



Chrono-nutrition for the prevention and treatment of obesity and type 2 diabetes: from mice to men

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Abstract

The proliferation in the rate of diagnosis of obesity and type 2 diabetes mellitus continues unabated, with current recommendations for primary lifestyle changes (i.e. modification to dietary patterns) having a limited impact in reducing the incidence of these metabolic diseases. Part of the reason for the failure to alter nutritional practices is that current dietary recommendations may be unrealistic for the majority of adults. Indeed, round-the-clock access to energy-dense, nutrient-poor food makes long-term changes to dietary habits challenging. Hence, there is urgent need for innovations in the delivery of evidence-based diet interventions to rescue some of the deleterious effects on circadian biology induced by our modern-day lifestyle. With the growing appreciation that the duration over which food is consumed during a day has profound effects on numerous physiological and metabolic processes, we discuss dietary protocols that modify the *timing* of food intake to deliberately alter the feeding–fasting cycle. Such chrono-nutrition functions to optimise metabolism by timing nutrient intake to the acrophases of metabolic rhythms to improve whole-body insulin sensitivity and glycaemic control, and thereby positively impact metabolic health.

Keywords Chronic energy restriction · Circadian disruption · Circadian rhythm · Diet · Food · Glycaemia · Intermittent fasting · Metabolic disease · Obesity · Review · Time-restricted eating

Abbreviations

BMAL1 Brain and muscle ARNT-like 1
CER Chronic energy restriction

CLOCK Circadian locomotor output cycles kaput
IF Intermittent fasting
IGT Impaired glucose tolerance
TRF Time-restricted feeding

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Introduction and background

The prevalence of obesity and type 2 diabetes mellitus continues to rise, with these two diseases predicted to become the biggest epidemics in history. While these conditions share some common risks (up to 80% of individuals with type 2 diabetes are obese), they are two separate diseases. Nevertheless, within the next 25 years, >600 million individuals will be diagnosed with type 2 diabetes globally, with roughly the same number developing impaired glucose tolerance (IGT), a condition that often precedes type 2 diabetes [1]. In the battle against these epidemics, North American and European Diabetes Guidelines continue to advocate primary lifestyle changes (i.e. dietary intervention and regular physical activity) as the first line of attack for the prevention and management of type 2 diabetes [2–5]. Unfortunately, knowledge and awareness that increasing physical activity and

modifying food quality and quantity can help reduce the risk for obesity and type 2 diabetes has met with limited success. Part of the reason for the failure to modify lifestyle habits is that current recommendations may be unrealistic for many adults. For example, changes in habitual dietary patterns are often considered more arduous than medical therapy [6]. Many preconceptions surround diet and exercise programmes, causing confusion and mistrust [7]. Evidence-based dietary guidelines now compete with an onslaught of real-time messages on social media from numerous celebrities (actors, chefs, personal trainers) who inevitably have no scientific training, but who willingly exploit their fame to promote their views on various ‘fad’ diets and sponsored diet products. Consequently, often the most popular, loudest and most extreme voices drown out the well informed. Here we focus the spotlight on dietary strategies that could help combat the rise in incidence of obesity and type 2 diabetes. Specifically, we consider regimens that reflect a growing appreciation that the duration over which food is consumed during a day (i.e. the feeding–fasting cycle) has profound effects on numerous physiological and metabolic processes, and that the *timing* of meals is critical for health and well-being.

Evolution of current dietary guidelines for patients with diabetes: How did we get here?

A large body of epidemiological nutrition research has assessed the relationships between the quality and quantity of food ingested on human health and well-being, and today it is generally accepted that both the macronutrient content of the diet as well as the total energy consumed are associated with disease risk, morbidity and mortality [8]. However, the association between macronutrient intake (i.e. high-fat, low-carbohydrate diets) and risk of metabolic diseases such as type 2 diabetes remains a controversial public health issue, with the scientific literature full of conflicting positions [9–11]. Support for the comparative benefits of different eating patterns in individuals with type 2 diabetes is, at best, weak, with current evidence suggesting that there is not an ideal contribution from any macronutrient to daily energy requirements for all individuals with, or at risk for diabetes [12]. Against this background, contemporary nutrition guidelines for the prevention and treatment of individuals with diabetes have evolved. Not surprisingly, these guidelines reflect many of the population recommendations for healthy nutrition, emphasising food-based goals, while simultaneously decreasing the quantity of foods and nutrients consumed to improve glycaemic control [5, 13] and metabolic health [3, 4, 14, 15].

