Time Restricted Eating: A Dietary Strategy to Prevent and Treat Metabolic Disturbances

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Time-restricted eating (TRE), a dietary approach limiting the daily eating window, has attracted increasing attention in media and research. The eating behavior in our modern society is often characterized by prolonged and erratic daily eating patterns, which might be associated with increased risk of obesity, diabetes, and cardiovascular diseases. In contrast, recent evidence suggests that TRE might support weight loss, improve cardiometabolic health, and overall wellbeing, but the data are controversial. The present work reviews how TRE affects glucose and lipid metabolism based on clinical trials published until June 2021. A range of trials demonstrated that TRE intervention lowered fasting and postprandial glucose levels in response to a standard meal or oral glucose tolerance test, as well as mean 24-h glucose and glycemic excursions assessed using continuous glucose monitoring. In addition, fasting insulin decreases and improvement of insulin sensitivity were demonstrated. These changes were often accompanied by the decrease of blood triglyceride and cholesterol levels. However, a number of studies found that TRE had either adverse or no effects on glycemic and lipid traits, which might be explained by the different study designs (i.e., fasting/eating duration, daytime of eating, changes of calorie intake, duration of intervention) and study subject cohorts (metabolic status, age, gender, chronotype, etc.). To summarize, TRE represents an attractive and easy-to-adapt dietary strategy for the prevention and therapy of glucose and lipid metabolic disturbances. However, carefully controlled future TRE studies are needed to confirm these effects to understand the underlying mechanisms and assess the applicability of personalized interventions.

Keywords: time restricted eating, circadian clock, chrononutrition, glucose metabolism, lipid metabolism, metabolic diseases
INTRODUCTION

A growing body of evidence suggests that our circadian clock tightly interacts with metabolic functions (1) and that meal timing is an important factor for metabolic regulation (2–4). Chrononutrition, a novel discipline investigating the relation between circadian rhythms, nutrition, and metabolism, has developed rapidly in recent years (5). Chrononutrition clearly demonstrated that when we eat is as critical as what and how much for the chronic disease progression (3). The eating behavior in our modern society is often characterized by prolonged and erratic daily eating patterns which, together with Western-type diet, sedentary lifestyle, and chronic sleep deprivation, might contribute to an increased risk of obesity, diabetes, and cardiovascular diseases (6). In contrast, time-restricted eating (TRE), a dietary approach limiting the daily eating window, has attracted an increasing attention as an easy-to-use tool supporting weight loss, improving cardiometabolic health, and overall wellbeing (7–9). However, clinical trials on TRE demonstrated controversial effects especially in regard to glycemic and lipid traits.

This review focuses on the impact of TRE on glucose and lipid metabolism based on the clinical trials published until June 2021. We will also discuss different aspects of the TRE study design and different characteristics of study subjects as possible reasons for result bias. Further, we will shortly address molecular and physiological mechanisms of TRE effects. Finally, we will debate research gaps, which have to be filled by future studies and discuss the potential of TRE for the prevention and therapy of metabolic diseases.

TIGHT INTERACTION OF CIRCADIAN CLOCK AND METABOLISM

The endogenous circadian clock has been widely accepted to play an important role in the adaptation of the physiology and behavior of living organisms to the day-night changes, including in humans. In particular, circadian rhythms with a period of approximately 24 h regulate the metabolism of humans by synchronization of metabolic pathways, detaching non-compatible physiological and biochemical mechanisms, as well as improving the energy expenditure (1). In humans, circadian dysruptions resulting from shift work or chronic jet lag are related to obesity, metabolic syndrome, and cardiovascular diseases, which are consequences of an unbalanced metabolic homeostasis (10–12). Similar results were observed in animals with genetic knockout of key clock genes (13, 14). This leads to the assumption that metabolic health is preserved by proper functioning of circadian clocks. In turn, obesity and metabolic diseases, e.g., type 2 diabetes, alter or blunt circadian rhythms (15–17), confirming a tight reciprocal interaction of circadian clock and metabolism.

