Endocrinology, 2020, Vol. 161, No. 12, 1–11
doi:10.1210/endocr/bqaa180
Mini-Review

Mini-Review

The Circadian Clock, Shift Work, and Tissue-Specific Insulin Resistance

Johanneke E. Oosterman,[1,2] Suzan Wopereis,[1*] and Andries Kalsbeek[2,3*]

[1]Department of Microbiology and Systems Biology, Netherlands Organization for Applied Scientific Research (TNO), 3704 HE Zeist, the Netherlands; [2]Department of Endocrinology and Metabolism, Amsterdam UMC, University of Amsterdam, 1105 AZ Amsterdam, the Netherlands; and [3]Hypothalamic Integration Mechanisms, Netherlands Institute for Neuroscience (NIN), An Institute of the Royal Netherlands Academy of Arts and Sciences (KNAW), 1105 BA Amsterdam, the Netherlands

ORCiD numbers: 0000-0002-1473-5839 (J. E. Oosterman); 0000-0001-9612-657X (S. Wopereis); 0000-0001-9606-8453 (A. Kalsbeek).

*S.W. and A.K. contributed equally to this work.

Abbreviations: BCF, β-cell function; BMAL1, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; Cry, Cryptochrome; GLP-1, glucagon-like peptide 1; HIIT, high-intensity interval training; IF, intermittent fasting; IR, insulin resistance; OGTT, oral glucose tolerance test; PER, Period; PFT, PhenFlex test; PPAR, peroxisome proliferator-activated receptor; SCN, suprachiasmatic nucleus; T2D, type 2 diabetes; TRF, time-restricted feeding.

Received: 30 July 2020; Accepted: 25 September 2020; First Published Online: 3 November 2020; Corrected and Typeset: 3 November 2020.

Abstract

Obesity and type 2 diabetes (T2D) have become a global health concern. The prevalence of obesity and T2D is significantly higher in shift workers compared to people working regular hours. An accepted hypothesis is that the increased risk for metabolic health problems arises from aberrantly timed eating behavior, that is, eating out of synchrony with the biological clock. The biological clock is part of the internal circadian timing system, which controls not only the sleep/wake and feeding/fasting cycle, but also many metabolic processes in the body, including the timing of our eating behavior, and processes involved in glucose homeostasis. Rodent studies have shown that eating out of phase with the endogenous clock results in desynchronization between rhythms of the central and peripheral clock systems and between rhythms of different tissue clocks (eg, liver and muscle clock). Glucose homeostasis is a complex process that involves multiple organs. In the healthiest situation, functional rhythms of these organs are synchronized. We hypothesize that desynchronization between different metabolically active organs contributes to alterations in glucose homeostasis. Here we summarize the most recent information on desynchronization between organs due to shift work and shifted food intake patterns and introduce the concept of phenotypic flexibility, a validated test to assess the contribution of each organ to insulin resistance (IR) in humans. We propose this test as a way to provide further insight into the possible desynchronization between tissue clocks. Because different types of IR benefit from different therapeutic approaches, we also describe different chronotherapeutic strategies to promote synchrony within and between metabolically active organs.

ISSN Online 1945-7170

Key Words: circadian timing system, eating pattern, insulin resistance, shift work, glucose

In healthy individuals, glucose homeostasis is a tightly regulated process involving the pancreas (producing the glucoregulatory hormones glucagon and insulin), liver (glycogenolysis and gluconeogenesis on glucagon stimulation, or glycogenesis and glycolysis on insulin stimulation), and muscle and fat tissue (glucose uptake from the blood via insulin). Lastly, the incretins gastric inhibitory polypeptide and glucagon-like peptide 1 (GLP-1) are secreted from the upper gastrointestinal tract in a glucose-dependent matter and augment insulin release from the pancreas (1). To maintain normoglycemia, it is important that these different processes act in synchrony. The internal circadian timing system controls the timing of our eating behavior, as well as the timing of insulin secretion from the pancreatic β cells, glucose production by the liver, insulin-dependent glucose transporter GLUT 4 expression in skeletal muscle, and gastric inhibitory polypeptide and GLP-1 secretion from the gastrointestinal tract (2, 3). Rodent studies have shown that eating out of phase with the endogenous circadian clock can result in desynchronization between rhythms of the central and peripheral clock systems (4, 5), between rhythms of different tissue clocks (eg, between liver and muscle clock), and even between rhythms of clock genes and clock-controlled genes within one organ (6, 7).

Owing to the rotation of the earth around its axis, most organisms experience a daily change in the exposure to sunlight. Consequently, in a broad range of species, a light-sensitive circadian clock evolved as an autonomous timekeeping system that permits anticipation of and entrainment to the ever-changing environmental light conditions (8, 9). In mammals, the central brain clock is located within the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. The SCN functions as a master clock that aligns behavioral patterns with the solar day and supports vital functions by anticipating and coordinating the required metabolic programs (8, 10). This anticipation is evolutionarily advantageous because species have a greater chance of survival when they are active and searching for food during the period in which the chances for encountering prey and avoiding predators are highest (8, 10). The SCN generates an approximate ("circa") 24 hour ("diem") rhythm by means of a transcriptional-translational feedback loop (9). The core of this circadian oscillator is formed by the transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1), which drive the expression of 3 Period (*Per 1-3*) and 2 Cryptochrome (*Cry 1-2*) genes. PER and CRY proteins heterodimerize and subsequently suppress their own transcription by interacting with the CLOCK:BMAL complex. An additional, stabilizing loop is formed by nuclear receptors that either activate or repress the transcription of *Bmal1* (11, 12). This circadian rhythm is entrained to the exact 24-hour rhythm of the environment mainly by light and is transmitted to other brain areas and the periphery via endocrine, autonomic, and behavioral signals, hence synchronizing peripheral clocks, most of which cannot receive photic input themselves (13). For many peripheral clocks, the most important external time giver, or "Zeitgeber," in addition to the SCN, is the feeding/fasting cycle (Fig. 1) (14).

In the healthiest situation, rhythms from the central and peripheral clocks are aligned. Epidemiological studies have shown that shift workers are at higher risk for developing obesity, and obesity-related pathologies, including type 2 diabetes (T2D) (15-17), presumably due to eating out of synchrony with the endogenous biological clock (18). Yet, in the contemporary Western 24/7 society, many more people than only shift workers might be at risk for similar metabolic derangement because eating moments are distributed over a great part of the day, including food ingested late in the evening (19). Short-term misalignment, for example, in case of a long-haul flight, can result in jet lag, fatigue, and bowel problems. However, chronic misalignment can be seen as a sustained stressor leading to an ongoing conflict between the endogenous central clock, peripheral clocks, and the environment (20). Therefore, it is not surprising that circadian misalignment contributes to a wide variety of medical conditions (21).