Over the past 25 years clinical practice guidelines for the nutritional management of individuals with diabetes have moved towards a broader, more flexible macronutrient

distribution that now emphasises quality over quantity [3]. The Diabetes UK 2011 guidelines encourage better carbohydrate management to control blood glucose, with a more flexible approach to weight loss [4]. But for many individuals, the most challenging part of any dietary intervention remains ‘what, and what not to eat’ and following meal plans. While the American Diabetes Association points out that meal planning should be individualised and ‘a variety of eating patterns are acceptable for the management of type 2 diabetes’ [2], educating individual patients about nutrition is time consuming: outside of specialised multidisciplinary diabetes centres where trained nutritionists/educators are available, advice on nutrition for individuals with diabetes is generic and often difficult to translate into free-living conditions. Clearly, there is a need for innovations in the delivery of evidence-based dietary interventions that are simple to understand and easy to incorporate into daily living, such that they induce clinically beneficial health outcomes.

Circadian biology and metabolic health

Circadian rhythms are defined as ~24 h oscillations in biological and metabolic pathways. A considerable number of these daily oscillations depend on endogenous molecular clocks that control a significant portion of the genome. The circadian clock is cell autonomous and present in the majority of both animal and human tissues/organs, and is organised in a hierarchical manner with the hypothalamic suprachiasmatic nucleus (SCN) functioning as the ‘master clock’ (for review, see [16, 17]). Light is the dominant ‘zeitgeber’ (time giver) for the SCN oscillator, which in turn orchestrates rhythms in the peripheral organs/tissues at appropriate phases. At the epicentre of the molecular complex that constitutes the circadian clock are the core transcription factors CLOCK and BMAL1 that collectively drive the transcription of a large array of clock-controlled genes [16]. CLOCK and BMAL1 also orchestrate the transcription of their own repressors, period (PER) and cryptochrome (CRY), forming a self-regulated feedback loop [16]. During daylight hours, increases in the transcription of *per* and *cry* genes results in the accumulation of the PER and CRY circadian repressors: these sequentially inhibit CLOCK-/BMAL1-driven transcription of *per*, *cry* and other clock-activated genes. The regulated degradation of PER and CRY alleviates transcriptional repression and permits CLOCK-/BMAL1-mediated transcription to proceed once again, thus underpinning the recurring and rhythmic cycles in circadian gene expression [16].

In addition to light, a powerful zeitgeber on peripheral clocks is food intake. Depending on the macronutrient content of the diet, circadian cycles are reprogrammed following specialised metabolic pathways [18]. Using high-throughput metabolomics, it was shown that all mouse tissues and organs

display oscillations for more than 50% of metabolites [18, 19]. Thus, the clock controls a large array of metabolic pathways that, depending on the time of day, will be more or less attuned to coping with various nutritional impacts. Reasonably then, time of food intake affects the phase of the clocks in peripheral tissues [20]. At the cellular level, the circadian clock regulates nutrient challenges through transcription factors that modulate the expression of genes with regulatory roles in nutrient transport, uptake, utilisation and storage [16]. Feeding and fasting acutely activate nutrient-sensing pathways that act at the transcriptional and post-transcriptional levels to maintain cellular nutrient homeostasis [16, 21].

