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REVIEW

Time Restricted Eating: A Valuable Alternative to Calorie Restriction for Addressing Obesity?

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Abstract

Purpose of Review In this review, we summarize the molecular effects of time-restricted eating (TRE) and its possible role in appetite regulation. We also discuss the potential clinical benefits of TRE in obesity.

Recent Findings TRE is an emerging dietary approach consisting in limiting food intake to a specific window of time each day. The rationale behind this strategy is to restore the circadian misalignment, commonly seen in obesity. Preclinical studies have shown that restricting food intake only during the active phase of the day can positively influence several cellular functions including senescence, mitochondrial activity, inflammation, autophagy and nutrients' sensing pathways. Furthermore, TRE may play a role by modulating appetite and satiety hormones, though further research is needed to clarify its exact mechanisms. Clinical trials involving patients with obesity or type 2 diabetes suggest that TRE can be effective for weight loss, but its broader effects on improving other clinical outcomes, such as cardiovascular risk factors, remain less certain.

Summary The epidemic proportions of obesity cause urgency to find dietary, pharmacological and surgical interventions that can be effective in the medium and long term. According to its molecular effects, TRE can be an interesting alternative to caloric restriction in the treatment of obesity, but the considerable variability across clinical trials regarding population, intervention, and follow-up duration makes it difficult to reach definitive conclusions.

Keywords Time restricted eating · Circadian rhythm · Biological clock · Obesity · Appetite

Introduction

The epidemic incidence of obesity and overweight causes urgency to find dietary, pharmacological and surgical interventions that can be effective [1]. The guidelines for the management of overweight and obesity in adults recommend reducing calories intake by the 25–30% of the total daily intake (1200–1800 kcals/day) [2], but weight loss is almost inevitably followed by weight regain. In fact, the organism physiologically reacts to energy restriction increasing appetite, reducing satiety and reducing energy expenditure [3–8]. This physiological compensation results from millennials of evolutionary adaptations to food scarcity [9, 10]. Hence, dietary strategies other than calorie restriction are necessary [11]. Time restricted eating (TRE) emerges as a new option, supported by an increasing body of evidence that defines its safety and therapeutic potential [12]. Moreover, interesting molecular findings highlight that fasting-feeding cycles positively interfere with some cellular process involved in metabolic functions, cell survival, inflammatory and mitochondrial processes [13, 14]. Furthermore, TRE seems to counterattack the circadian misalignment involved in the development of some metabolic alterations in obesity [15]. In fact, beyond weight loss, therapeutic programs should consider the multisystemic face of obesity and the chronic and progressive natural history of this disease [16].

In this review, we summarize the mechanisms that make TRE a viable therapeutic option for treating obesity. Its influence on the biological clock can impact intracellular mechanisms and hormones secretion, improving metabolic signaling and finally contributing to weight loss and to better

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control of cardiovascular risk factors in patients affected by obesity [15].

Time Restricted Eating: Not What, But When

Circadian Rhythm, Master Circadian Pacemaker and Peripheral Clocks

Nearly all living organisms, from single-celled cyanobacteria to mammals, developed a system to guarantee that physiological functions take place at appropriate times during the night or the day and to adapt the activity/rest cycle to energy intake and expenditure [17, 18]. The circadian clock mechanisms evolved to enable organisms to anticipate recurrent and periodical changes in their environment, so that biological processes can be stimulated or inhibited in advance as needed to benefit the organism [15, 17]. For example, DNA replication may be inhibited during UV radiation exposure to prevent DNA mutations, and food consumption and energy expenditure may be synchronized by the sleep–wake rhythm [19, 20].

In mammals, this system functions as an endogenous clock, which consists of a master clock located in the brain and secondary clocks located in the peripheral tissues. The central clock influences the peripheral clocks in a hierarchal chain [21] and both these systems regulate a cycle that is called circadian rhythm.

Circadian rhythm happens throughout the 24-h and entails modifications in biology and behavior, ranging from visible changes in activities, like the sleep–wake and fasting-feeding cycles, to more subtle and involuntary rhythms such as blood pressure oscillation, body temperature regulation, hormone blood release and many other metabolic processes [19]. Evidence suggests that dysfunction in these rhythms contributes to ageing and to the development of chronic diseases [22–24].

The master circadian clock is situated in the hypothalamic suprachiasmatic nucleus (SCN) [25] and it is regulated by changes in the environment, called *zeitgebers* [19]. The principal *zeitgeber* of the SCN is the change in light–dark cues [21], that is detected by the melanopsin-containing ganglion cells in the retina [15]. Regarding peripheral clocks, it seems that food consumption is the main *zeitgeber* [14], as mealtimes can directly affect the activity of peripheral clocks located in liver and gut [21].

Circadian clocks are present in every single cell of the human body and function in a self-regulated manner oscillating autonomously, following an endogenous period of 24 h, relying on a network of transcription-translation feedback [21, 25]. This 24-h cycle functions thanks to autoregulatory transcriptional feedback, depending on the rhythmic expression of clock-controlled genes [25, 26]. Transcriptional activators of the cellular clocks include the circadian locomotor output cycles kaput (CLOCK) [25] and brain and muscles ARNT-like1 (BMAL1) proteins [25, 27]. CLOCK and BMAL1 form a heterodimer (CLOCK:BMAL1) that positively regulates the expression of clock-controlled genes (CCGs) and the transcription of its self-repressors, the transcriptional repressor period 1 and 2 (PER1 and PER2, respectively) and cryptochrome 1 and 2 (CRY1 and CRY2). PER and CRY accumulate in the cytoplasm over time, forming a complex that migrates into the nucleus and inhibits the CLOCK:BMAL1 heterodimer. Thus, this system works as negative feedback with delay [28]. The complex CLOCK:BMAL1 stimulates the transcription of the retinoic acid receptor-related orphan receptor (ROR), and the nuclear hormone receptors REV-ERB; both ROR and REV-ERB coordinate CCGs, regulating their cyclical oscillation [29].

Although both the central and peripheral clocks are based on the same CCGs network, their dominating *zeitgebers* are dark–light changes and food consumption, respectively [29].

However, experiments on animal models demonstrated that rodents exposed to daytime feeding or nighttime feeding developed different effects on both central and peripheral circadian clocks [30], while mice exposed to nighttime feeding or freely fed uncoupled the central and secondary clocks synchronization compared to daytime fed mice [30]. Moreover, according to Stokkan et al., feeding cycles can regulate hepatic circadian clock even in SCN lesioned mice [31]. So, even though the central clock appears to regulate the peripheral clocks in a hierarchical way [21], changing a peripheral *zeitgeber* such as meal timing can actually have an effect on the central clock.

Definition of Time Restricted Eating

The term fasting indicates the abstinence from food and beverages over a defined period of time [32]. Fasting has been practiced for millennia for hygienic and religious reasons, which were related to food preservation capabilities and seasonal access to fruits, leaves and grains [15, 33]. Various religions have been regulating food intake during certain times of the year, such as the Muslim Ramadan [34, 35] and the catholic Lent [36].