It can be hypothesized that asynchrony between different organs plays an important role in the etiology of T2D, because such a circadian misalignment will cause a mismatch of glucose and lipid fluxes between the various organs. Otherwise, disrupted tissue clocks may possibly cause insulin resistance (IR) at the tissue level (22). Yet, the exact mechanisms involved in the metabolic derangements resulting from circadian disruption remain to be resolved.

In the present mini-review, we provide a summary of what is known today on organ desynchronization in the context of glucose metabolism by evaluating studies that focused on shift work and shifted food intake patterns. We introduce the concept of tissue-specific IR, which could be a consequence of organ desynchronization. However, in humans it remains difficult to study organ desynchronization by assessing tissue-specific clock gene expression. We therefore propose the concept of phenotypic flexibility as a validated way to assess the contribution of each organ to IR in

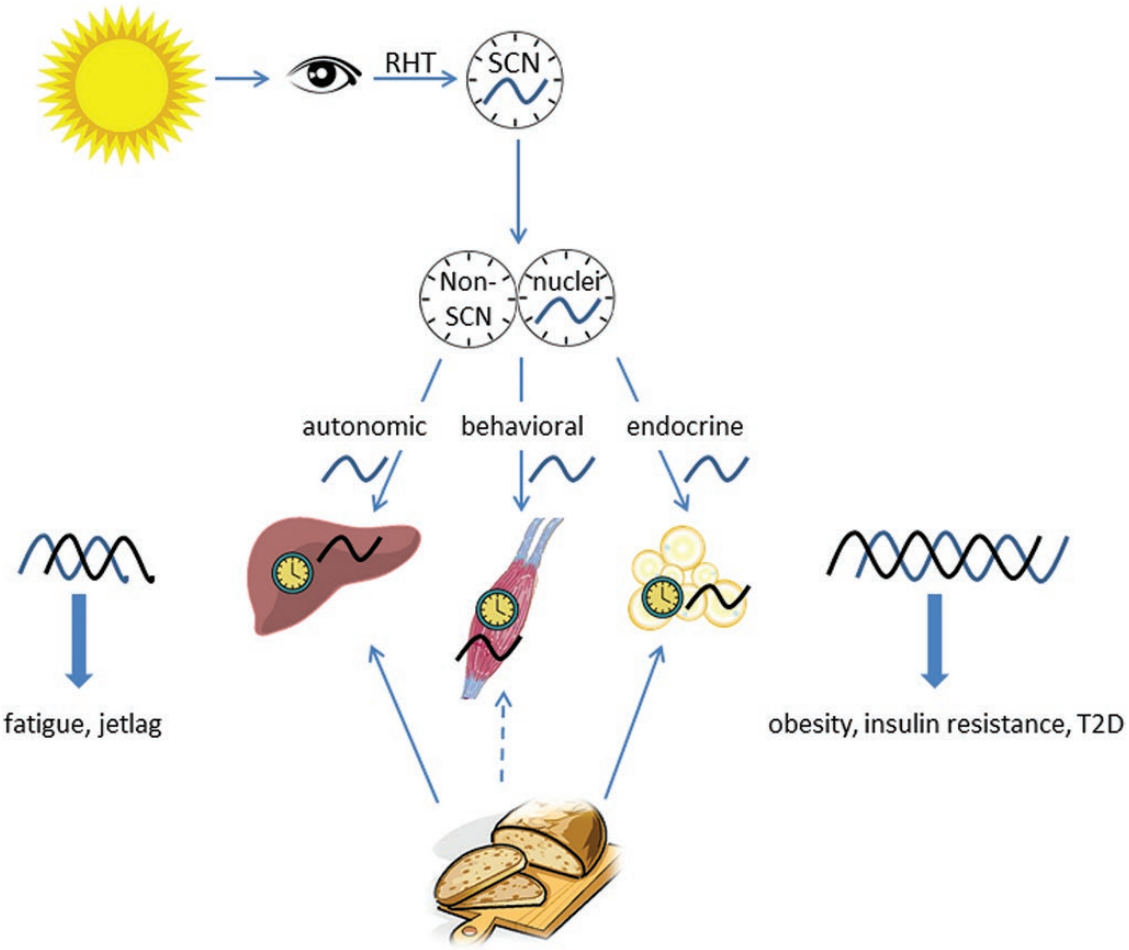

Figure 1. The circadian timing system. The suprachiasmatic nucleus (SCN) generates an approximate 24-hour (ie, circadian) rhythm, which is set to exactly 24 hours by the light/dark cycle. Light information is transmitted from the retina to the SCN through the retinohypothalamic tract (RHT). Subsequently, the SCN transmits its rhythmic information to other hypothalamic nuclei and peripheral organs, which also contain endogenous clocks. These clocks are synchronized not only by the SCN, but also by external signals, of which the feeding/fasting cycle is the most important. Conflicting signals between SCN-driven and feeding-driven rhythms may result in desynchronized rhythms, leading to jetlag, and when regularly present, contribute to the development of obesity and type 2 diabetes mellitus. Reproduced with permission from Oosterman et al (14).

humans. Finally, we provide an overview of different interventions that specifically target organ desynchronization or tissue-specific IR. We conclude that in addition to personalized lifestyle interventions, the timing of those interventions is important as well and should be considered for the next generation of interventions.

Search Strategy

A nonstructured PubMed search was performed, searching for articles related to shift work and insulin resistance, circadian variation in glucose tolerance, shifts in clock gene expression in different organs, as well as tissue-specific insulin resistance. Known literature was used to search for "similar articles" within PubMed. In addition, Google was used to search for specific topics, to find important papers on PubMed.

Clock Control of Insulin Sensitivity

It is the interplay of clock-controlled glucose uptake and release processes in different organs, including the pancreas, liver, muscle, and adipose tissue that ultimately maintains blood glucose homeostasis throughout the day.

The central brain clock (SCN) is responsible for the 24-hour rhythm in plasma glucose concentrations peaking at the start of the active period, independent of feeding conditions (23, 24). Furthermore, glucose transporters and glucagon receptors fluctuate with the circadian cycle, and synthesis of glucose via gluconeogenesis is highly rhythmically controlled (10). The SCN also regulates the daily variation in glucose tolerance, which is highest at the beginning of the activity period, followed by a gradual reduction toward the end of the activity period (25). The higher morning glucose tolerance is partly the result of increased

β-cell responsiveness, accompanied by a tendency to improved insulin action and lower hepatic insulin extraction as compared to later in the day (25). Skeletal muscle has a day-night rhythm in mitochondrial respiratory capacity (26), thereby contributing to the daily rhythm of carbohydrate and lipid oxidation. Besides the crucial role of the central brain clock in regulating glucose homeostasis, the timing of food intake is also an important determinant for glucose regulation, as feeding at "inappropriate" times of the day can cause hyperglycemia and evokes insulin release at a phase opposite to the phase of other physiological rhythms dictated by the SCN master clock, and hence contributes to metabolic imbalance (23, 27, 28).