Eating patterns are affected by food availability, hunger and satiety, social habits and convenience. At the biological level, eating schedules are predominantly dictated by an inherent timing mechanism. At the behavioural level, when feeding occurs at a regular, anticipated time, the circadian clock initiates nutrient-sensing pathways to act synergistically to maintain nutrient homeostasis [21]. However, when feeding occurs at random times, these same nutrient-responsive pathways provide feedback to the circadian clocks to ‘phase shift’ so that on subsequent days food is anticipated at the new feeding time [21]. Such circadian disruption acutely impacts glycaemic control through impairments to beta cell function and insulin sensitivity, increasing the risk of developing type 2 diabetes (for review, see [22]). The importance of the circadian clock and its role in protecting against metabolic disorders is clearly demonstrated from results in genetically manipulated mouse models [23]. Mice with whole-body or tissue-specific loss of function or hypomorphic alleles of circadian genes develop profound disturbances in glucose [24] and lipid homeostasis [25] and the gut microbiome [26], predisposing them to insulin resistance and other hallmark features of metabolic disease [27]. These genetically altered mouse models display aberrant feeding patterns, suggesting that irregular/disrupted feeding schedules may underpin the metabolic abnormalities. Indeed, disruption of feeding/fasting rhythms, rewiring of circadian gene expression, or, in most cases, both, is commonly found in animal models of obesity and dysmetabolism. For example, mice with diet-induced obesity may consume food outside of their normal nocturnal window [25] and undergo metabolic and genomic reprogramming [18]. This is accompanied by changes in the oscillation of circadian clock-controlled genes involved in metabolism. As the timing of meals profoundly affects skeletal muscle insulin sensitivity, manipulating daily meal timing would appear to be a plausible strategy to help alleviate lifestyle-related diseases. Hence, ‘chrono-nutrition’ refers to food administration in coordination with the body’s daily rhythms, and reflects the notion that, in addition to the quality and quantity of food, meal timing is also critical for the well-being of an organism [16, 28].

Chrono-nutrition

Manipulation of the macronutrient composition of the diet, coupled with reductions in energy intake, have been traditional tools to improve metabolic health. However, a growing body of evidence suggests that periodic fasting and restricting the daily duration over which food is consumed can delay and often reverse the symptoms associated with metabolic disorders. Permutations in the pattern of daily food consumption in such dietary regimens are numerous [17, 29, 30] but broadly encompass three approaches: (1) sustained periods of chronic energy restriction (CER), in which daily energy intake is reduced by up to 40%, but meal frequency and timing remain unchanged; (2) intermittent fasting (IF), where one day or several days of fasting are interspersed with normal ad libitum eating patterns, and meal frequency and timing remaining unchanged on the days of food intake; and (3) time-restricted feeding (TRF), in which food is consumed ad libitum throughout a set time period. In TRF the daily eating duration (i.e. the time between the first and last energy intake) is typically reduced from a 12–14 h/day ‘eating window’ to <10 h/day. It should be emphasised that CER and IF are not chrono-nutritive therapies per se, in that they do not restrict food consumption to between specified times of day to play off of chronobiology. Instead, their therapeutic value and positive health outcomes are mainly derived from chronic or intermittent energy restriction. A comprehensive discussion of these dietary approaches and the underlying metabolic and molecular alterations they elicit is beyond the scope of this article, and the reader is referred to recent reviews [16, 29, 30–32]. A feature common to these dietary interventions is the manipulation of the feeding–fasting cycle, along with the assumption that reducing the time spent in a postprandial and postabsorptive state improves glycaemic control, and that perturbing feeding–fasting cycles drive robust oscillations in metabolism and circadian rhythms that confer health benefits [16, 17, 30, 31].

Compared with ad libitum feeding, periods of CER or IF can delay or even reverse several processes underpinning diabetes pathogenesis, such as obesity, insulin resistance, dyslipidemia and hypertension [17, 30, 32, 33]. In mice, alternate-day IF improves insulin sensitivity even without a major reduction in body weight [34] and independently of portion size and macronutrient composition [35], while TRF can reverse the progression of dysmetabolism in mice with pre-existing obesity and insulin resistance [36]. TRF also affords protection against the development of obesity from a variety of obesogenic diets [36]. Increased susceptibility of mice with mutations in genes or proteins involved in the circadian clock machinery to several metabolic disease states has led to the notion that the circadian clock is essential for cellular homeostasis and metabolic health. However, in many clock mutant mouse models, the feeding–fasting cycle is altered,