Intermittent fasting is an umbrella term referring to various dietary therapies that restrict the timing of meal intake rather than the content [15]. The most popular modalities of fasting are 1) alternate-day fasting which consists in the alternation of days with and without caloric intake; 2) alternate-day modified fasting, that alternates days without calorie restriction and days with a caloric intake limited to 25% of daily energy requirement; 3) period fasting, which consists of ad libitum eating days mixed with caloric restriction days over a one week long cycle; 4) TRE [15], a dietary approach in which food consumption is limited in a specific

time window during the day (from 4 to 12 h) without caloric restriction [14]. Therefore, TRE stands out from the other kinds of intermittent fasting regimes because it does not need calories counting during the day [14].

Recently, fasting regimes gained attention as an alternative to caloric restriction regimes due to their potential to improve metabolic health by eliciting adaptative changes such as lowering basal metabolic rates, triggering ketogenesis and lipolysis, lowering oxidative stress, and influencing hormones' hematic concentration [15, 32, 37]. Data found that intermittent fasting attempts to improve metabolic health by leveraging food intake with circadian physiology [15]. Particularly, most research implies that the advantages of TRE, including greater insulin sensitivity, may depend on aligning the fasting-feeding cycle with the circadian rhythm [14].

Effects of TRE on Peripheral Tissues Circadian Clocks

Time restricted feeding (TRF) was initially studied in rodents to understand food anticipatory activity and behaviors, leading to the discovery that food providing is the main *zeitgeber* for the peripheral circadian clock, particularly in the liver [38, 39]. Accordingly, TRE may influence the expression of circadian clock related genes in peripheral organs such as adipose tissue, gut, muscles and liver itself [14, 15].

Liver

TRE may have a significant impact on hepatic circadian clock, as its expression of CCGs is modulated by mealtimes [40]. According to Vollmers et al., food intake and temporal pattern of feeding determined the amplitude and the phase of circadian transcriptome in wild type mice' liver, compared to CRY1 and CRY2 knock-out mice [41]. TRF can induce metabolic rhythms also in liver-specific BMAL1 and REV-ERB knock-out mice [42]. Furthermore, fasting can induce the expression of agouti-related peptide [43, 44], which triggers liver rhythm-related transcriptional factors, such as BMAL1, CLOCK, PER and CRY. [43] Hatori et al. demonstrated an increase in both adenosine monophosphate (AMP) concentrations and AMP-activated protein kinase (AMPK) activity in the liver of rodents exposed to a 18-weeks long TRF regimen [45]. AMPK, activated by fasting, controls the expression and degradation of a lot of circadian proteins, such as CRY1, CRY2, PER and CLOCK:BMAL [46–48]. On the other hand, also mammalian target of rapamycin complex (mTORC1), which is activated by feeding, interacts with several circadian clock proteins [49, 50]. It is interesting, though, that AMPK and mTOR mutually inhibit [51].

Evidence suggests that TRE can regulate also the rhythmicity of hepatic cAMP-response element binding protein (CREB)c, enhancing the interaction between CREB and its coactivator CREB-regulated transcription coactivator 1 (CRTC1). Thus, it promotes the binding of the complex CREB-CRTC1 with the histone acetyltransferase CREB binding protein (CBP) [52]. By its side, the CREB-CRTC1-CBP complex stimulates hepatic clock genes *PER1* and *PER2* [52], while the CRY-cAMP-CREB axis regulates gluconeogenesis [41, 53].

Skeletal Muscle

Data on adult mice describe that fasting can affect circadian clock in skeletal muscle directly by modulating tissues clock genes (*BMAL1* and *PER*) and indirectly by modulating some clock genes regulators including ribosomal protein S6 and tripartite motif containing 63 *(TRIM63 or MuRF1*) [54]. In skeletal muscles the activity of AKT/mTOR pathway promotes protein synthesis by phosphorylating two major targets, S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) [55]. Phosphorylating activity of AKT/mTOR exhibits temporal regulation in fasting animals, as period of fasting results in large decreases in phosphorylation of both AKT and S6K1 in muscles, indicating inactivation [56]. On the other hand, mTOR, stimulated by feeding, increases the availability of insulin and amino acids and regulates glucose and protein metabolism [56].

Studies on Drosophila and mice found that obesity can disrupt skeletal muscles' circadian clock and function, and TRF may play a role in preventing muscle disruption and maintaining circadian rhythm in muscles mitochondrial respiration [56]. On the other hand, mice fed with a TRF regimen during inactive phase the diurnal regularity of mitochondrial respiration in skeletal muscles was disrupted [56].

Adipose Tissue

Also, white adipose tissue clock regulators may be affected by TRE. Several of adipose tissue's functions cyclically oscillate, particularly the expression of fibroblast growth factor 21 (FGF21) [57] and hormone sensitive lipase (HSL) [57, 58]. TRF can prevent the disruption of FGF21 circadian oscillation secondary to a high fat diet [57]. Matoba et al. linked fasting to the secretion of Kruppel-like factor 15 (KLF15), which is capable of adapting lipid metabolism to nutrient availability through the promotion of lipolysis during fasting and lipid synthesis during feeding [59]. An interesting study showed that fasting can modulate the transcription of circadian clock genes in human adipose tissue, independent of the time of day, corroborating the hypotheses that meal timing can improve metabolism regulation [60].

Gut

Regarding the effects of TRE on gut, Brooks et al. described how the intestinal microbiota coordinates a rhythmic innate immune response that is linked to meal timing in order to anticipate gut exposure to microbes [61]. Circadian clock tailored by food intake rhythms and subsequent epithelial attachment by segmented filamentous bacteria (SFB) coordinates the expression of antimicrobial protein and the activation of an immunological circuit involving group 3 innate lymphoid cells. STAT3 itself regulates immune response through the expression of antimicrobial proteins such as regenerating islet-derived protein 3γ (REG3G), lipocalin-2 (LCN2) and S100A8 [61]. These oscillations have been found to be perturbed by a high fat diet [62] and to be restored by TRF [62–65].

Effect of TRE on Circadian Misalignment

Studies have shown that TRE may have a noteworthy benefit on metabolic dysregulation in people with circadian misalignment [15]. Circadian misalignment is described as dysregulated cyclical recurrent behaviors, such as sleeping/activity and eating/fasting, during the 24-h cycle. This misalignment can alter metabolic homeostasis [66] and increases the risk of metabolic, renal and cardiovascular disease [67–69]. Evidence from knockout mice models clarify the role of the circadian clock in metabolic homeostasis. For example, Rudic et al. demonstrated that the inactivation of BMAL1 and CLOCK suppresses the 24-h variation in glucose and triglycerides concentration in circulating blood, depresses gluconeogenesis after insulin-induced hypoglycemia, but does not impact the counterregulatory response of glucagon and corticosterone [70]. This knowledge comes not only from mice but also from observational studies in people working in non-standard shifts and from simulated shift work or forced desynchrony experimental protocols [15]. Evidence agrees that circadian misalignment causes insulin resistance, decreases oral glucose tolerance and increases sensitivity to DNA damage [71–73]. Intermittent fasting regimens have shown, both in rodents' and humans', the ability to reduce circadian misalignment [15]. Particularly, TRE prevents the increase in adiposity and body weight, and attenuates glucose intolerance, β-cells dysfunction and consequent circadian misalignment triggered by shift work [74, 75].