Over the past decades it has become apparent that all organs involved in glucose homeostasis contain a functional clock (29), and studies with organ-specific clock-gene knockouts show that a functional clock is crucial for maintaining normal glucose homeostasis. SCN-lesioned mice completely lack daily rhythms of plasma glucose (23), and whole-body loss of clock function (eg, *Clock* or *Bmal1* knockout animals) leads to hyperglycemia, glucose intolerance, and ultimately obesity and metabolic syndrome (reviewed in [10]). Ablation of the liver clock results in fasting-induced hypoglycemia due to impaired glycogenesis and in reduced hepatic glucose production (29), whereas ablation of the pancreas clock can induce diabetes due to β-cell failure, indicating opposing consequences of clock dysfunction in liver and pancreas (20). Furthermore, specific disruption of the muscle clock results in diminished insulin sensitivity in the muscle, causing hyperglycemia in the nonfasting condition and glucose intolerance (30).

In patients with T2D, the daily rhythm of glucose tolerance is abolished or even inverted compared to healthy individuals, with an increase in insulin sensitivity toward the evening (31, 32). The peripheral clock may be impaired in (obese) individuals with T2D, as dampened daily rhythms were found in clock gene expression in peripheral leukocytes (33) and subcutaneous adipose tissue (34) compared with nondiabetic controls. However, whether the impaired clock is the cause or the result of impaired glucose regulation remains unanswered.

Problems in Glucose Homeostasis Arising from Misalignment/Shift Work

Temporary circadian misalignment introduced in a controlled laboratory setting, similar to what occurs during jet lag or chronically during shift work, results in decreased glucose tolerance and insulin sensitivity, lower leptin levels, higher mean arterial pressure, lower sleep efficiency, and a complete reversion of the cortisol profile. The abnormally high cortisol levels at the beginning of the sleep period have been proposed to contribute to the development of IR and hyperglycemia (35, 36). Circadian misalignment affected postprandial glucose more than fasting glucose levels, suggesting that misalignment affects fat/muscle metabolism or β-cell function (BCF) more than hepatic gluconeogenesis (35). During a short-term misalignment study, Wefers et al found that endogenous glucose production, measured with a 2-step hyperinsulinemic euglycemic clamp, was not affected. In contrast, circadian misalignment resulted in decreased muscle insulin sensitivity (37), indicating that indeed the process of glucose uptake, rather than glucose production, is disturbed during misalignment.

In healthy rotational shift workers, higher postprandial glucose peaks, accompanied by a lower first-phase insulin response, were observed during a simulated night shift than during a simulated day shift, suggesting reduced β-cell responsivity during the night shift. This resembles the pattern observed in people with impaired glucose tolerance or diabetes, hence indicating how circadian misalignment during shift work may contribute to the development of T2D. The shift-work conditions cause people to consume their food at a time of day when the β-cell response is reduced because of the normal daily variation (38). Notably, factors such as gastrointestinal absorption, hepatic glucose production suppression, and non–insulin-dependent glucose metabolic pathways will also contribute to the circadian misalignment effects on glucose tolerance (39).

Morris and colleagues showed that the detrimental effects of shift work (ie, being awake and consuming food at night) on glucose tolerance are the result of 2 different mechanisms: the internal circadian timing system (ie, lower glucose tolerance in the biological evening due to lower β-cell response) as well as circadian misalignment (lower glucose tolerance when eating during night time than during day time due to lower insulin sensitivity) (39). It is likely that an internal desynchronization between tissue clocks in the liver, muscle, and pancreas further contributes to the observed effects of circadian misalignment on glucose metabolism (39).

Desynchronization Between Organs

In rodents, the rhythms of the SCN and peripheral clocks can be uncoupled by restricting food access to an inappropriate time of day, because peripheral clocks rapidly entrain to the reversed feeding schedule, whereas the central clock does not (5, 40). Moreover, not all peripheral clocks may entrain at the same pace to the shifted food availability (6, 41, 42) and not all organs are synchronized by the SCN in the same manner (43), all of which may contribute to a desynchronization between organs.

Recently, it was shown that desynchronization between the central clock and peripheral clocks also occurs in humans. Shifting mealtime resulted in a shift in the phase of plasma glucose rhythms and caused a delay in the phase of the clock gene *PER2* in white adipose tissue, but did not shift rhythms of melatonin and cortisol (output parameters of the SCN), indicating misalignment between the SCN and peripheral rhythms (44). By applying a constant routine protocol (in which participants are kept in constant conditions and receive no photic or timing information) after either 3 days of simulated night shifts or day shifts, Skene et al showed that traditional markers of SCN phase (melatonin, cortisol and expression of the core clock gene *PER3*) remained relatively stable, whereas 95% of the studied plasma metabolites dissociated from the SCN rhythm and aligned with the shifted behavioral cycles of feeding/fasting and sleep/wake. This disruption in the circadian organization might represent a pathway through which shift work is associated with metabolic disease (45). The observation that these altered rhythms persisted under constant routine conditions in the absence of any externally imposed rhythm suggests an aftereffect of night-shift work on metabolism, indicating the long-term negative effects of shift work.

Next to the dissociation of peripheral rhythms from the SCN, shifting food intake may cause internal desynchronization between organs, leading to disruption of otherwise coordinated processes. Core clock gene expression in muscle tissue did not shift on a short-term misalignment protocol, resulting in a misalignment of the skeletal molecular clock relative to the shifted behavioral cycle (37). In addition, shifting mealtime resulted in a shift in the circadian phase of the adipose tissue molecular clock and affected glucose homeostasis and lipid metabolism differentially, thereby dissociating the temporal regulation of these key processes (44). These distinct differences in tissue responses to the timing of food cues suggest discrete routes of entrainment in different organs.

Phenotypic Flexibility to Study Metabolic Dynamics

Metabolic flexibility is the ability to respond or adapt to conditional changes in metabolic demand. Recent evidence shows that circadian variation in the molecular metabolic machinery also influences metabolic flexibility (20).

Phenotypic flexibility is the broader concept of metabolic flexibility and can be defined as the metabolic adaptation to a disturbance of homeostasis. The magnitude of the amplitude and duration of the homeostatic disturbance of these "adaptive response systems" determine to what extent a person can adequately respond to a standardized external perturbation and can be used to quantify the individual's health status. Phenotypic flexibility is thus the orchestration of all mechanisms and processes involved in the adaptation capacity to maintain a healthy metabolic phenotype (46).