The circadian clock, in mammals, includes a master and a peripheral clock (1). The master clock is located at the hypothalamus in the suprachiasmatic nucleus (SCN). Peripheral oscillators orchestrated by the master clock are present in nearly every tissue, including metabolically active organs, such as the liver, adipose tissue, pancreas, and skeletal muscle. The molecular clock mechanism existing in almost every cell consists of interlocked transcriptional-translational feedback loops (2), including transcription factors aryl hydrocarbon receptor nuclear translocator, like (ARNTL, also known as BMAL1), clock circadian regulator (CLOCK), period (PER1, PER2, PER3), cryptochrome (CRY1, CRY2), retinoic acid-related orphan receptors (ROBs), and nuclear receptor subfamily 1 group D (NR1D1/2, also known as Rev-Erbα/B). One cycle of this molecular machinery takes approximately 24 h and controls the expression of so-called clock-controlled genes (CCG), which include key metabolic transcription factors and enzymes generating circadian oscillations of metabolic functions (1, 2, 18). Indeed, 10% to 30% of the tissue transcriptome and 15% of circulating metabolome, as well as a number of circulating metabolic hormones—adipokines and cytokines involved in the regulation of carbohydrate, cholesterol, lipid, and energy metabolism—demonstrate circadian rhythms (19–24).

Notably, circadian clock itself undergoes metabolic and nutritional regulation. The reason is that food and feeding regimens are external cues (Zeitgeber), which can adjust (entrain) circadian rhythms in peripheral tissues. In mice fed with high-fat diet (HFD) and in mouse models of obesity, altered rhythms of core clock and a reorganisation of whole circadian transcriptome were observed (25–29). In humans, altered clock gene expression in human adipose tissue was found in obesity and metabolic syndrome (16, 17), and a blunted rhythm of clock gene expression in blood leucocytes was observed in type 2 diabetes (15). Our group showed in human intervention trials that both calorie intake and food composition affect circadian rhythms of clock and metabolic genes in blood monocytes and of circulating metabolic biomarkers (30, 31).

ROLE OF MEAL TIMING IN METABOLIC REGULATION

Because of the tight interaction between the circadian clock and metabolism, timing of eating is an important parameter for modulating body weight and metabolic state. First evidence was obtained in mouse studies showing that animal feeding in the light (i.e., inactive) phase leads to a desynchronization between peripheral tissues and the central clock and induces weight gain and metabolic disturbances (32–34).

Studies involving humans provide similar results. Shift work or chronic jetlag and, as a result, consuming meals at the “wrong” or unusual time increase the risk of developing type 2 diabetes, cardiovascular diseases, and obesity (3, 12). This could be, at least in part, due to a lifestyle-induced discrepancy between sleep/wake, as well as fasting/feeding phase and internal circadian cycles, which may result in disruption of the fatty acid metabolism, glucose intolerance, and dysregulation of the body clock transcriptome as confirmed by experimental human studies on circadian misalignment (35–37). To note, other confounding factors, like sleep deprivation, decreased physical activity, or an unhealthy diet, may also negatively influence metabolism in case of shift work.
Notably, experimental human studies identified that parameters like glucose tolerance, insulin sensitivity, beta-cell responsiveness, and postprandial thermogenesis show better profiles in the morning than in the evening or afternoons (35, 38, 39). We and others demonstrated that meal consumption in the morning results in lower postprandial glucose concentrations and altered secretions of insulin, C-peptide, and of the incretins glucagon-like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP) compared to the consumption of the same meal in the afternoon (39–41). In healthy adults, late dinner (10 pm) causes shift in the postprandial period, overlapping with the sleep phase (42). Independent of this shift, higher glucose, triglyceride peak delay, and lower free fatty acids and dietary fatty acid oxidation in the postprandial period were observed. Interestingly, late dinner did not affect sleep architecture, but increased plasma cortisol. Disturbances in circadian rhythms (alterations in the daily patterns of body-temperature and cortisol) were similarly observed in school-aged children consuming late dinner (43). Notably, the delay of meal timing or even change of the timely distribution of the calorie intake within the day without changing of sleeping times can shift expression rhythms of key clock genes in adipose tissue and blood cells (37, 44), possibly via postprandial hormone and metabolite changes.

In agreement with this, several human studies show that the timing of meals influences the outcome of weight loss therapy. Individuals consuming their lunch in the late hours lost less weight than the early eaters, although both groups consumed a hypocaloric diet (45). High caloric intake during breakfast has a positive effect on hunger scores, weight, as well as glucose, insulin, and ghrelin concentrations in comparison to the same intake during dinner (46). Late and delayed eating is associated with weight gain, dysfunction in energy expenditure, and abnormalities in the circadian rhythms of appetite, stress, and sleep hormones in most reports (47), although some epidemiological studies do not confirm these effects (48, 49). Notably, the night-eating syndrome clearly correlates with obesity (42). Furthermore, several experimental human studies show that eating in the evening worsens metabolic parameters in comparison with the improvement in daytime eaters (50–54).