Fasting-Feeding Cycles Effects on Cellular Mechanisms

Several molecular pathways appear to be influenced by the timing of feeding, not only metabolic signaling but also mechanisms involved in mitochondrial functions, cellular senescence, autophagy and inflammatory response [13] (Fig. 1). Dysregulation in these pathways can lead to the development of several chronic diseases such as cancer,

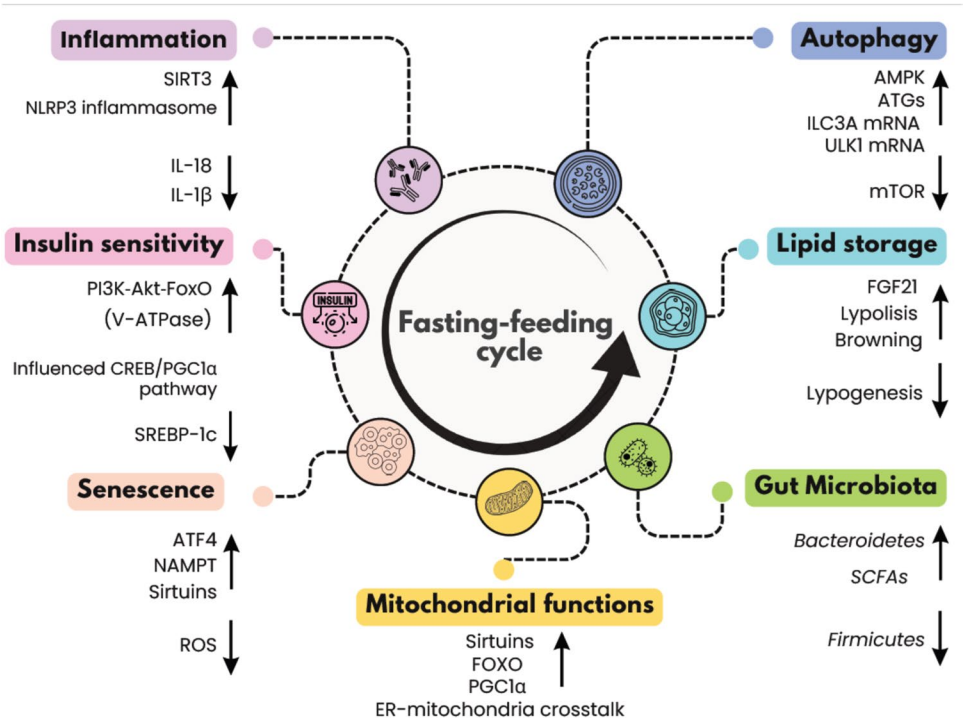

Fig. 1 Fasting-feeding cycle affects several cellular mechanisms and influences gut microbiota. Abbreviations: *ER*, endoplasmic reticulum; *ROS*: reactive oxygen species; *SCFAs*: short chain fatty acids

neurological disease, and metabolic dysfunctions such as insulin resistance and dyslipidemia [14, 15, 76].

Autophagy

Autophagy refers to the variety of intracellular homeostatic and protective processes that activate in order to provide energy to cells, when nutrients are insufficient. This process happens through the formation of autophagosomes. Autophagosomes incorporate organelle or intracytoplasmic matter and fuse with lysosomes for their enzymatic degradation [77]. The formation of autophagosomes is mediated by a complex pathway that involves many molecules, overall, the autophagy-related (ATG) family proteins [78]. Starvation seems to trigger autophagy directly inducing deacetylation of ATG4B [79]. Furthermore, AMPK and mTOR—activated respectively by fasting and feeding—work together to control autophagy. In fact, AMPK can directly trigger autophagy by phosphorylating the Unc-51-like kinase 1 (ULK1, an ortholog of ATG1) [80], activating the pro-autophagy vacuolar protein sorting 34 (VPS34) complex (which works with the ATG members proteins) [81], and indirectly by inhibiting mTOR. mTOR can inhibit autophagy by phosphorylation of ULK1, ATG13 and ATG14L in the VPS34 complex [51, 82]. Also, mTOR inhibits the transcription factor EB (TFEB), a transcriptional factor of lysosomal and autophagy genes [83]. ATG1 and ATG8a are expressed following circadian rhythms and studies showed that TRF upregulates their expression through CCGs [84, 85]. In humans, TRE seems to enhance expression of *LC3A* gene, which encodes for another structural component of the autophagosomes' membranes [86]. Moreover, TRE enhances the expression of ULK1 by increasing the levels of miRNA involved in mTOR signaling pathway [87]. The relationship between obesity and autophagy is complex and not completely understood [88]. Even if there is limited evidence about TRE effects on autophagy in humans, it seems that fast-feed cycle can re-establish the physiological interplay between all the protagonists of this important homeostatic mechanism.

Mitochondrial Dysfunction

Mitochondrial dysfunction refers to the incapacity of mitochondria to produce an adequate quantity of ATP in response to the cell's demand [89]. Mitochondria and the endoplasmic reticulum (ER) are the most important organelles involved in the control of metabolic flexibility, which is the ability to adapt metabolism to nutrient availability [90]. The chronic inflammatory state that characterizes obesity leads to an overproduction of reactive oxygen species (ROS), causing mitochondrial dysfunction [91]. Another reason is that an excessive amount of nutrients, overburdens the Krebs cycle and the respiratory chain [92]. CR and fasting intervene in this scenario via the activation of AMPK, which mediates the phosphorylation of several transcriptional co-activators of mitochondrial genes, such as peroxisomal proliferator-activated receptor-gammacoactivator1-alpha (PGC1α) and fork-head box O (FOXO) [93]. Furthermore, AMPK enhances the activity of sirtuins (SIRT), such as SIRT1 and SIRT3. SIRT1 plays a positive role in various cellular functions, including senescence, autophagy, lipid homeostasis and insulin sensitivity [94, 95]. Therefore AMPK and SIRT1 reciprocally activate in response to CR [96]. On the other hand, SIRT3 is positively involved in numerous mitochondrial functions, such as the protection from ROS and deacetylation of several proteins involved in fatty acid oxidation [97], in respiratory chain [98] and in cell death programs [99]. Mitochondria cooperate with ER in the maintenance of metabolic flexibility and energy metabolism [100]. ER membranes express inositol 1,4,5-trisphosphate receptor (IP3R), essential for the diffusion of Ca2+ from ER to mitochondria [101]. Alterations in this mechanism are involved in the development of metabolic disfunction such as insulin resistance [102] and metabolic dysfunction-associated steatotic liver disease (MASLD) [103]. During fasting state, cAMP can phosphorylate IP3R enhancing the interaction between ER and mitochondria [90]. Castro-Sepulveda and colleagues demonstrated that fasting-to-feeding transition reduces the interaction between ER and mitochondria and reduces mitochondrial cristae density in human peripheral blood mononuclear cells (PBMCs) [104].