making it difficult to determine if the adverse metabolic outcomes are associated with clock mutations and/or irregular feeding patterns. In this regard, compared with mice with unrestricted access to food, clock-deficient mice with food access restricted to 9–10 h/day were protected from glucose intolerance and insulin resistance, without changes in activity or energy intake [36]. Nevertheless, while feeding–fasting cycles dictate fluxes through metabolic pathways and subsequently modulate circadian gene expression, the transcriptional response to fasting appears to operate through molecular mechanisms that are distinct from those induced by TRF. CER appears to blunt the rhythmicity of core clock genes and proteins in liver and skeletal muscle, with the rhythmic genomic response to such insults sustained for up to 48 h and then reversed by refeeding [37]. In contrast, TRF restores cyclic gene expression, even in arrhythmic mutant mice. Vollmers et al [38] monitored the effect of distinct feeding and fasting paradigms on hepatic transcription in wild-type (WT) and arrhythmic *Cry1*^{−/−}; *Cry2*^{−/−} mice [38]. They showed that both food availability and the temporal pattern of feeding determined the repertoire, phase and amplitude of the circadian transcriptome in WT liver, but in the absence of feeding only a small subset of transcripts continued to express circadian patterns. In contrast, TRF restored rhythmic transcription of hundreds of genes in oscillator-deficient mouse liver [38].

Many of the health benefits conferred from these dietary protocols elicit evolutionary conserved cellular responses that act in an organ-wide coordinated fashion to upregulate intrinsic defences against oxidative and metabolic stress, resulting in switches in substrate metabolism and enhanced cellular turnover to maintain protein homeostasis [see 17, 29, 30, 32]. Nevertheless, physiological and metabolic differences between small model organisms and humans make it hard to predict whether comparable dietary interventions impart similar physiological and metabolic effects.

From mice to men: preclinical trials of IF and TRF

Several inter-species differences need to be considered when attempting to extrapolate the results from studies undertaken in mice to human clinical populations (Fig. 1). These include, but are not limited to: (1) scaling issues related to differences in body mass/size; (2) nocturnal patterns of voluntary physical activity during the active phase in mice vs diurnal patterns of sedentary behaviour in humans (the inactive phase); (3) divergent feeding patterns in which mice typically consume their entire daily food supply in a few hours vs repeated and prolonged meals in humans, typically with 12–14 h between the first and last energy intake of the day; and (4) differences in patterns of substrate handling and oxidation, especially

during exercise, during which mice have a greater reliance on blood-borne substrates while humans rely to a greater magnitude on intramuscular fuels.

Notwithstanding differences between the species, investigations of various rodent models of disease have demonstrated that assorted protocols of CER, IF and TRF improve multiple cardiometabolic biomarkers associated with reduced obesity and type 2 diabetes risk, including improved insulin sensitivity, reduced ectopic fat accumulation, increased lean mass and reduced systemic inflammation [21, 31, 35, 37, 38]. With regard to TRF, it should be noted that this intervention has vastly different metabolic outcomes when it is undertaken in the active vs the inactive phase of the day. In *db/db* mice, compared with the inactive phase, TRF during the active phase is able to restore a normal sleep–wake cycle and also increase the duration of the sleep bout [39]. When humans ate and slept ~12 h out of phase from their habitual active vs inactive phase there were significant increases in postprandial glucose and insulin concentrations, a complete reversal of daily cortisol rhythms, increased mean arterial pressure and reduced sleep efficiency [40, 41]. Generalising the results from various animal models to human clinical cohorts is not straightforward; while animal studies provide robust evidence of ‘proof of concept’, there is currently a scarcity of long-term data from human interventions, especially in clinical populations (i.e. individuals with overweight/obesity, the metabolic syndrome and type 2 diabetes). While CER improves several cardiometabolic risk factors in nonobese humans, the data are somewhat equivocal in cohorts with various comorbidities. Several short-term studies report that IF is as effective for weight loss as standard weight-loss diets (see [29]), whereas a 12 month study that compared IF (one day on, one day off), CER and a control diet found that, although the two intervention groups lost weight, insulin sensitivity, blood lipid levels and blood pressure were not improved [42]. In secondary analyses of 43 insulin-resistant participants from that study, weight loss was not different between IF and CER interventions after 1 year, with both diet interventions having similar effects on reductions in fat mass and BMI [43]. However, IF induced greater decreases in fasting insulin and insulin sensitivity compared with both CER and the control regimen by month 12, despite a similar decrease in weight.