Interestingly, novel studies suggest that certain time windows are more suitable for the consumption of certain kinds of food to maintain metabolic health. We recently showed that a consumption of high carb meals in the evening (in combination with high-fat meals in the morning) induces higher blood glucose levels and worsen glycemic control in subjects with an impaired glucose metabolism compared with a reverse pattern of meal composition (39). In agreement with this, epidemiological human studies report the positive effect of morning carbohydrate intake on the prevention of metabolic disorders (55, 56). Moreover, timing of carbohydrates and fat intake also affected circulating adipokine concentrations (57) and diurnal variation of the plasma lipidome (20).

Taken together, most published studies suggest that early eating is in alignment with our metabolic clock and therefore might be beneficial for metabolic health.

**TIME-RESTRICTED EATING: IDEA, DEFINITION, AND OVERVIEW OF EFFECTS**

In our modern society, prolonged and erratic daily eating patterns often take place. In American and Indian adults, eating periods of 15 h or longer every day were observed in more than half of the individuals. In addition, more than a third of the daily caloric intake occurred in the evening (6, 58). This eating period is often shifted to a later time on weekends indicating a “social jet lag” (59). Notably, reduction of the eating window in overweight individuals to 10 to 12 h resulted in sustained weight loss and improved subjective sleep quality after 16 weeks and 1 year of intervention (6). These data suggest that a shortening of the eating time and the accompanying elongation of the fasting time (≥12 h) might have beneficial effects on metabolic parameters in humans (60).

In the last years, time-restricted eating (TRE) has attracted increasing attention in public media as a strategy to lose weight and improve overall health. First data on TRE were collected in rodents where such diet is defined as “time-restricted feeding” (TRF). In mice, TRF increases the amplitude of circadian clock rhythms and is protective against HFD-induced obesity, glucose intolerance, leptin resistance, hepatic steatosis, and tissue inflammation compared with *ad libitum* HFD feeding (26, 61).

In humans, the increased research interest to TRE initiated a number of intervention trials evaluating the effects of several TRE regimens with daily eating periods between 4 and 11 h on healthy individuals or participants with metabolic abnormalities (summarized in the Table 1). Most of them were short-term trials (4 days to 12 weeks) conducted in a relatively small number of subjects (8 to 80 participants) except for the study by Cai et al. with 174 subjects (63). In these studies, TRE not only appears to be a well-tolerated treatment strategy for overweight and obese patients but also generates beneficial metabolic effects (7, 59) (Figure 1), as discussed below. Most TRE studies reported modest reduction of body weight (6, 63–66, 68, 71–75, 77, 78, 82, 83, 85, 86), overall and visceral fat (62–65, 72, 74, 77, 78, 85, 86), and waist circumference (72, 73, 83, 86), which could be partly explained by the self-reported reduction of energy intake observed in many trials (6, 65, 66, 71, 82, 86, 87). Unexpectedly, TRE decreased feeling of hunger and desire to eat (76, 79, 80, 84) and the level of hunger hormone ghrelin (69, 70), although in one study fasting ghrelin level was increased (71) (Table 1). The data on satiety hormones, PYY and leptin, are also inconsistent (69, 70, 84), whereas adiponectin was increased in two studies (77, 78). TRE also reduced inflammatory markers (74, 78), blood pressure (67, 77, 84, 86) and oxidative stress markers (65, 84). In several studies, subjects reported an improvement of sleep quality, quality of life, and felt more energetic at the end of the intervention (6, 88). However, one study found no TRE effect on the gut microbiome (67), whereas another trial observed higher microbial diversity (87). Interestingly, TRE also affected gene expression of markers of the circadian clock, aging, and autophagy (69, 87).

Furthermore, many TRE trials demonstrated improvement of glucose intolerance, and postprandial thermogenesis show better profiles in the morning than in the evening or afternoons (35, 38, 39). We and others demonstrated that meal consumption in the morning results in lower postprandial glucose concentrations and altered secretions of insulin, C-peptide, and of the incretins glucagon-like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP) compared to the consumption of the same meal in the afternoon (39–41). In healthy adults, late dinner (10 pm) causes shift in the postprandial period, overlapping with the sleep phase (42). Independent of this shift, higher glucose, triglyceride peak delay, and lower free fatty acids and dietary fatty acid oxidation in the postprandial period were observed. Interestingly, late dinner did not affect sleep architecture, but increased plasma cortisol. Disturbances in circadian rhythms (alterations in the daily patterns of body-temperature and cortisol) were similarly observed in school-aged children consuming late dinner (43). Notably, the delay of meal timing or even change of the timely distribution of the calorie intake within the day without changing of sleeping times can shift expression rhythms of key clock genes in adipose tissue and blood cells (37, 44), possibly via postprandial hormone and metabolite changes.