An important aspect of health is the ability to maintain homeostasis under a large variety of continuously changing environmental conditions, including dietary perturbations. To quantify health as a function of the resilience to daily stressors, a standardized mixed meal challenge test was developed named the PhenFlex test (PFT) (47), which can be regarded as an extension of the oral glucose tolerance test (OGTT). The PhenFlex drink is a 400-mL beverage consisting of high amounts of fat (60 g), glucose (75 g), and protein (20 g), corresponding to an intake of 920 kCal. Individuals drink the PFT in the morning after an overnight fast, following which blood is drawn at time (t) = 0, 0.5, 1, 2, 4, and, optionally, 6 and 8 hours (47). With the PFT, 132 markers over a maximum 8-hour time course can be quantified, reporting on 26 metabolic processes originating from seven organs (gut, liver, adipose tissue, pancreas, vasculature, muscle, and kidney), as well as determination of a systemic stress response (ie, systemic IR, chronic low-grade inflammation, oxidative stress, and metabolic flexibility). In this way, the PFT can reveal the adaptive capacities of a broad set of metabolic processes (48, 49). In patients with T2D, quantification of the PFT response was more sensitive in demonstrating disturbances in metabolic health as compared to overnight fasting measures (48, 49). Furthermore, the PFT test showed additional and new markers that were different between individuals with T2D and healthy controls, revealing new processes underlying metabolic health (49).

Phenotypic Flexibility and Tissue-Specific Insulin Resistance

T2D refers to a metabolic glucose dysregulation resulting from defective insulin action (also referred to as *IR*), insulin secretion, or both. IR is the most powerful predictor of future development of T2D. The primary pathophysiological defects in T2D are IR of the liver, muscle, and/or adipose tissue, and a failing pancreatic BCF, resulting in reduced and/or impaired insulin secretion (reviewed in [50]). Although skeletal muscle and liver are the main insulin-sensitive target tissues (51), IR development can originate from many more tissues, including the brain (52, 53). The pathophysiology of T2D also differs between individuals because people differ in terms of their genetics, phenotype, lifestyle, and environment. Additionally, the severity of IR may differ among various tissues (54). Recently, it has been shown that T2D subtypes could be identified based on the IR of muscle, liver, or a combination of these, (55) and that these IR phenotypes have a different etiology (56, 57).

Through determination of phenotypic flexibility using the standardized PFT, the orchestration, as well as disruptions, of glucose metabolism by different organs and processes can be quantified (49), allowing for assessment of the degree of BCF and IR of the primary involved organs. Establishing the diabetic subtype can be achieved by measuring glucose and insulin plasma levels at baseline and during the 30-minute intervals up to 2 hours in response to the PFT or OGTT, following which several indices indicative for BCF and IR of different tissues/organs can be calculated. A combination of a high fasting plasma glucose level with a high plasma insulin level is indicative of hepatic IR (54), whereas muscle insulin sensitivity can be derived from the decline in glucose levels especially in the second half of the 2-hour response curve (54). The BCF can be defined as the mathematical product of glucose absorption and insulin secretion during the acute phase of the metabolic challenge test corrected for whole-body insulin sensitivity (58-60), and adipose tissue IR is calculated as fasting plasma insulin × fasting plasma nonesterified fatty acid concentrations (61, 62). These indices are all validated against the glucose clamp, the gold standard to determine organ-specific IR and very well described in the literature (58, 61).

Phenotypic Flexibility and the Circadian Clock

In light of the differential effects of shift work and shifted meal timing on the different metabolic organs (eg, circadian misalignment affected liver and muscle function differentially [37, 39]), it can be hypothesized that differences in tissue IR are related to changes in the circadian clock.

Because desynchronization in clock gene expression is difficult to assess in living humans, determining tissue-specific IR could be a way to gain more insight into the possible desynchronization between organs. For this, it is important to quantitate which tissues (muscle, liver, pancreas, and/or adipose tissue) are resistant to insulin (54). Yet, assessing tissue-specific IR can be laborious. For example, the IR of adipose tissue is an important feature of obesity-related metabolic disease, but assessment of lipolysis in humans requires labor-intensive and expensive methods (61). Using the PFT or OGTT is a relatively easy and minimally invasive strategy to quantify IR within different organs. Another beneficial aspect of the PFT and OGTT is the aspect of dynamic testing. Circadian clock disruption mainly affects postprandial glucose metabolism and β-cell responsiveness (35, 63), highlighting the importance of a dynamic test (meal tolerance test) when studying and diagnosing circadian clock involvement in IR and T2D.

Interventions to Shift or Repair the Clock

Depending on the tissue in which IR is most abundant, specific therapeutic approaches may be more or less beneficial. Therefore, it is important to identify different subclasses of T2D, as well as the magnitude of the IR, to improve the efficacy of personalized, tissue-specific interventions.

These interventions include increasing physical activity in case of muscle IR, polyunsaturated vs saturated fatty acid balance for adipose IR, energy restriction for hepatic IR, and weight loss and thiazolidinediones (peroxisome proliferator-activated receptor γ [PPAR-γ] agonists) for muscle and hepatic IR (64). In terms of dietary interventions, a low-fat diet was beneficial for hepatic IR, whereas individuals with muscle IR benefited more from a Mediterranean diet (55). Interestingly, caloric restriction was not effective in individuals with T2D with an impaired BCF (65).

Because food intake and exercise both can affect clock genes and clock-output genes in various organs, it can be hypothesized that these interventions, when timed correctly, can be used to resynchronize a disrupted clock. Improving these dysregulated daily rhythms might help ameliorate negative metabolic consequences, for example, in shift workers who are at risk of metabolic disease (66). Increased amplitudes of the circadian rhythm might result in increased tolerance to shift work.

Although it can be hypothesized that individuals with muscle IR may respond better to timing of exercise as a lifestyle intervention than those with liver IR, to date there is no information on differential responses to timed lifestyle interventions specifically tailored for T2D subclasses. Thus, this could be another angle of treatment to consider in individuals with IR or T2D, especially for people who regularly experience misalignment, such as night-shift workers.

Eating in line with circadian time

Timing the majority of calorie consumption to coincide with the time that the endocrine system is most responsive, that is, during daytime, seems most beneficial for health. As described previously, in nondiabetic individuals, glucose tolerance is highest in the morning and decreases throughout the day. This coincides with the finding that carbohydrate oxidation was highest during the biological morning and lowest during the biological evening, whereas for lipid oxidation the pattern was inverted (67). This means that the largest portions of carbohydrates can be best consumed during the morning as opposed to the evening. In lean men, breakfast consumption resulted in higher diet-induced thermogenesis than dinner consumption, which further encourages a high-caloric breakfast over a large dinner (68). In line with this, meal timing has

been associated with weight loss effectiveness, both during regular weight loss (69) and after bariatric surgery (70).