Gill and Panda [44] were the first to report that TRF in overweight humans induced a modest weight loss after individuals decreased their eating window from >14 to ~10 h/day for 16 weeks. Although participants in that study were not asked to change nutritional quality or quantity, food diaries revealed a 20% reduction in energy intake, making this effectively a study of CER. With a small number of participants (*n* = 8) and no control group, wider interpretation of the results of this study is limited. While other investigations confirm that TRF induces modest weight loss (see [45]), these interventions have been over the short term (≤12 weeks) with no

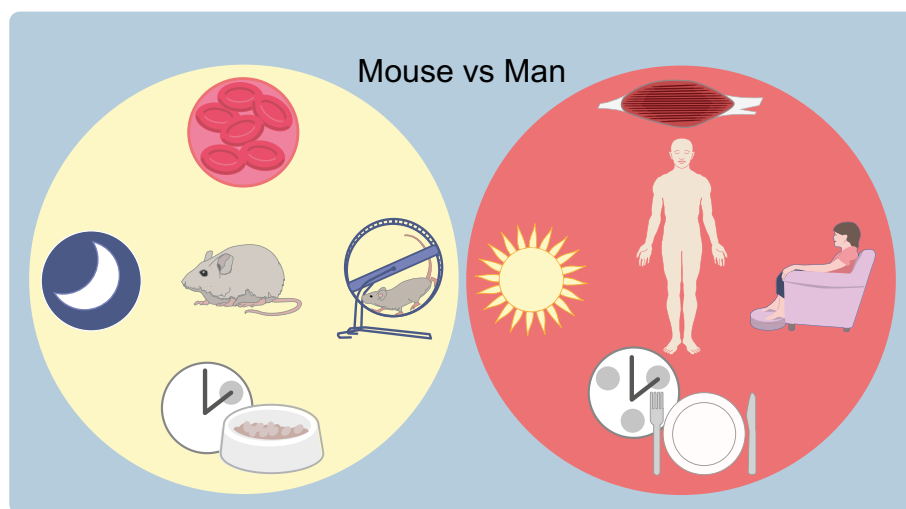


Fig. 1 From mice to men. Several inter-species differences should be considered when attempting to generalise the results from studies undertaken in various mouse models of metabolic disease to human clinical populations. These include issues relating to scaling for differences in body mass, as well as temporal patterns of nocturnal vs diurnal food intake and physical activity/inactivity, that affect substrate handling,

tissue storage profiles and whole-body metabolism. Many genetically modified mouse models provide major advantages for examining cellular and molecular mechanisms that may ultimately be of direct translational value for discovering the processes underpinning several human metabolic diseases. This figure is available as a [downloadable slide](#)

follow-up. Nevertheless, some of the health benefits of TRF appear to be independent of weight loss. Sutton et al [46] performed a 5 week, randomised, crossover, isoenergetic controlled feeding trial of early TRF (08:00–15:00 hours) vs a controlled 12 h feeding window in overweight and obese (BMI 25–50 kg/m²) adult males with elevated levels of HbA_{1c} (5.5–6.4%, 36.6–46.4 mmol/mol) and IGT. TRF augmented beta cell function, reduced blood pressure and oxidative stress [46] and improved 24 h glycaemic control [47]. However, such an extreme TRF approach in which all meals were consumed before 15:00 hours limits the applicability of these findings and the social acceptance of this protocol. In a subsequent study, Hutchison et al [48] studied the effects of 7 days of early TRF (08:00–17:00 hours every day) vs delayed TRF (12:00–21:00 hours every day) in men at risk for type 2 diabetes who were overweight or obese. Both TRF protocols improved glucose tolerance and fasting triacylglycerols independent of the time that TRF was initiated. Recently, Parr et al [45] determined the effects of TRF (8 h/day, meals consumed at 10:00, 13:00 and 17:00 hours) vs extended feeding (15 h/day, consuming meals at 07:00, 14:00 and 21:00 hours) on 24 h and postprandial metabolism in men who were overweight or obese. TRF improved nocturnal and postprandial blood glucose control and this protocol was well accepted by the men who participated in the study [45].