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TABLE 1 | Clinical trials on TRE with outcomes regarding glucose and lipid metabolism.

| Reference                        | Cohort (Male/Female) | Study design TRE Regimen (Fasting/Feeding) | Study duration | Calorie intake/weight change | Glucose metabolism                                                                 | Lipid metabolism                                                                 | Other effects                                                                 |
|----------------------------------|----------------------|-------------------------------------------|----------------|-----------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------|
| Antoni et al., 2018 (62)         | n = 13 (1/12) healthy adults age: 29-57 years | non-randomized controlled trial parallel arm TRE: daily feeding duration shortened by 3 h | 12 weeks: | - ad libitum food access          | ↓ fasting glucose (primarily driven by an increase among controls) | ↓ body fat mass                                               | ↓ fat mass                  |
| Cai et al., 2019 (63)            | n = 174 (52/122) NAFLD patients age: 34.1 ± 6.6 years | RCT parallel arm TRE (16:8) self-selected feeding window | 12 weeks intervention: | - ad libitum food access          | ↑ glucose and insulin                    | ↓ LDL, HDL, and total cholesterol | ↔ physical activity                |
| Chow et al., 2020 (64)           | n = 20 (3/17) overweight adults with a prolonged eating window >15 h/day: age: 45.5 ± 12.1 years | RCT parallel arm TRE (13-16: 8-11) self-selected hour window | 16 weeks: | - ad libitum food intake          | ↔ fasting glucose (time fasting glucose time blood levels within target [70-180 mg/dL]) (CGM measure) | ↔ HDL, LDL, and total cholesterol | ↔ visceral fat                        |
| Cienfuigues et al., 2020 (65)    | n = 49 (5/44) obese adults age: 47 ± 2 years | RCT parallel arm (a) TRE (18:6) 1-2-7 h | 10 weeks: | - ad libitum food intake          | ↔ fasting glucose, fasting insulin                      | ↔TG, HDL, and LDL                     | ↔ visceral fat                        |
| Gabel et al., 2018 (66) Gabel et al., 2020 (67) | n = 23 (2/20) obese adults age: 50 ± 2 years | historically controlled study TRE (16:8) 10±4 h | 14 weeks: | - ad libitum food intake          | ↔ fasting glucose, insulin                   | ↔ TG, HDL, and LDL                     | ↔ visceral fat                        |
| Hutchison et al., 2019 (68)      | n = 15 (5/10) prediabetic men age: 55 ± 3 years | RCT crossover design (a) eTRE (15:9) 8 h to 5 h | 5 weeks: | - ad libitum food intake          | ↓ mean fasting glucose in eTRE (CGM data) | ↔ HDL, LDL | ↔ visceral fat                        |
| Jamshed et al., 2019 (69)        | n = 11 (7/4) overweight adults age: 32 ± 7 years | RCT crossover design eTRE (18:6) 8±2 h | 3 days each intervention: | 5-6 weeks: | - ad libitum food intake          | ↓ mean 24-h glucose | ↔ insulin sensitivity; glucose uptake of skeletal muscle | ↔ visceral fat                        |
| Jones et al., 2020 (71)          | n = 16 (16) healthy men age: 23 ± 2 years | Non-randomized trial two groups recruited & tested temporally apart (a) eTRE (16:8) 8±4 h | 3 weeks: week 1 baseline 2 weeks intervention | - ad libitum food intake          | ↔ fasting glucose, fasting insulin                      | ↔ TG, HDL, and LDL                     | ↔ visceral fat                        |
| Karras et al., 2020 (72)         | n=60 (17/43) orthodox fasting (11/26) TRE n=23 (8/17) overweight, metabolically healthy adults age: 48.3 ± 8.9 years | non-randomized, parallel arm trial (a) orthodox fasting and (b) eTRE (16:8) 8±4 h | 12 weeks: | - ad libitum food intake          | ↔ fasting glucose, fasting insulin, insulin resistance (partly driven by a worsening in control group) | ↓ HOMA-IR, AUCInsulin/AUCGlucose | ↔ visceral fat                        |
| Kesutys et al., 2019 (73)        | n = 40 (9/31) abdominally obese adults age: 49.1 ± 12.4 years | single arm trial TRE (15-16:8-9) self-selected hour window single arm trial TRE (16:8) 8±4 h | 12 weeks intervention: | - ad libitum food intake          | ↔ fasting glucose, fasting insulin, insulin resistance (orthodox and control) | ↔ total cholesterol, LDL, TG | ↔ visceral fat                        |
| Li et al., 2021 (74)             | n = 15 (9/6) women with anovulation and PCOS age: between 18 and 31 years | single arm trial TRE (15:6-8) 8±4 h | 6 weeks: week 1 baseline 5 weeks after intervention | - ad libitum food intake          | ↔ fasting glucose, insulin resistance (orthodox and control) | ↓ LDL, HDL, and total cholesterol | ↔ visceral fat                        |
| Lowe et al., 2020 (75)           | n = 116 (70/46) in-person tested: n = 50 (28/22) overweight, obese adults age: 46.5 ± 10.5 years | RCT parallel arm TRE (16:8) 12±6 h | 12 weeks intervention: | - ad libitum food intake          | ↔ fasting glucose, fasting insulin, insulin AUC | ↓ cholesterol, LDL, TG | ↔ visceral fat                        |
| Martens et al., 2020 (76)        | n = 22 (10/12) healthy, non-obese adults age: 67 ± 1 years | RCT crossover design TRE (16:8) consistent self-selected | 7 weeks: week 1 baseline 4 weeks each intervention | - ad libitum food intake          | ↔ fasting glucose, fasting insulin, insulin AUC | ↓ cholesterol, LDL, TG | ↔ visceral fat                        |