Cellular Senescence

Mitochondrial dysfunction is strictly connected with cellular senescence and can be both the cause and consequence of this condition. Senescence refers to the permanent state of cell cycles arrest, that occurs in proliferating cells, due to various kinds of cellular stresses. When senescent cells accumulate, the aging process starts, leading to functional decline and increase in morbidity and mortality [105]. Fasting can affect cellular senescence in several ways. Several biochemical pathways have been shown to promote longevity, among these, a central role is reserved for AMPK and mTOR pathways [106].

Interesting findings regarding activating transcription factor 4 (ATF4) have been discovered. ATF4, in fact, is a transcriptional factor with different target genes involved in cell survival, apoptosis, autophagy and protein synthesis, in response to various stress conditions [107]. It has been shown that ATF4 has a circadian behavior, with its levels rising with light and decreasing with darkness, as CLOCK:BMAL1 transactivates the ATF4 gene, while ATF4 controls *Per2* gene transcription [108]. Additionally, elevation in ATF4 levels in liver and fibroblasts seems to increase longevity and lifespan in mice [109]. Quiros and

his colleagues found that ATF4 is the main factor activated in response to mitochondrial stress and mitonuclear stress [110]. On the other hand, in response to a fasting phase, ATF4 stimulates the transcription of *FGF21* gene [111]. FGF21 has multiple positive effects on metabolism, particularly on insulin sensitivity, body weight and glycemic control, and it is also associated with an increased lifespan in mice [112]. Taken together, these findings suggest that ATF4 pathway is another possible mechanism that could mediate the beneficial effects of TRE, but its role must be examined more in depth.

Additionally, fasting can decrease cell senescence by enhancing the activity of various members of the sirtuin family [113]. By decreasing SIRT4 levels, fasting rises the levels of α-ketoglutarate (αKG), an endogenous metabolite [114] capable of reducing the senescence-associated secretory phenotype (SASP) and inhibiting mTOR signaling pathway, while increasing AMPK activity [115]. In Drosophila, starvation induces SIRT4 and its deficiency correlates with decreased cellular longevity [116]. Conversely, CR and fasting reduce oxidative-stress and DNA damage by enhancing SIRT3 activity [117, 118]. Furthermore, in a study on patients with overweight or obesity, TRE appears to enhance SIRT1 expression [86].

Another essential coenzyme involved in cellular redox reactions is NAD. Nicotinamide phosphoribosyltransferase (NAMPT), also known as visfatin or pre-B cell colony enhancing factor (PBEF), is a controller of intracellular NAD + level [119]. NAMPT transcription is activated in a circadian manner by CLOCK and BMAL1 forming a complex with SIRT1 [120]. The regulation of its transcription leads to circadian oscillation of NAD + levels [121]. It has been shown that NAMPT-controlled NAD + levels can promote cell survival [122], starvation, in turn, increases both the levels of NAMPT and NAD + [123]. Interestingly, while NAMPT is expressed in all human tissue, it is highly expressed in adipose tissue and its circulating levels correlate with obesity and metabolic syndrome [124].

NLRP3 Inflammasome and Chronic Low-Grade Inflammation

It is well-demonstrated that obesity is characterized by a chronic low-grade systemic inflammation [125]. Briefly, dysfunctional adipose tissue and consequent lipotoxicity lead to the development of a pro-inflammatory immune infiltration, resulting in the production of adipokines and cytokines, and ultimately establishing systemic inflammation [126]. Among various pathways, obesity-related inflammation is particularly influenced by the activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [127]. NLRP3 is a complex of the innate immune system that activates in response to various pathogen-associated molecular patterns (PAMPs) and/or danger-associated molecular patterns (DAMPs), leading to the production and activation of IL-18 and IL-1β and consequently amplifying systemic inflammation [128, 129]. The NLRP3/IL-1β pathway is also implicated in inducing insulin-resistance [130, 131]. An increasing body of evidence demonstrates that fasting reduces NLRP3-mediated inflammation via activation of SIRT3. For instance, a study showed that after 48 h of fasting, macrophages from wild-type mice produce lower quantities of IL-1β compared to those from SIRT3 knock-out mice. Additionally, SIRT3 reduces NLRP3 activity by inducing superoxide dismutase 2 (SOD2), thereby decreasing mitochondrial ROS levels [118]. Similar effects have been demonstrated by measuring IL-1β and IL-18 levels in human PBMCs during fasting and re-feeding: levels are lower during fasting and increase after re-feeding [132]. Moreover, it has been shown that after 24 h of administering a SIRT3 agonist to healthy volunteers, IL-1β and IL-18 production from PBMCs followed a similar trend as observed in the fasting state [132]. Based on previous studies demonstrating how NLRP3 inhibition ameliorates insulin-resistance [133, 134], Liang and colleagues demonstrated that fasting improves insulin sensitivity in mice and reverses insulin resistance in vitro, specifically in adipocytes used as a cellular model of insulin resistance. They also found that fasting inhibits the production of inflammatory markers (c-reactive protein, IL-1β, IL-18) induced by insulin resistance. This inhibition was counteracted by an NLRP3 agonist used to treat adipocytes in vitro, suggesting that the inhibition of NLRP3 induced by fasting may play a role in improving insulin sensitivity [135]. Furthermore, the inhibition of NLRP3 inflammasome by injecting a selective inhibitor into the peritoneum of mice after re-feeding reduced the production of IL-1β in hepatocytes and ameliorated fasting-induced hepatic lipid deposition [136]. Although an evaluation on NLRP3 activity was not performed, another study showed decreased levels of IL-1β and reduced inflammatory response in hepatocyte of mice treated with every-other day feeding regimen [137]. Inhibiting NLRP3 and other members of the NLRP3 family (such as NLRP1) through intermittent fasting also reduces cells death following chronic and acute hypoperfusion [138, 139].

Metabolic Signaling and Nutrients' Sensing Pathways

TRE can control several metabolic signaling pathways in different organs, such as adipose tissue, liver and muscle [14, 140, 141]. In adipose tissue, prolonged fasting influences the expression of genes such as *GLUT4*, *IRS2* and *AKT*. Specifically, it enhances the transcription of perilipin 2 and ATG, involved in lipolysis, while reducing perilipin 1. It reduces the transcription of adiponectin, adiponectin

receptor, insulin-like growth factor-1 (IGF-1), resistin and leptin, although contrasting data has been collected on factors related to hemostasis, angiogenesis and immunity [142]. Conversely, in adults affected by overweight and obesity, late isocaloric eating enhanced the expression of genes involved in lipogenesis (*GPAM, ACLY, AACS,* and *CERK*), while reducing those involved in lipid breakdown (*PLD6, DECR1,* and *ASAH1*), as well as lipolysis genes such as *ABDH5*, which is inhibited by perilipin 1 [143].