Interestingly, although the diurnal variation in glucose tolerance is altered in patients with T2D (31, 32), increasing the caloric load of breakfast and reducing that of dinner improved insulin sensitivity and decreased body weight, glucose excursions, and glycated hemoglobin among patients with obesity and T2D (3, 71, 72). Furthermore, in individuals with T2D, a high-energy breakfast and low-energy dinner led to overall increased GLP-1 and insulin levels and reduced hyperglycemia throughout the day compared with a reverse meal schedule, despite a similar total caloric content (3). The other way around, skipping breakfast results in an increased postprandial glycemic response and is associated with an increased risk of T2D (73, 74), and a meta-analysis showed a trend between body mass index and evening energy consumption (75). In late eaters, IR was more prevalent than in early eaters (69). Thus, timing food intake during the day may be a therapeutic strategy to improve glycemic control in patients with T2D. However, the causality, timing, and direction of the underlying mechanism—whether timed treatments repair desynchronization and/or whether timed treatments directly repair IR in the context of desynchronization—are still unclear and merely speculation.

Intermittent fasting

Intermittent fasting (IF) is a broad term including a spectrum of eating regimens that intentionally prohibit energy consumption for extended periods. This includes time-restricted eating in which energy intake is restricted to a short period of the day, as well as full fasting during several days a week, alternate-day modified fasting, the 5:2 diet, fasting-mimicking diet, etc (76). IF has been shown to improve insulin sensitivity, reduce glucose and/or insulin levels, lower blood pressure, improve plasma lipid profiles, and reduce markers of inflammation and oxidative stress, but contradictory results have also been shown, and the beneficial effects of IF could often not be seen independently from weight loss (reviewed in [76]).

Only a few randomized clinical trials have been published on IF in patients with T2D. Although IF reduced body weight and improved glycated hemoglobin (HbA1c), fasting glucose levels, quality of life, and blood pressure, it did not affect the homeostasis model assessment of IR, but most important, the results were not different from the calorie-restricted group (77). Thus, the question remains whether the observed effects of IF are due to the timing of food intake or due to calorie restriction.

Time-restricted feeding

Time-restricted feeding (TRF) without caloric reduction in rodents has been shown to prevent obesity and obesity-related diseases in a fasting-duration–dependent manner (78-80) and has been shown to prevent the deleterious effects of shift work (being active and awake during the rest phase) on glucose homeostasis (81). Furthermore, dark-phase TRF normalized clock gene expression in diabetic mice of which the daily rhythm in locomotor was dampened and clock gene rhythms were shifted (82). TRF can help adapt to a changing light-dark schedule, hence providing a promising strategy to expedite the adaptation of the circadian system (83) or prevent shifting during shift work.

Restricting the time of food intake to 10 to 12 hours per day in overweight individuals reduced body weight and improved sleep because of the self-chosen reduced time frame of caloric intake (84). Even in young, healthy, trained participants, TRF to a period of 8 hours decreased fat mass, increased fat-free mass, and improved several health-related biomarkers (85).

Early TRF, with an eating period of 6 hours and completing all meals before 3 PM, as compared to eating periods of 12 hours in men with prediabetes, improved β-cell responsiveness, blood pressure, oxidative stress, and appetite, independent of weight loss (76). This suggests the importance for timing of food intake, irrespective of caloric intake. Early TRF did not improve glucose levels, but it reduced mean and peak insulin values and improved insulin sensitivity and β-cell responsiveness (76).

Although it would intuitively be healthier to shift food intake with the shifted (work) activity (for them to be aligned) during night work, this appears not to be the case. Eating during a simulated night shift, as opposed to not eating during the night shift, in healthy men led to higher glucose area under the curve, indicating that withholding food intake at night may limit impairment in glucose tolerance (63). This suggests that rhythms in different organs shift with different paces, which has been shown in rodents (41, 86), with indeed the muscle clock adapting much more slowly to the new feeding situation than the liver clock. Timing the moment of food intake could be especially beneficial for individuals with liver IR.

Physical activity

In addition to eating, exercise is another well-known nonphotic phase-shifting cue (87). Because exercise is known to reset clock genes in skeletal muscle and other tissues, it could be hypothesized that appropriately, and recurrently, timed exercise can help to reset the daily clock and improve pathologically deteriorated circadian rhythms. In

rodents, exercise can advance the phase of the circadian rhythm in peripheral clocks such as the liver and gastrocnemius muscle (86), and exercise-induced reentrainment depends on the timing of exercise and differs between peripheral tissues (88).

Several studies have demonstrated that exercise modifies the rhythm of the clock machinery in skeletal muscle; however, the optimal timing of exercise for health and the potential of exercise training to ameliorate the effects of disrupted circadian rhythms have not been fully elucidated yet (reviewed in [66]). Using a constant routine protocol, differential effects of high-intensity exercise on the melatonin rhythm were observed, with a phase-advancing effect of acute exposure to evening exercise on the human circadian system (89, 90). Exercise in the morning and afternoon, when higher levels of physical activity often occur in real life, appeared to have no consistent effect on circadian phase (89). Exercise in very dim light resulted in a phase delay of the human circadian pacemaker, showing a nonphotic pathway that facilitates phase delays of the human endogenous circadian pacemaker (91). Exercise has been shown to facilitate adaptation to night-shift work in a field study that exposed participants to a 9-hour phase delay with daytime sleep (91).

Another important factor to take into consideration when evaluating the phase-shifting effects of exercise is chronotype: whether someone is a morning type ("early bird") or evening type ("night owl"). In healthy, young sedentary adults, morning exercise induced greater phase shifts than evening exercise. Late chronotypes experienced phase advances following morning or evening exercise, whereas early chronotypes had phase advances from morning exercise, but phase delays from evening exercise (92). This is an important finding because it demonstrates that it is possible to shift someone's circadian phase by timed exercise, which may be a way to alleviate circadian misalignment. Because the evening chronotype is associated with higher obesity, timed exercise may be a strategy to adopt an earlier chronotype, hence diminishing the deleterious effects on metabolism of the late chronotype.

Timed exercise as a way to shift the circadian timing system and/or improve blood glucose levels in individuals with T2D has not been examined often. A short, randomized, controlled trial showed that afternoon high-intensity interval training (HIIT) was more efficacious than morning HIIT at improving blood glucose in men with T2D. Strikingly, morning HIIT had an acute, deleterious effect, increasing blood glucose (93). This is an area that should be investigated more in the coming years because it may be a relatively easy way to improve glucose control.