(Continued)
| Reference | Cohort (Male/Female) | Study design TRE Regimen (Fasting: Feeding) | Study duration | Calorie intake/weight change | Glucose metabolism | Lipid metabolism | Other effects |
|-----------|---------------------|---------------------------------------------|----------------|-----------------------------|-------------------|-----------------|---------------|
| McAllister et al., 2019 (77) | n = 22 (22/0) physically active men age: 22 ± 2.5 years | RCT parallel arm (16:8) | 4 weeks intervention | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |
| Moro et al., 2016 (78) | n = 34 (34/0) healthy resistance trained men age: 29.21 ± 3.8 years | RCT crossover design (16:8) | 3 weeks:5 days each intervention 10 days washout | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |
| Parr et al., 2020 (79) | n = 19 (9/10) adults with T2D and eating window >12 h/day age: 50 ± 9 years | single arm trial (15:9:10) | 6 weeks: 2 weeks baseline 4 weeks intervention | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |
| Parr et al., 2020 (80) Lundelli et al. 2020 (81) | n = 11 (11/0) sedentary men with overweight/obesity age: 38 ± 5 years | RCT crossover design (16:8) 10 AM–PM extended feeding of 15 h/day 7 AM–10 PM | 3 weeks each: 5 days intervention 10 days washout | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |
| Peeke et al., 2021 (82) | n = 60 (7/53) obese adults age: 44 ± 11 years | RCT parallel arm, virtual trial (12:12) | 8 weeks intervention | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |
| Phillips et al., 2021 (83) | n = 45control n=20adults with eating windows >14 h/day and at least one metabolic syndrome component age: 43.4 ± 13.3 years | RCT parallel arm TRE (12:12) self-selected hour window | 7 months: 4 weeks baseline 6 months intervention | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |
| Sutton et al. 2018 (84) | n = 8 (8/0) overweight men with prediabetes age: 56 ± 9 years | RCT crossover design eTRE (18:6) dinner before 3 PM | 17 weeks: 6 months intervention | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |
| Tindley et al. 2019 (85) | n = 40 (34/6) PP: n = 24 (0/24) healthy resistance syndrome and eating window ≥14 h/day females age: 22.1 ± 2.6 years | ITT: n = 40 (4/36) RP: n = 24 (0/24) | 3 meals and 1 snack provided per day | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |
| Wilkinson et al., 2020 (86) | n = 19 (13/6) adults with metabolic syndrome and eating window ≥14 h/day age: 59 ± 11 years | single arm trial TRE (14:10) 12 h/day + placebo +RT | 14 weeks: 2 weeks baseline 12 weeks intervention | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |
| Zeb et al., 2020 (87) | n = 80 (90/0) control n=24young aged healthy men age: n/a | RCT parallel arm TRE (16:8) 7:30 AM–3:30 AM | 25 days intervention | calorie intake/weight change | glucose metabolism | lipid metabolism | other effects |