Regarding insulin signaling, fluctuations in insulin levels during fasting and feeding cycles interact with the clock machinery. For instance, TRE can control *per2* expression by reducing IGF-1 and insulin production during fasting [144]. Goldbraikh et al., demonstrated that during fasting, the ubiquitin-specific protease 1 (USP1) de-ubiquitination activity is reduced, with a consequent increase in Akt ubiquitination, PI3K-Akt-FoxO signaling, and glucose uptake [145]. Also in humans, early-TRE may improve insulin-sensitivity by increasing the expression of AKT2, a downstream member of the insulin signaling pathway [86]. Fasting seems also to enhance the phosphorylation of insulin receptor substrates 1 and 2 (IRS1 and IRS2) with a consequent increase in the association with PI3-kinase in liver and muscle [146]. Glucose starvation increases vacuolar H + -ATPase (V-ATPase) assemblage [147], a proton pumps that controls glycolysis, insulin secretion, glucose transporter and that takes part in various pathophysiological mechanisms leading to diabetes [148]. SREBP-1c, a member of the sterol regulatory element binding proteins (SREBP) family, is a downstream effector of the insulin signaling, involved in fatty acids synthesis and insulin induced metabolism [149]. In diabetics rats' liver, intermittent fasting seems to reduce SREBP1-c and increase PPAR-γ levels [150], in mice liver also, SREBP1-c levels were reduced after starvation [151]. A study on humans showed that after 48 h of starvation, in skeletal muscle the expression of SREBP1-c is decreased, whereas IRS1 and IRS2 levels do not change [152]. However, in adipose tissue of patients with obesity obese and type 2 diabetes, SREBP-1c mRNA expression was found to be decreased in comparison with lean subjects [149]. In the liver, the fasting-feeding cycle also drives rhythmic expression of other molecular participants in metabolic pathways. In mice fed with ad libitum high-fat diet, hepatic levels of pCREB are constitutively elevated. CREB controls lipolysis, lipogenesis and particularly gluconeogenesis in liver [153]. In mice fed with a normal chow or high-fat diet under a time-restricted feeding regimen, several changes were observed: 1) a restoration of daytime peaks in pCREB, 2) increased levels of the transcriptional repressor Rev-erb-α, leading to the repression of fatty acid synthase and reduction in levels of several long-chain free fatty acids, and 3) increased expression of Per2, which inhibits PPARγ and subsequently attenuates the transcription of lipogenic genes [29, 45]. Furthermore, CREB is an activator also of the coactivator 1α (PGC1α). The axis CREB/PGC1α, according to Besse-Patin et al., activates genes that trigger lipid catabolism and gluconeogenesis during fasting [154]. As shown also in chapter 2, these findings are supported by previous research demonstrating how both the temporal pattern of food intake and circadian clock rhythmically regulate the transcription of numerous hepatic genes, including those involved in metabolic pathways such as *CREB*, *AKT*, and *AMPK* [40, 41].

Effects of TRE on Metabolism and Appetite Control Players

Restoring the tissues' circadian expression of genes involved in metabolic pathways could be the key for protecting against metabolic disorder caused by excessive food intake and consequent obesity. Obesity is characterized by mitochondrial dysfunctions and systemic low-grade inflammation, both important drivers for the development of its comorbidities and complications. A dietary regimen that blunts this inflammatory status and promotes mitochondrial activity could be the initial step in a comprehensive therapeutic program. However, one of the most important factors for the adherence to a dietary protocol is appetite control, while the adherence to a dietary prescription is the best predictor of weight loss, over the short and long term [155]. Therefore, we decided to explore the effects of TRE on hormones involved in appetite control [156, 157], summarized in Table 1.

Hypothalamic Hormones

Appetite is regulated by a complex integration of several neuronal and peripheral signaling [158]. Briefly, the hypothalamus arcuate nucleus (ARC) plays a pivotal role, expressing hormones' receptors such as leptin, ghrelin and insulin and thus acting as an energy sensor [159]. ARC includes neurons releasing neuropeptide Y (NPY) and agouti-related peptide (AgRP) that stimulate food intake, and pro-opiomelanocortin (POMC) cells expressing α-melanocyte-stimulating hormone (α-MSH) and cocaine- and amphetamine-regulated transcript (CART) that inhibit food intake. NPY/AgRP and α-MSH/CART receptors are expressed on several hypothalamic nuclei, such as paraventricular nucleus (PVN), dorsomedial hypothalamus (DMH), lateral hypothalamic nucleus (LHA) and ARC itself for feedback regulation. PVN releases thyroid releasing hormone (TRH), corticotropin releasing hormone (CRH) and oxytocin which show anorexigenic effects. LHA releases melanin-concentrating hormone [66] and orexin A and B, which act as orexigenic hormones [160].

Table 1 Hormones and neurotransmitters involved in appetite regulation

Tissue / organ	Hormone or neurotransmitter	Effect on appetite	TRE influence
Hypothalamus	NPY	Orexigenic	↑
	AgRP	Orexigenic	None
	Orexin	Orexigenic	None
	MCH	Orexigenic	Not known
	POMC	Anorexigenic	Conflicting evidence
	TRH	Anorexigenic	
	CRH	Anorexigenic	Not known
	CART	Anorexigenic	↓ None
Gut	Ghrelin	Orexigenic	↓/=
	CCK	Anorexigenic	↓
	PYY	Anorexigenic	Conflicting evidence
	GLP-1	Anorexigenic	↓/=
Pancreas	PP	Anorexigenic	↑
	Amylin	Anorexigenic	None
	Insulin	Anorexigenic	Conflicting evidence
Adipose tissue	Leptin	Anorexigenic	↓
	Adiponectin	-	↑
Gut microbiota	SCFAs	Anorexigenic	↑

NPY: neuropeptide *Y*; *AgRP*: agouti-related peptide; *MCH*: melanin-concentrating hormone; *POMC*: pro-opiomelanocortin; *TRH*: thyroid releasing hormone; *CRH*: corticotropin releasing hormone; *CCK*: cholecystokinin; *PYY*: peptide YY; *GLP-1*: glucagon-like peptide-1; *PP*: pancreatic polypeptide

In fasting protocols, NPY expression has been extensively studied [157]. Intermittent fasting increases the expression of NPY mRNA in ARC [161–164], thus suggesting a counterregulatory process to short-term weight loss induced by calorie restriction. However, in another study NPY mRNA expression was not influenced by intermittent fasting [165]. Yoshihara et al. demonstrated that in rats under restricted feeding conditions NPY levels showed a pre-feeding peak, suggesting that NPY is also regulated by the fasting-feeding circadian rhythm [166].

On the other hand, conflicting evidence exists regarding POMC concentrations: after intermittent fasting, they have been found to be either increased [163] or unchanged [164]. Mice knockout for melanocortin 4 receptor (MC4R, the α-MSH receptor), do not show a significant weight loss when compared to wild type mice fed according to a dark restricted feeding protocol (in other words, fed only in the active phase). This evidence suggests that melanocortin system may play a role in weight loss during TRF [167].

Orexin, AgRP and CART expression are less studied, but it seems they are not influenced by intermittent fasting [164, 168].

Gut Hormones

Ghrelin is mostly secreted by X/A cells in gastric fundus. Its levels reach their maximum during fasting and minimum just after the meal [169]. Ghrelin increases gastric motility and secretion in advance of food ingestion and it stimulates arcuate nucleus receptors in the hypothalamus, inducing the production of NPY and AgRP and therefore stimulating appetite [170].