Conclusions and Further Research

In this review, we report that the circadian timing system is important for the daily variations in all aspects of metabolism. Living out of sync with the normal daily rhythm can lead to metabolic alterations, possibly due to desynchronization between peripheral rhythms and the central clock, as well as desynchronization between different organs, leading to a mismatch in the otherwise well-coordinated system of, for instance, glucose homeostasis.

Studies in rodents and humans have shown metabolic problems as a result of desynchronization (eg, obesity and T2D in shift workers), as well as alterations in peripheral clock gene rhythms in metabolic tissues. However, to date there is little literature on desynchronization between different organs, especially in humans. We hypothesized that misalignment between organs involved in glucose homeostasis could lead to tissue-dependent IR—muscle IR rather than hepatic IR. Because desynchronization in clock gene expression between organs is very difficult to assess in living humans, we proposed the PFT as a way to assess desynchronization between organs. Further studies are needed to assess how tissue-specific IR is related to clock gene alterations in those tissues. It will also be interesting to assess the effect of shift work or misalignment on tissue-specific IR. Determining the tissue that contributes most to the IR could help in adjusting a personalized lifestyle intervention (eg, focus on physical activity vs focus on caloric intake). In addition to personalized lifestyle interventions, the timing of those interventions is important as well and should be considered for the next generation of interventions.

All in all, we have come a long way, but there also still lies a long way ahead in optimizing lifestyle intervention for shift workers, with or without T2D.

Additional Information

Correspondence: Andries Kalsbeek, PhD, Amsterdam UMC, location AMC, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: a.kalsbeek@nin.knaw.nl.

Disclosure Summary: J.E. Oosterman and S. Wopereis are employees of the Netherlands Organization for Applied Scientific Research (TNO); the latter is a not-for-profit research organization collaborating in several public–private partnerships or business-to-business research projects that receive funding from companies. In general, the co-funders of the precompetitive research focusing on phenotypic flexibility had no role in study design, data collection, analysis, interpretation of the data, nor in the preparation of the manuscripts. The other authors have nothing to disclose.

Data Availability: Data sharing is not applicable to this article because no data sets were generated or analyzed for this review.

References

1. MacDonald PE, El-Kholy W, Riedel MJ, Salapatek AM, Light PE, Wheeler MB. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. *Diabetes*. 2002;**51**(Suppl 3):S434-S442.
2. Salera M, Giacomoni P, Pironi L, et al. Circadian rhythm of gastric inhibitory polypeptide (GIP) in man. *Metabolism*. 1983;**32**(1):21-24.
3. Jakubowicz D, Wainstein J, Ahrén B, et al. High-energy breakfast with low-energy dinner decreases overall daily hyperglycaemia in type 2 diabetic patients: a randomised clinical trial. *Diabetologia*. 2015;**58**(5):912-919.
4. Asher G, Schibler U. Crosstalk between components of circadian and metabolic cycles in mammals. *Cell Metab*. 2011;**13**(2):125-137.
5. Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev*. 2000;**14**(23):2950-2961.
6. Reznick J, Preston E, Wilks DL, Beale SM, Turner N, Cooney GJ. Altered feeding differentially regulates circadian rhythms and energy metabolism in liver and muscle of rats. *Biochim Biophys Acta*. 2013;**1832**(1):228-238.
7. Salgado-Delgado RC, Saderi N, del Carmen Basualdo C, Guerrero-Vargas NN, Escobar C, Buijs RM. Shift work or food intake during the rest phase promotes metabolic disruption and desynchrony of liver genes in male rats. *PLoS One*. 2013;**8**(4):e60052.
8. Hastings MH, Reddy AB, Maywood ES. A clockwork web: circadian timing in brain and periphery, in health and disease. *Nat Rev Neurosci*. 2003;**4**(8):649-661.
9. Aschoff J. Circadian timing. *Ann N Y Acad Sci*. 1984;**423**:442-468.
10. Reinke H, Asher G. Crosstalk between metabolism and circadian clocks. *Nat Rev Mol Cell Biol*. 2019;**20**(4):227-241.
11. Bass J, Takahashi JS. Circadian integration of metabolism and energetics. *Science*. 2010;**330**(6009):1349-1354.
12. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature*. 2002;**418**(6901):935-941.
13. Hastings M, O'Neill JS, Maywood ES. Circadian clocks: regulators of endocrine and metabolic rhythms. *J Endocrinol*. 2007;**195**(2):187-198.
14. Oosterman JE, Kalsbeek A, la Fleur SE, Belsham DD. Impact of nutrients on circadian rhythmicity. *Am J Physiol Regul Integr Comp Physiol*. 2015;**308**(5):R337-R350.
15. Knutsson A. Health disorders of shift workers. *Occup Med (Lond)*. 2003;**53**(2):103-108.
16. Lowden A, Moreno C, Holmbäck U, Lennernäs M, Tucker P. Eating and shift work—effects on habits, metabolism and performance. *Scand J Work Environ Health*. 2010;**36**(2):150-162.
17. Esquirol Y, Bongard V, Mabile L, Jonnier B, Soulat JM, Perret B. Shift work and metabolic syndrome: respective impacts of job strain, physical activity, and dietary rhythms. *Chronobiol Int*. 2009;**26**(3):544-559.
18. Zarrinpar A, Chaix A, Panda S. Daily eating patterns and their impact on health and disease. *Trends Endocrinol Metab*. 2016;**27**(2):69-83.
19. Gupta NJ, Kumar V, Panda S. A camera-phone based study reveals erratic eating pattern and disrupted daily eating-fasting cycle among adults in India. *PLoS One*. 2017;**12**(3):e0172852.
20. Bass J, Lazar MA. Circadian time signatures of fitness and disease. *Science*. 2016;**354**(6315):994-999.
21. Smolensky MH, Hermida RC, Reinberg A, Sackett-Lundeen L, Portaluppi F. Circadian disruption: new clinical perspective of disease pathology and basis for chronotherapeutic intervention. *Chronobiol Int*. 2016;**33**(8):1101-1119.
22. Stenvers DJ, Scheer FAJL, Schrauwen P, la Fleur SE, Kalsbeek A. Circadian clocks and insulin resistance. *Nat Rev Endocrinol*. 2019;**15**(2):75-89.
23. La Fleur SE, Kalsbeek A, Wortel J, Buijs RM. A suprachiasmatic nucleus generated rhythm in basal glucose concentrations. *J Neuroendocrinol*. 1999;**11**(8):643-652.
24. Van Cauter E, Blackman JD, Roland D, Spire JP, Refetoff S, Polonsky KS. Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. *J Clin Invest*. 1991;**88**(3):934-942.
25. Saad A, Dalla Man C, Nandy DK, et al. Diurnal pattern to insulin secretion and insulin action in healthy individuals. *Diabetes*. 2012;**61**(11):2691-2700.
26. van Moorsel D, Hansen J, Havekes B, et al. Demonstration of a day-night rhythm in human skeletal muscle oxidative capacity. *Mol Metab*. 2016;**5**(8):635-645.
27. Mauvoisin D, Wang J, Jouffe C, et al. Circadian clock-dependent and -independent rhythmic proteomes implement distinct diurnal functions in mouse liver. *Proc Natl Acad Sci U S A*. 2014;**111**(1):167-172.
28. Adamovich Y, Rousso-Noori L, Zwighaft Z, et al. Circadian clocks and feeding time regulate the oscillations and levels of hepatic triglycerides. *Cell Metab*. 2014;**19**(2):319-330.
29. Kalsbeek A, la Fleur S, Fliers E. Circadian control of glucose metabolism. *Mol Metab*. 2014;**3**(4):372-383.
30. Harfmann BD, Schroder EA, Kachman MT, Hodge BA, Zhang X, Esser KA. Muscle-specific loss of *Bmal1* leads to disrupted tissue glucose metabolism and systemic glucose homeostasis. *Skelet Muscle*. 2016;**6**:12.
31. Boden G, Chen X, Urbain JL. Evidence for a circadian rhythm of insulin sensitivity in patients with NIDDM caused by cyclic changes in hepatic glucose production. *Diabetes*. 1996;**45**(8):1044-1050.
32. Peter R, Dunseath G, Luzio SD, Chudleigh R, Roy Choudhury S, Owens DR. Daytime variability of postprandial glucose tolerance and pancreatic B-cell function using 12-h profiles in persons with Type 2 diabetes. *Diabet Med*. 2010;**27**(3):266-273.
33. Ando H, Takamura T, Matsuzawa-Nagata N, et al. Clock gene expression in peripheral leucocytes of patients with type 2 diabetes. *Diabetologia*. 2009;**52**(2):329-335.
34. Stenvers DJ, Jongejan A, Atiqi S, et al. Diurnal rhythms in the white adipose tissue transcriptome are disturbed in obese individuals with type 2 diabetes compared with lean control individuals. *Diabetologia*. 2019;**62**(4):704-716.
35. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A*. 2009;**106**(11):4453-4458.

