night phase specificity. TRF could be a dietary intervention for circadian disruption. However, the results also demonstrate that the effects of TRF in rodent species were not necessarily dependent on the presence of the intact circadian clock. Future investigation of neuroendocrine mechanisms underlying central clock connection with systemic metabolism will help understand the etiology of time-related metabolic conditions and provide insights into therapeutic dietary interventions that manipulate temporal meal patterns.

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