Cholecystokinin (CCK) is secreted by duodenal and jejunal I cells after meals, especially high-fat ones, when it stimulates the secretion of bile and pancreatic enzymes and, binding its receptors on vagus nerve, suppresses hunger [171].

Peptide YY (PYY) is secreted by ileum and colon L cells proportionally to calorie intake after meals and exerts its anorexigenic function at the level of the arcuate nucleus, inhibiting NPY and PYY secretion [172].

Glucagon like peptide-1 (GLP-1) is produced by intestinal L cells in response to glucose presence in the luminal intestinal space. It stimulates insulin secretion, inhibits glucagon production, slows gastric emptying and reaches hypothalamus to promote satiety and reduce food intake [173].

Subjects affected by obesity have low levels of ghrelin during fasting and show an impaired suppression of ghrelin secretion after meal, as an adaptive response to chronic positive energy balance [170]. Furthermore, they show lower post-prandial levels of GLP-1 and PYY [172], suggesting that satiety is not reached, and that the next meal will be desired earlier [173]. During dietary intervention, PYY and CCK levels were reduced, while ghrelin levels were increased, with a consequent reduction of the feeling of fullness [171]. This is one of the most powerful compensatory responses that counteract weight loss [174].

Even if TRE seems to improve satiety and appetite control, evidence about how it influences gut hormones production is less consistent [156, 175]. In animal models of restricted feeding protocols, when compared to ad libitum protocols or high fat diet, ghrelin levels have been found both lower [176] and higher [167, 177]. In humans, early-TRE lowered the fasting levels of ghrelin [178, 179]. These results are in line with a previous study, showing that if caloric intake is higher at breakfast than at dinner, the levels of ghrelin, insulin and fasting glucose decrease when compared to an opposite distribution of caloric intake [180]. A study on Ramadan period showed a decrease in ghrelin levels during daytime [181], while in other studies there were no effects on ghrelin concentrations [175, 182–185]. In contrast, only one study showed that a period of alternate-day fasting led to an increase in ghrelin [186].

Evidence about PYY and GLP-1 levels is controversial. In humans studies, TRE was found to decrease [182,

187], increase [178] or not affecting at all [179, 188] PYY concentrations.

According to some evidence, TRE reduces fasting GLP-1, while it has no effect on postprandial GLP-1 [178, 179], but in other studies GLP-1 fasting levels were not affected by TRE [187, 188].

Finally, only one study explored CCK concentrations in humans and showed decreased levels after Ramadan period [182].

Pancreatic Hormones

Pancreatic polypeptide (PP) is mostly secreted by pancreatic islets of Langerhans PP cells and to a lesser extent by intestinal cells after meals. Its functions are to slow down stomach emptying, intestinal motility and pancreatic enzymes secretion. Moreover, via the vagus nerve, it inhibits hunger and stimulates satiety [189].

Amylin is secreted by pancreatic β− cells (together with insulin) in response to nutrients intake. It acts as anorexigenic hormone, suppressing glucagon secretion and stimulating satiety [190].

Insulin is produced by β-cells in the pancreatic islets of Langerhans. After meals, glucose level rises, and β-cells release insulin. Binding its receptors on skeletal muscle, adipose tissue and liver, it allows glucose to enter the cells in order to produce energy [191]. Insulin reaches also some brain receptors, crossing the blood-barrier via transporters, in order to decrease food intake, with anorexigenic effect [192]. When glucose levels arise because of excessive food intake, β-cells improve their function to increase glucose uptake, resulting in hyperinsulinemia. Furthermore, the presence of pro-inflammatory cytokines, above all TNF alpha, IL-6 and IL-1, causes insulin receptor downregulation, with decreased signaling glucose uptake. These modifications lead to the establishment of insulin resistance, where insulin hematic concentration is increased but with no effect on its receptor [193].

Most of the studies concentrated on insulin secretion, while amylin and PP are poorly studied in TRE or under fasting conditions [156]. Only one study investigated PP levels after five days of absolute fasting in healthy humans, and found that PP serum concentrations increased progressively [194]. As regards amylin, in a study by Hutchinson et al. TRF had no effect on fasting or postprandial amylin levels [179].

Several evidence show that TRE do not influence fasting and postprandial insulin levels [156, 179, 188, 195], while other studies suggest TRE effectiveness in reducing insulin levels and ameliorating insulin-resistance [196]. Although insulin signaling has been extensively studied in the context of TRE, studies have proposed different definitions of TRE in different populations, making it difficult to draw firm conclusions [156]. For example, Barnosky et al. demonstrated that there is no difference in reducing fasting insulin levels between CR and fasting protocols [197]. In contrast, TRE reduced insulin levels, in women with polycystic ovarian syndrome [198], in subjects with type 2 diabetes [199], in men with prediabetes [187] and in healthy individuals [200]. Clinical outcomes of TRE on insulin sensitivity in the context of obesity are discussed more in detail in paragraph 5.

Adipose Tissue and Adipokines

Far from being a simple depot, adipose tissue acts as a true endocrine organ capable of producing adipokines, chemokines and other molecules that interact with other tissues [201]. Alterations in the quantity, quality and distributions of adipose tissue can cause dysfunctions in its complex regulation [202].

Leptin and adiponectin are primarily secreted by white adipose tissue, but also by other tissues such as bone marrow and mammary epithelial cells. Leptin induces satiety and decreases food assumption. Adiponectin promotes fatty acid oxidation and decreases fat mass accumulation and gluconeogenesis. Its levels are inversely proportional to fat mass [201]. In obesity, the levels of leptin increase proportionally to fat mass, while its receptors' sensibility decreases resulting in a loss of anorexigenic action, in a process called leptin-resistance [203]. Adipokines release is strictly connected with insulin sensitivity, therefore modifications in leptin and adiponectin levels may be due to an improvement in insulin sensitivity, in fact fasting insulin reduction and HOMA-IR improvement has been recorded after fasting protocols [204]. This interaction is linked especially with adiponectin, that promotes muscle fatty acids oxidation and inhibits liver gluconeogenesis through the activation of AMPK to increase GLUT1 and GLUT4 receptors expression, to improve glucose uptake, activating glycolysis and reducing liver gluconeogenesis [205].

In general, several studies reported that TRE and intermittent fasting increase adiponectin levels, while decrease leptin concentrations [156, 196]. When compared to caloric restriction, TRE showed greater reduction in leptin levels, an increase in adiponectin levels and a decrease in leptin/adiponectin ratio in both overweight women [174] and normal weight men [204]. Another study showed leptin reduction both in caloric restriction and in fasting protocols, independent of weight loss [206]. However, other data show that leptin levels do not change if TRE is not associated with caloric restriction [187, 188].

Gut Microbiota

Increasing burden of evidence shows that gut microbiota has a therapeutic potential in many pathophysiological mechanisms.

Firmicutes and Bacteroidetes represent about 90% of all bacteria present in gut [207]. Obesity is associated with dysbiosis, particularly with a reduced diversity in bacterial components, and an increased presence of Firmicutes instead of Bacteroidetes [208]. This dysbiosis influences the secretion of hormones such as PYY, CCK and leptin, resulting in an alteration of central satiety mechanisms [209, 210].