36. Leproult R, Holmbäck U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes*. 2014;**63**(6):1860-1869.
37. Wefers J, van Moorsel D, Hansen J, et al. Circadian misalignment induces fatty acid metabolism gene profiles and compromises insulin sensitivity in human skeletal muscle. *Proc Natl Acad Sci U S A*. 2018;**115**(30):7789-7794.
38. Sharma A, Laurenti MC, Dalla Man C, et al. Glucose metabolism during rotational shift-work in healthcare workers. *Diabetologia*. 2017;**60**(8):1483-1490.
39. Morris CJ, Yang JN, Garcia JI, et al. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. *Proc Natl Acad Sci U S A*. 2015;**112**(17):E2225-E2234.
40. Stokkan KA, Yamazaki S, Tei H, Sakaki Y, Menaker M. Entrainment of the circadian clock in the liver by feeding. *Science*. 2001;**291**(5503):490-493.
41. de Goede P, Sen S, Oosterman JE, et al. Differential effects of diet composition and timing of feeding behavior on rat brown adipose tissue and skeletal muscle peripheral clocks. *Neurobiol Sleep Circadian Rhythms*. 2018;**4**:24-33.
42. Opperhuizen AL, Wang D, Foppen E, et al. Feeding during the resting phase causes profound changes in physiology and desynchronization between liver and muscle rhythms of rats. *Eur J Neurosci*. 2016;**44**(10):2795-2806.
43. Guo H, Brewer JM, Champhekar A, Harris RB, Bittman EL. Differential control of peripheral circadian rhythms by suprachiasmatic-dependent neural signals. *Proc Natl Acad Sci U S A*. 2005;**102**(8):3111-3116.
44. Wehrens SMT, Christou S, Isherwood C, et al. Meal timing regulates the human circadian system. *Curr Biol*. 2017;**27**(12):1768-1775.e3.
45. Skene DJ, Skornyakov E, Chowdhury NR, et al. Separation of circadian- and behavior-driven metabolite rhythms in humans provides a window on peripheral oscillators and metabolism. *Proc Natl Acad Sci U S A*. 2018;**115**(30):7825-7830.
46. van Ommen B, van der Greef J, Ordovas JM, Daniel H. Phenotypic flexibility as key factor in the human nutrition and health relationship. *Genes Nutr.* 2014;**9**(5):423.
47. Stroeve JHM, van Wietmarschen H, Kremer BHA, van Ommen B, Wopereis S. Phenotypic flexibility as a measure of health: the optimal nutritional stress response test. *Genes Nutr.* 2015;**10**(3):13.
48. van den Broek TJ, Bakker GCM, Rubingh CM, et al. Ranges of phenotypic flexibility in healthy subjects. *Genes Nutr.* 2017;**12**:32.
49. Wopereis S, Stroeve JHM, Stafleu A, et al. Multi-parameter comparison of a standardized mixed meal tolerance test in healthy and type 2 diabetic subjects: the PhenFlex challenge. *Genes Nutr.* 2017;**12**:21.
50. Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;**58**(4):773-795.
51. Matthaei S, Stumvoll M, Kellerer M, Häring HU. Pathophysiology and pharmacological treatment of insulin resistance. *Endocr Rev.* 2000;**21**(6):585-618.
52. Wiernsperger N. Hepatic function and the cardiometabolic syndrome. *Diabetes Metab Syndr Obes*. 2013;**6**:379-388.
53. Goodpaster BH, Sparks LM. Metabolic flexibility in health and disease. *Cell Metab*. 2017;**25**(5):1027-1036.
54. Abdul-Ghani MA, Matsuda M, Balas B, DeFronzo RA. Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. *Diabetes Care*. 2007;**30**(1):89-94.
55. Blanco-Rojo R, Alcala-Diaz JF, Wopereis S, et al. The insulin resistance phenotype (muscle or liver) interacts with the type of diet to determine changes in disposition index after 2 years of intervention: the CORDIOPREV-DIAB randomised clinical trial. *Diabetologia*. 2016;**59**(1):67-76.
56. van der Kolk BW, Kalafati M, Adriaens M, et al. Subcutaneous adipose tissue and systemic inflammation are associated with peripheral but not hepatic insulin resistance in humans. *Diabetes*. 2019;**68**(12):2247-2258.
57. van der Kolk BW, Vogelzangs N, Jocken JWE, et al; DiOGenes Consortium. Plasma lipid profiling of tissue-specific insulin resistance in human obesity. *Int J Obes (Lond)*. 2019;**43**(5):989-998.
58. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999;**22**(9):1462-1470.
59. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes*. 1993;**42**(11):1663-1672.
60. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C. Oral glucose tolerance test minimal model indexes of β-cell function and insulin sensitivity. *Diabetes*. 2001;**50**(1):150-158.
61. Ter Horst KW, van Galen KA, Gilijamse PW, et al. Methods for quantifying adipose tissue insulin resistance in overweight/obese humans. *Int J Obes (Lond)*. 2017;**41**(8):1288-1294.
62. Søndergaard E, Espinosa De Ycaza AE, Morgan-Bathke M, Jensen MD. How to measure adipose tissue insulin sensitivity. *J Clin Endocrinol Metab*. 2017;**102**(4):1193-1199.
63. Grant CL, Coates AM, Dorrian J, et al. Timing of food intake during simulated night shift impacts glucose metabolism: a controlled study. *Chronobiol Int*. 2017;**34**(8):1003-1013.
64. van Ommen B, Wopereis S. Next-generation biomarkers of health. *Nestle Nutr Inst Workshop Ser.* 2016;**84**:25-33.
65. Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. *Cell Metab*. 2018;**28**(4):547-556.e3.
66. Gabriel BM, Zierath JR. Circadian rhythms and exercise—re-setting the clock in metabolic disease. *Nat Rev Endocrinol*. 2019;**15**(4 Suppl 2):197-206.
67. Zitting KM, Vujovic N, Yuan RK, et al. Human resting energy expenditure varies with circadian phase. *Curr Biol*. 2018;**28**(22):3685-3690.e3.
68. Richter J, Herzog N, Janka S, Baumann T, Kistenmacher A, Oltmanns KM. Twice as high diet-induced thermogenesis after breakfast vs dinner on high-calorie as well as low-calorie meals. *J Clin Endocrinol Metab*. 2020;**105**(3):dgz311.
69. Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee YC, Ordovás JM, Scheer FA. Timing of food intake predicts weight loss effectiveness. *Int J Obes (Lond)*. 2013;**37**(4):604-611.
70. Ruiz-Lozano T, Vidal J, de Hollanda A, Scheer FAJL, Garaulet M, Izquierdo-Pulido M. Timing of food intake is associated with