Studies investigated effects of a single meal consumed at different times of the day are not included in the table. ↑, increase; ↓, decrease; ↔, no significant change. AUCtotal, total 24-h area under the curve; CGM, continuous glucose monitoring; CON, control/calcium restriction intervention; eTRE, early time-restricted eating; EXF, extended feeding; HbA1C, glycated hemoglobin A1c; HDL, high density lipoprotein; HMB, β-hydroxy β-methylbutyrate; HOMA-IR, homeostatic model assessment of insulin resistance; IAUC, incremental area under the curve; ITT, intention to treat; LDL, low density lipoprotein; ITRE, late time-restricted eating; MAGE, mean amplitude of glycemic excursions; ND, normal diet; NEFA, nonesterified fatty acids; ns, non-significant modification (p > 0.05); OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PP, per protocol; PYY, peptide YY; RCT, randomized controlled trial; RT, resistance training; T2D, type 2 diabetes; TG, triglycerides; TRE, time-restricted eating; n/a, not available.
found no or adverse effects of TRE on glycemic and lipid traits which will be discussed in detail in the next two chapters.

EFFECTS OF TRE ON GLUCOSE METABOLISM

Eight studies revealed positive changes in glucose levels because of TRE (62, 64, 68, 69, 76, 78, 80, 82), although this was not universally observed (63, 65, 66, 72, 74, 75, 77, 79, 83, 85). Nonetheless, TRE interventions significantly lowered fasting glucose levels (62, 64, 69, 78, 82), postprandial glucose levels in response to a standard meal or oral glucose tolerance test (OGTT) (68, 76), and night-time glucose (80). Few TRE trials applied continuous glucose monitoring (CGM) to monitor the glucose concentration over the 24 h per day as opposed to only certain time points. The beneficial effects appear even in CGM data, e.g., decreased mean 24-h glucose, glycemic excursions (69), and mean fasting glucose (68). HbA1c, as an important indicator of long-term glycemic control, decreased in two trials after TRE intervention in overweight and obese participants (73, 86), whereas no changes were detected in three other studies (75, 79, 83). Moreover, TRE could be shown to significantly lower fasting insulin levels, as well as insulin resistance (65, 69, 74, 78, 84) and increase insulin sensitivity (71, 84). Again, these results are not consistent in all conducted studies as other TRE interventions had no notable effect on insulin levels or insulin resistance (63, 66, 68, 72, 75–77, 79, 80, 85).

Improvement of glucose metabolism with TRE could be, at least in part, due to caloric restriction and associated weight loss (7, 8) (Table 1). Nevertheless, four TRE trials revealed beneficial effects on the glucose metabolism, regardless of caloric restriction or weight loss (62, 69, 76, 84). These findings suggest that the TRE dietary habit could produce positive metabolic effects, independent of energy balance.

EFFECTS OF TRE ON LIPID METABOLISM

Observed effects of TRE on plasma lipid levels are highly variable. Therefore, the triglyceride (TG) levels decreased significant in five TRE-studies (63, 64, 68, 78, 87), whereas no significant changes in TG levels occurred in 12 other studies (65, 66, 69, 71, 73–75, 77, 79, 83, 85, 86), and in two isocaloric trials, the fasting TG concentration actually increased (72, 84). Concerning cholesterol levels (total, HDL and LDL), the current state of improvements through TRE is inconsistent. In most TRE interventions, no significant changes of cholesterol levels emerged (Table 1). Nevertheless, in some cases, the shortened time of caloric intake improved participants cholesterol levels, by either decreasing total cholesterol and LDL (86, 87) or notably increasing HDL blood concentrations (77, 87). Contrarily, in one study, the TRE protocol leads to an increase of total and LDL cholesterol (76). Similar to glucose metabolism, TRE can affect lipid metabolism regardless of weight loss/caloric restriction (76, 84, 87).

The present work indicates that the effects of TRE on glycemic control are apparently less variable than effects of TRE on plasma lipid profiles. One possible explanation of this phenomenon might be the known diurnal rhythm of glucose tolerance, which decreases from morning to evening and night, whereas it is established that lipid circadian rhythms show substantial inter-individual variability (89).