Intestinal bacteria produce short-chain fatty acids (SCFAs) via fiber fermentation. SCFAs can control satiety by the activation of G protein-coupled receptor 41 (GPR41) and GPR43, thus inducing the production of GLP-1, PYY, and leptin [211, 212]. Bacteroidetes are positively associated with higher concentrations of SCFAs, while Firmicutes show an inverse relationship [213].

TRE in humans determines an increase in richness and diversity of gut microbiota [64, 214, 215]. Moreover, when TRE was performed during the early hours of the day, the effect was even more marked [215].

Intermittent fasting increases the production of SCFAs [214, 216–218] also by inducing an increase in Prevotellaceae, which can in turn enhance the production of SCFAs [219].

Furthermore, intermittent fasting enhances the presence of Lactobacillus spp. and Akkermansia, both associated with positive effects on metabolic regulation [212, 214, 215]. Indole, a catabolite produced by Bacteroides, Lactobacillus, and Bifidobacterium, can enhance GLP-1 release, thus improving appetite regulation [212, 220].

However, in other studies, fasting protocols did not influence SCFAs production, both in humans and in mice [213, 221].

Appetite Control and Circadian Rhythm

The disruption of circadian rhythm, with an increase in evening activities and the delay in the last meal of the day, determines a dysregulation in many physiological processes such as basal metabolism, hormone secretion, body temperature regulation and sleep/wake cycle, that altogether determines an increase in cardiovascular risk. Also appetite control follows the circadian rhythm, and the restoring of the inner biological clock could be helped by the resynchronization of food intake with the physiological hormonal secretion [222].

Melatonin secretion is fundamental in guiding daily rhythms [223]. In the first hours of daylight, melatonin levels decrease with a reduction in inhibiting cortisol production. Therefore, cortisol levels reaches its peak at 8 am circa, together with ghrelin, in order to stimulate appetite for the increase in energetic demands induced by morning activity [224]. Ghrelin has a second and third peak also round 1 pm and 6 pm and its levels decrease after meal [223]. Adiponectin reaches its peak at 11 am, promoting glucose uptake and avoiding fat accumulation, while its secretion ends at 8 pm [223]. Insulin reaches peak at 5 pm stimulating fatty acids synthesis and inhibiting gluconeogenesis and fatty acid oxidation, leading to fat accumulation [225]. PYY land PP levels counteract food intake during daytime since its levels are higher during the day than during the night [169, 226]. Leptin levels start rising in the first afternoon and reach a peak in the first few hours of the habitual sleep timing and decrease across the remainder of the sleep episode in order to suppress hunger during the inactive phase [169, 223]. Following this circadian oscillation of hormone production, it can be supposed that the last meal should not be later than 6 PM [169].

Therefore, eating earlier in the day should be preferred with respect to evening meals [227]. Different studies showed that eating at nighttime was associated with greater caloric intake, more frequent meals and at more irregular times [228]. As we have shown, fasting protocols proposing meals early in the day, compared to evening or night eating, improve diet quality, reduce caloric intake [229], reduce snacking [230], regulate eating times and also reduce appetite, leading to greater weight loss [231–234].

Dashti et al. [235] examined a large cohort of subjects affected by obesity during weight loss intervention and divided them in early and late eaters, showing that weight loss is lower in late eaters, which also exhibited a dysregulation in the secretion of the hormones involved in appetite control. In the same way, Vujović et al. [143] hypothesized that late eating could promote positive energy balance increasing the drive for energy intake in relation to increased ghrelin and decreased leptin levels.

Clinical Outcomes in the Context of Obesity

We have seen how TRE produces direct effects on cellular energy metabolism and hormonal regulation of appetite. It is therefore interesting to look at the results of clinical studies on TRE conducted in the context of obesity, focusing on weight loss and cardiovascular risk factors such as glycemic control, lipid profile and blood pressure.

Clinical studies on TRE in humans are very recent. In literature, we can only find them starting from the late 2010s, with a noteworthy increase in available data from 2022. In Supplementary Table 1, we summarized the main clinical trials on adult subjects affected by obesity, indicating the type of intervention applied, the study population and the most relevant findings.

It is important to note that these studies encompass various types of interventions under the "umbrella term" of TRE. TRE refers to dietary interventions that require eating within a specific timeframe, regardless of its duration [14]. Most studies [188, 236–247] applied the common "8-h" TRE, which involves an 8-h eating window followed by a 16-h fasting period, and only one study evaluated narrower 4- and 6-h eating windows [248]. Some studies defined also a more precise eating window, that for example had to start in 3 h from waking up (early-TRE) [249]. Usually during the fasting period only non-caloric liquids (water, tea, coffee) are allowed, while guidelines for the eating window are less stringent. A minority of the studies also incorporated calorie restriction in addition to TRE [241, 249–252], only one study requested a "isocaloric" TRE (further discussed in the next paragraph) [253] while the others simply did not request calorie counting. As a result, these studies presented different types of interventions, varying in duration (ranging from 5 days [188]) to 12 months [240, 241, 245]) and evaluated outcomes (for example, not all the studies registered body weight or blood pressure variation). This heterogeneity creates challenges in drawing firm conclusions on clinical effects of TRE.

Weight Loss

Regarding weight loss, trials consistently show that TRE can induce significant weight loss compared to baseline, even in short periods such as three weeks [250]. However, most randomized controlled trials comparing TRE with caloric restriction have not demonstrated significant differences in weight loss between the two regimens [236, 240, 243, 244, 254]. These results indicate not a lack of effectiveness of TRE in inducing weight loss, but rather an effect comparable to that of more common CR regimes. Only two studies showed a significantly higher impact of TRE on weight loss compared to CR [239, 246]. Interestingly, in the randomized controlled trial by Kotarsky and colleagues both TRE and CR groups underwent concomitant exercise training, suggesting that the use of TRE and concurrent exercise training could reduce fat mass and increase lean mass in a more favorable way than CR [239]. In two other studies, participants who underwent exercise training (such as high intensity interval training or functional training) while applying TRE achieved higher weight loss compared to those who only did TRE [247, 255]. These results reinforce the indication that a comprehensive lifestyle intervention should always include an increase in physical activity, but they also suggest that the best weight loss results are achieved by creating an energy balance that is as negative as possible. The weight loss effect of TRE may be primarily due to reduced caloric intake: indeed, a study found that patients practicing TRE reduced their energy intake by ~550 kcal/day compared to controls, without calorie counting [200]. Moreover, in a randomized controlled trial testing a 10-h isocaloric TRE (that means, a protocol in which the participants would continue to consume their usual daily calories but within a restricted time window) for 12 weeks, there was no difference in weight loss between TRE and controls [253]. Therefore, reducing calorie intake is key for weight loss.