weight loss evolution in severe obese patients after bariatric surgery. *Clin Nutr.* 2016;**35**(6):1308-1314.
71. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring)*. 2013;**21**(12):2504-2512.
72. Jakubowicz D, Froy O, Wainstein J, Boaz M. Meal timing and composition influence ghrelin levels, appetite scores and weight loss maintenance in overweight and obese adults. *Steroids*. 2012;**77**(4):323-331.
73. Mekary RA, Giovannucci E, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in men: breakfast omission, eating frequency, and snacking. *Am J Clin Nutr.* 2012;**95**(5):1182-1189.
74. Jakubowicz D, Wainstein J, Ahren B, Landau Z, Bar-Dayan Y, Froy O. Fasting until noon triggers increased postprandial hyperglycemia and impaired insulin response after lunch and dinner in individuals with type 2 diabetes: a randomized clinical trial. *Diabetes Care*. 2015;**38**(10):1820-1826.
75. Fong M, Caterson ID, Madigan CD. Are large dinners associated with excess weight, and does eating a smaller dinner achieve greater weight loss? A systematic review and meta-analysis. *Br J Nutr.* 2017;**118**(8):616-628.
76. 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;**27**(6):1212-1221.e3.
77. Horne BD, Grajower MM, Anderson JL. Limited evidence for the health effects and safety of intermittent fasting among patients with type 2 diabetes. *JAMA*. 2020;**324**(4):341-342.
78. Chaix A, Manoogian ENC, Melkani GC, Panda S. Time-restricted eating to prevent and manage chronic metabolic diseases. *Annu Rev Nutr.* 2019;**39**:291-315.
79. Chaix A, Zarrinpar A, Miu P, Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. *Cell Metab*. 2014;**20**(6):991-1005.
80. Hatori M, Vollmers C, Zarrinpar A, et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab*. 2012;**15**(6):848-860.
81. Salgado-Delgado R, Angeles-Castellanos M, Saderi N, Buijs RM, Escobar C. Food intake during the normal activity phase prevents obesity and circadian desynchrony in a rat model of night work. *Endocrinology.* 2010;**151**(3):1019-1029.
82. Kudo T, Akiyama M, Kuriyama K, Sudo M, Moriya T, Shibata S. Night-time restricted feeding normalises clock genes and *Pai-1* gene expression in the *db/db* mouse liver. *Diabetologia*. 2004;**47**(8):1425-1436.
83. Schilperoort M, van den Berg R, Dollé MET, et al. Time-restricted feeding improves adaptation to chronically alternating light-dark cycles. *Sci Rep*. 2019;**9**(1):7874.
84. Gill S, Panda S. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab*. 2015;**22**(5):789-798.
85. Moro T, Tinsley G, Bianco A, et al. 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.
86. Sasaki H, Hattori Y, Ikeda Y, et al. Phase shifts in circadian peripheral clocks caused by exercise are dependent on the feeding schedule in PER2::LUC mice. *Chronobiol Int*. 2016;**33**(7):849-862.
87. Aoyama S, Shibata S. The role of circadian rhythms in muscular and osseous physiology and their regulation by nutrition and exercise. *Front Neurosci*. 2017;**11**:63.
88. Yamanaka Y, Honma S, Honma KI. Mistimed wheel running interferes with re-entrainment of circadian *Per1* rhythms in the mouse skeletal muscle and lung. *Genes Cells*. 2016;**21**(3):264-274.
89. Buxton OM, Lee CW, L'Hermite-Baleriaux M, Turek FW, Van Cauter E. Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. 2003;**284**(3):R714-R724.
90. Miyazaki T, Hashimoto S, Masubuchi S, Honma S, Honma KI. Phase-advance shifts of human circadian pacemaker are accelerated by daytime physical exercise. 2001;**281**(1):R197-R205.
91. Barger LK, Wright KP Jr, Hughes RJ, Czeisler CA. Daily exercise facilitates phase delays of circadian melatonin rhythm in very dim light. 2004;**286**(6):R1077-R1084.
92. Thomas JM, Kern PA, Bush HM, et al. Circadian rhythm phase shifts caused by timed exercise vary with chronotype. *JCI Insight*. 2020;**5**(3).
93. Savikj M, Gabriel BM, Alm PS, et al. Afternoon exercise is more efficacious than morning exercise at improving blood glucose levels in individuals with type 2 diabetes: a randomised crossover trial. *Diabetologia*. 2019;**62**(2):233-237.