CURRENT RESEARCH GAPS AND OPEN QUESTIONS

Taken together, TRE represents a promising and simple dietary approach for the prevention and therapy of disturbances in glucose and lipid metabolism (e.g., obesity, type 2 diabetes, metabolic syndrome, etc.) in the general population (because it
does not require extensive nutritional knowledge) and medical practice. Published TRE studies included several different subject groups varying from lean and healthy adults (62, 71, 76–78, 87), overweight, and obese subjects (64–66, 69, 70, 72, 73, 75, 80, 82) up to adult individuals with metabolic disturbances such as prediabetes (68, 84), type 2 diabetes (79), metabolic syndrome (83, 86), or NAFLD (63). These discrepancies between study participants should be noted as it is more likely to observe in this TRE only in consultation with and supervision by a physician.

Teenagers who are actively growing, subjects taking drugs or insulin injections to lower blood sugar, especially people with type 1 diabetes, subjects with acute illness, eating disorders, pregnancy or are breastfeeding, as well as individuals with severe kidney and liver diseases and cancer. TRE might be harmful to these subjects, consequently they should consider TRE only in consultation with and supervision by a physician.

Further, there is a range of research gaps and open questions in this field of TRE research, which need further investigation. The main question raised is the reason for the inconsistencies in metabolic outcomes between TRE studies. This might be explained by the different study designs (e.g., fasting/eating duration, daytime of eating, changes of calorie intake, duration of intervention) and study subject cohorts (metabolic status, age, gender, chronotype, etc.) as already mentioned above. The next important limitation is that the wide spectrum of TRE regimens with daily eating periods between 4 and 11 h and food consumption early (eTRE) or late in the day (lTRE) makes the dietary effects scarcely comparable. In particular, optimal duration of the eating window is unknown, suggesting that a direct comparison of varying eating windows (e.g., 6 h vs 9 h vs 12 h) has to be performed in the future studies upon the careful controlling of caloric intake as discussed below.

Early morning is likely to be an optimal TRE time to induce maximal metabolic benefits. In most eTRE studies, restricting food intake to the morning resulted in an improvement of insulin sensitivity, beta-cell responsiveness, blood pressure, inflammation, and oxidative stress (69–71, 84). In contrast, on lTRE, restricting food intake to the late afternoon or evening (after 4 PM) did not change or even worsen blood glucose, beta-cell responsiveness, and lipid levels (65, 75, 76, 78, 85). Notably, until now, only one study directly compared eTRE and ITRE in a cross-over design (68) where postprandial glucose and fasting triglycerides decreased after consuming both diets, whereas mean fasting glucose assessed by CGM improved only with eTRE. Trials in which eating window was restricted to the middle of the day or self-defined window but was not precisely matched, resulted in a reduced body weight or fat mass, with contradictory results concerning fasting glucose, insulin, and lipids (6, 66, 80, 81, 86). This, in combination with generally small sample sizes (and correspondingly low power) and lack of long-term interventions makes published results hard to interpret and to formulate dietary recommendations.

In most trials that investigated TRE under free-living conditions, participants were adherent to the prescribed eating windows on more than 80% of days throughout the intervention period (63–66, 71, 73, 75, 76, 86). Only Parr et al. (79) reported adherence rates to a 9-h TRE intervention to be minimally lower, with 72 ± 24%. In summary, the adherence to TRE over short periods is high, suggesting that TRE is a feasible and easy-to-adapt dietary strategy. However, the long-term practicality of a dietary approach is crucial for beneficial health outcomes (90), and therefore, future trials should examine the adherence to TRE in real life settings over longer periods.

Notably, implementing of eTRE may be challenging for general population because the meals in the evening, consumed after work, are an important family and social event. Late TRE leading to skip breakfast would be better compatible with social life, but is less effective or can even induce adverse metabolic effects as mentioned above. Moreover, shifting of the meal time to a later time of day can induce clock phase delay in peripheral tissues (50); however, metabolic consequences still needs to be further investigated. Thus, timing of meals is considerably associated with quality of life and TRE adherence. Until now, only several trials analyzed individual’s life quality on TRE and reported its improvement when using self-defined eating windows (6, 88). Future studies comparing effects of various TRE windows on the life quality are needed. The next question is whether individual’s chronotype has to be considered when prescribing optimal eating times. Chronotype is a behavioral manifestation of an individual’s internal clock; and late chronotype (“owls”) and early chronotype (“larks”) are the two extremes which strongly differ in peak times of metabolic function, body temperature, cognitive faculties, and sleeping (59) as well as eating habits (91, 92). Whether late chronotypes can profit in the same manner from the eTRE as early chronotypes or the ITRE is more suitable for such individuals also needs future investigation.