While TRF reduces the risks of metabolic diseases in individuals with overweight/obesity, type 2 diabetes patients often undergo pharmacotherapy in conjunction with lifestyle interventions. Wilkinson et al [49] assessed whether TRF can act synergistically with standard medical care in a small cohort of patients with the metabolic syndrome who had an unrestricted

eating pattern (14 h/day). They showed that TRF (10 h/day for 12 weeks) reduced waist circumference and whole-body and visceral fat, lowered blood pressure and decreased HbA_{1c} [49], indicating an additive effect of TRF to standard medical practice to treat metabolic diseases. Finally, we have recently reported that there is a time-of-day and meal-composition dependence of reprogramming of the human metabolome by divergent nutritional challenges. The overall effect of different nutritional challenges on the serum and skeletal muscle metabolome was a distinct rewiring of the morning vs evening metabolic profiles in response to both the timing and type of dietary challenge [50]. The identification of metabolomics ‘signatures’ unique to each individual in response to different dietary interventions may guide the discovery of diagnostic and mechanistic biomarkers so that clinicians can monitor perturbations in individual metabolic states. Such ‘personalised medicine’ may be a critical first step in providing information to underpin clinical therapeutic strategies and may help to ‘fine-tune’ chrono-nutritional approaches to assist in the management of chronic disease states such as obesity and type 2 diabetes.

Time for a change?

The current ‘obesogenic’ environment presents numerous challenges for individuals attempting to adhere to strict dietary regimens. Indeed, long-term changes in habitual dietary patterns are typically considered to be more demanding than medical therapy. While there exists an extensive menu of dietary options available to improve metabolic health

outcomes, their success/failure, as with any lifestyle intervention, depends on long-term adherence. In most societies there is a long-held belief that it is important to eat three or more meals per day on a regular basis, so changes to this traditional pattern of intake would likely be met by resistance. The abundance and ready access to food, along with manipulative marketing strategies to promote ‘miracle diets’ conspire to make changes to dietary habits improbable. Hence, there is a need to implement dietary approaches that are socially acceptable, feasible and achievable over the long term. While energy-restricted diets (CER, IF) confer rapid and favourable changes to a multitude of biomarkers of health and disease risk, long-term compliance is challenging. While data from studies of time-restricted eating in animals and a small number of clinical populations are encouraging, there is a need for multicentre, randomised clinical trials of comparisons between different eating patterns across a range of human cohorts to determine the most efficacious intervention. In addition to conventional biomarkers of health, these investigations should assess psychological, emotional, cognitive and social consequences of altered timing of meals. Finally, the time has come for dietary guidelines worldwide to acknowledge that in addition to the quality and quantity of food consumed, the *timing* of meals is a critical determinant of metabolic health. Improving patient education and raising awareness that the timing of eating carries metabolic implications should be part of the arsenal of weapons at the disposal of healthcare professionals in the fight against the current diabetes epidemic.

Note added in proof As this review was going to press, we were shocked and saddened to learn of the sudden and unexpected passing of our friend, colleague and collaborator, Professor Paolo Sassone-Corsi. We both feel privileged to have had the opportunity to work with Paolo and witness at first hand a brilliant mind, a passion for the pursuit of scientific excellence, and generous mentorship. Paolo was an extraordinary talent and will be missed by many in the fields of epigenetics, circadian biology and metabolism. We will endeavour to finish the work we started, in his memory. *John A. Hawley and Juleen R. Zierath*

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