Restricting the eating window decreases the likelihood of consuming excess calories and can yield better weight loss results, as shown in a study that compared 10-h TRE to 12-h TRE [256]: in 8 weeks both groups achieved a satisfactory weight loss compared to baseline, but there was a significant difference in favor of the 10-h TRE group. This suggests that eating windows of less than 8 h may achieve even better results, but in the study of Cinfuegos and colleagues 4-h and 6-h TRE achieved comparable results in the same 8 weeks period [200], highlighting a need for studies directly comparing TRE regimens with eating window difference higher than 2 h.

A fundamental element in dietary interventions is adherence to the diet itself. Most studies agree in defining TRE as "feasible" [257, 258]. The simplicity of not needing to count calories can be liberating for some patients, who may find it easier to follow a simple time-based guideline rather than a specific and oppressive diet plan [259]. Adherence is directly correlated with weight loss, as demonstrated by a study in which participants who adhered to TRE for more than 5 days a week achieved better results than those who did not [238]. Nowadays, technology offers new tools to incentivize adherence to therapeutic prescriptions [260]: in a study by Prasad and colleagues, participants received push notifications on their smartphones that alerted them to the opening and closing of the TRE window, achieving better weight loss results compared to controls [261]. Further studies that include these new technologies are necessary to understand if the approach is cost-effective.

In summary, TRE can be a valid alternative to CR in the treatment of obesity, as it is a regimen that in adherent patients can lead to clinically meaningful weight loss reducing overall calorie intake, but more studies are needed to define the best TRE protocol.

Cardiovascular Risk Factors

A comprehensive treatment for obesity should address not only weight loss, but also to the control of important cardiovascular risk factors such as insulin-resistance, atherogenic lipid profile and high blood pressure.

We have seen that from the "cellular" point of view TRE has the potential for ameliorating glucose metabolism. In a randomized controlled crossover trial, 11 men with obesity followed a 8-h TRE protocol and at the 5th day underwent a 24-h laboratory assessment: area under the curve

for venous glucose tended to be lower for TRE compared to controls [188], suggesting a potential role for TRE in restoring insulin-sensitivity. Other non-randomized studies showed a slight reduction in fasting glucose or Hb1Ac [262, 263], however most of the randomized controlled studies in patients with obesity but without type 2 diabetes agree that TRE do not have a significant impact on glycemic control or insulin sensitivity [188, 236, 239–243, 245, 249–253]. Differently, TRE induced a reduction in Hb1Ac when associated with physical activity (high intensity interval training) [255], but in this case the effect could be mediated by the weight loss achieved.

Evidence on TRE in obesity complicated by type 2 diabetes is less consistent. When compared to mediterranean diet, a TRE protocol specifically designed to remodulate the daily uptake of carbohydrates failed to achieve a better glycemic control after 12 weeks of treatment [264], while a 8-h TRE regimen induced a significant reduction in Hb1Ac in 6 months, comparable to that of patients that underwent a CR intervention [246]. These results suggest that a potential confounder can be also the duration of the follow-up: probably shorter interventions have less potential to determine an impact on Hb1Ac, even if insulin-sensitivity is temporarily restored. Furthermore, even if the 8-h TRE is the most studied protocol, the eating windows can vary: according to our circadian rhythm, the most effective window is likely from early morning to early afternoon, but most of the studies used the noon-to-dinner window [15].

In terms of duration of the eating window, no differences in fasting glucose were evidenced when 4-h and 6-h TRE regimens were compared [248], as well as 10-h and 12-h TRE [256]. Also in this case, there is a need for studies comparing TRE regimens with longer eating window difference.

Finally, in the context of type 2 diabetes it is also important to pay attention to possible side effects of prolonged fasting in patients using hypoglycemic drugs [199]. For insulin-dependent patients, it is reasonable to assume that insulin therapy may need to be adjusted according to the prescribed eating schedule.

As regards lipid profile, only a single-arm trial showed a reduction in LDL cholesterol with 10-h TRE in 12 weeks [262], while all randomized controlled studies agree that TRE do not induce a significant variation in LDL cholesterol [236, 237, 240, 241, 245, 248, 249, 252, 255], regardless of the duration, the type of intervention and the weight loss achieved. However, if associated with organized physical activity, TRE seems to reduce total cholesterol and triglycerides levels [247, 265] and increase HDL cholesterol [255], thus suggesting an important role for exercise rather than fasting.

In the same way, evidence from all randomized controlled trials show that TRE does not present additive beneficial effects on systolic and diastolic blood pressure when compared to other weight loss interventions in the context of obesity [236, 237, 240, 241, 245, 250–252, 255]. However, it is important to underline that also in this case TRE represents a valid alternative to CR: in the study by Liu and colleagues (that is the longest trial on TRE in obesity, lasting 12 months) 8-h TRE determined a mean 8.0 kg weight loss and a consistent reduction of 8.1 mmHg in systolic blood pressure and of 5.1 mmHg in diastolic blood pressure, slightly more (but the difference is not statistically significant) than CR [240].

Metabolic-Dysfunction Associated Steatotic Liver Disease

An emerging and interesting field of study is metabolic-dysfunction associated steatotic liver disease (MASLD), a very common and early complication in patients affected by obesity [266]. When compared to mediterranean diet, TRE seems to reduce both intrahepatic stiffness and hepatic steatosis assessed via controlled attenuation parameter (CAP) [267]. Early-TRE and late-TRE equally determined a significant reduction of intrahepatic fat and improvements in liver function [268]. However, another study measured intrahepatic triglycerides content via magnetic resonance imaging (MRI) after a period of 6 months of TRE and then after 6 months of additional follow up, showing no differences between TRE and control group [244]. In summary, TRE seems to be a dietary strategy to take into consideration also for patients with MASLD to reduce hepatic steatosis and ameliorate liver function [269], but further studies are needed.

Conclusions and Future Perspectives

Circadian misalignment is a significant risk factor for the development of metabolic diseases such as obesity, metabolic syndrome and type 2 diabetes. TRE, a dietary approach that limits food consumption to a specific window of the day, has emerged as a novel dietary strategy to face obesity and its associated metabolic complications. Fasting/feeding cycle acts as an important *zeitgeber* for peripheral clocks and restricting eating to daylight time helps restore the circadian expression of several molecular targets. TRE positively affects metabolic pathways involved in mitochondrial functions, autophagy, senescence, inflammation, insulin signaling, lipid productions and storage.

However, clinical trials examining if these effects can determine clinical benefits for people suffering from obesity have shown less consistent evidence. TRE can lead to significant weight loss compared to baseline, mainly due to reduced calorie intake. Its efficacy correlates with adherence and the duration of the fasting phase, and, in

fact, the narrower the eating window, the better the result. However, clinical trials failed to show a net benefit of TRE compared to other weight loss strategies. Regarding cardiometabolic risk factors, TRE does not appear to provide an advantage in terms of fasting glucose, lipid profile or blood pressure.

However, TRE seems to be safe and at least non-inferior to caloric restriction in terms of clinical outcomes, thus emerging as an alternative option in patients who have difficulty and poor adherence in following other dietary strategies.

The vast heterogeneity in clinical trials in terms of population, intervention and follow-up does not allow us to draw firm conclusions, thus more studies are needed to define TRE potential benefits in health and in which patients can be more effective.

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