The further important question is whether beneficial metabolic effects of TRE and even the weight loss are resulting from the reduction of energy intake alone or also from the shortening of the eating window (and corresponding prolongation of fasting). Most published trials reported a reduction of energy intake because individuals are often not able to consume all usual food quantity within the limited time window. Nevertheless, four carefully controlled or short-term (4–5 days) TRE trials revealed beneficial effects on the glucose metabolism without caloric restriction or weight loss (62, 69, 76, 84), suggesting that timing factor alone can improve metabolic state. Further, most of the published human TRE studies did not carefully monitor dietary macronutrient content, which could lead to false data interpretation, e.g., if subjects have to skip high-fat or sweet snacks or alcohol drinks often consumed in the evening.

This opens a next question concerning physiological and molecular mechanisms underlying metabolic TRE effects. One
effects of TRE: (1) carefully monitoring macronutrient and induced by TRE.

provide new data on physiological and molecular mechanisms quality, and food intake (e.g. using smartphones) would continuous monitoring of glucose, physical activity, sleep markers, gene expression in muscle or adipose tissue) and biomarkers (e.g., adipokines, cytokines, oxidative stress clock rhythms in humans. Further analyses of novel mechanisms are activated by exercise and prolonged fasting machinery ATP ratio and cellular availability of NAD+, regulating clock RORs, and Rev-Erbs (96). In particular, fasting increases AMP/mTOR, S6K, AMPK, PPARs, ORs, and Rev-Erbs (96). In particular, fasting increases AMP/ATP ratio and cellular availability of NAD+, regulating clock machinery via AMPK and SIRT1, respectively (8). Notably, the careful timing of the physical activity in the context of TRE could intensify its metabolic effects because several common mechanisms are activated by exercise and prolonged fasting (97). However, most of these mechanisms were described in rodents and require intensive investigation in human TRE studies. In particular, it is unknown whether eTRE is more beneficial than iTRE for the synchronization and improvement of clock rhythms in humans. Further analyses of novel biomarkers (e.g., adipokines, cytokines, oxidative stress markers, gene expression in muscle or adipose tissue) and using modern techniques and portable devices for the continuous monitoring of glucose, physical activity, sleep quality, and food intake (e.g. using smartphones) would provide new data on physiological and molecular mechanisms induced by TRE.

Taken together, further human trials are needed to investigate effects of TRE: (1) carefully monitoring macronutrient and calorie intake (possibly via conducting an isocaloric TRE); (2) directly comparing effects of eTRE and iTRE; (3) comparing varying eating window duration; (4) in long-term studies; (5) in a large number of study participants; (6) comparing TRE effects in subjects with different chronotypes; (7) including analyses of physiological and molecular mechanisms underlying the TRE-induced changes. In particular, calling for research that balances feasibility of TRE interventions (e.g., timing and duration of eating windows) with long-term adherence and metabolic benefits could be recommended.

Confirming a large scientific and practical interest to the TRE approach, there are more than 20 ongoing intervention trials applying TRE approaches to improve body weight and metabolic state of individuals as based on published study protocols and a search in ClinicalTrials.gov database. A few trials will be conducted in larger cohorts with more than 100 participants, however several trials are planned in smaller cohorts with well-defined participants, e.g., with specific medical conditions linked to obesity. Moreover, most interventions are still short term with intervention periods lasting 2 to 12 weeks, and only eight studies scheduled longer interventions (up to 1 year). Solely, four trials will be directly comparing TRE at different daytime. Moreover, none of the ongoing trials aims to compare TRE in individuals with different chronotypes, although the subjects’ chronotype will be assessed in several studies. In consequence, even though many TRE trials are ongoing, it remains unclear if these trials will be sufficient to answer all the abovementioned research gaps and formulate dietary recommendations for the general public.

**CONCLUSIONS AND PERSPECTIVES**

TRE represents an attractive and easy-to-adapt dietary strategy for the prevention and therapy of glucose and lipid metabolic disturbances. It might be widely used to restore disturbed circadian rhythms and to improve metabolic health in obesity, insulin resistance, metabolic syndrome, and cardiovascular diseases. In the best way, TRE approach has to be used in combination with healthy dietary composition, an increased physical activity, and adequate sleep quality and duration to support optimal health. However, future carefully controlled TRE studies are needed to formulate dietary recommendations for the general population and medical practice.

**AUTHOR CONTRIBUTIONS**

OP-R generated the idea and performed the supervision of the manuscript preparation. All authors contributed to the article and approved the submitted version.

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