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Sutton E, Beyl R, Early K, Cefalu W, Ravussin E, Peterson C. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. Cell Metabolism. 2018;27(6):1212-1221.e3.

What We Know, Think We Know, or Are Starting to Know

In rodent models, restricting access to food to their biological day/activity period prevents against cardiometabolic disease, effects that occur independent of energy intake as the restricted feeding time protects rodents from high-fat rodent diets designed to induce adiposity [1-5]. These rodent models, together with emerging human research suggest that the interaction between timing of food intake and metabolic function is mediated by circadian rhythms*.

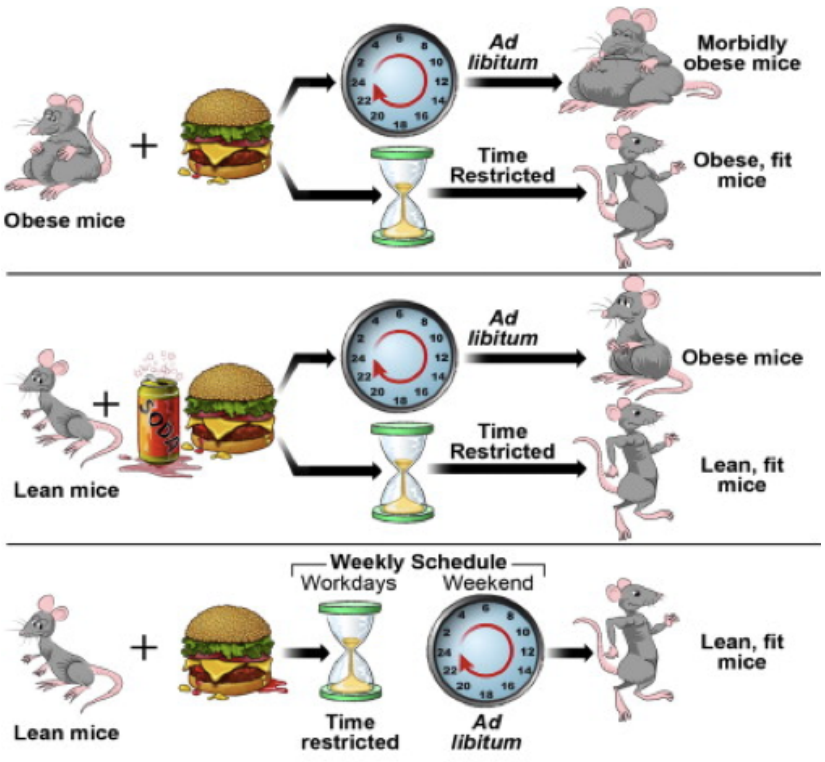

***Figure** taken from Chaix et al. [1] illustrating benefits to time-restricted feeding demonstrated in animal models using various TRF regimens.*

*Geek Box: Circadian Rhythms

What are 'circadian rhythms'? The term 'circadian' is derived from the Latin 'circa', meaning 'around', and 'diem', meaning 'day': 'around the day'. Circadian rhythms provide an organisation to internal physiological processes, and are synchronised with our external environment. Circadian rhythms are considered an evolutionary advantage, as they allow an organism to anticipate changes in its environment. This allows an organism to anticipate and coordinate the appropriate responses relative to the time of day, for example desire to sleep in the evening, or appetite in the morning (in humans, of course...some animals are nocturnal!).

In humans, light is the most potent signal to synchronise our internal circadian rhythms with the external environment. The suprachiasmatic nucleus [SCN], located in the hypothalamus, is the master circadian control centre. In the eye, specialised cells contain a light receptor, known as melanopsin, which detects and responds to light, and relays these signals directly to the SCN through a dedicated pathway. These specialised cells, and the "master clock" in the SCN, are maximally sensitive to blue light with a short wavelength of 460-480 nanometres [nm]. This wavelength, which provides the blue colouring for the natural daytime sky, provides the primary daily signal for the master circadian clock by activating "CLOCK" [and "BMAL1"] genes in the SCN, which are responsible for generating the 24-hour circadian rhythms in cellular and endocrine processes.

However, although light is the primary entraining signal to the SCN, circadian rhythms in peripheral tissues – including the intestines, liver, heart, lung, adrenals, and adipose tissue – are synced through other external periodical time-cues, including meal timing and physical activity. Peripheral tissues have their own self-sustaining circadian rhythms, and also require input from the master clock to maintain rhythmicity. Their self-sustaining rhythms are also synchronised through meal timing and the cycle of feeding/fasting, which intertwines with the light/dark cycle. Meal timing is thus one of the most important external time-cues and synchronisers for peripheral tissues.

From a nutritional perspective, the waking period is also the period of food procurement and intake, and the processes involved in coordinating appetite, hunger, digestion, absorption, and utilisation of nutrients, are aligned with this period for optimal metabolic function [(6)]. Emerging literature suggests metabolic health may be influenced by timing of food intake. Controlled lab studies have shown that glucose tolerance varies over the course of the day, with glucose disposal amplified in the early biological day and reduced in the biological evening [(7)].

Circadian "clocks" in the pancreas enhance insulin action during the waking and feeding period, however, timing in glucose rhythms in the liver can be shifted by late meal timing [8]. Carbohydrate oxidation decreases significantly as a result of circadian dysregulation and late meal timing [7,9]. Late meal timing and distribution of daily energy intake may not be conducive to metabolic health, and emerging data in humans suggests that consumption of greater proportions of daily energy in the evening [>4pm] results in negative metabolic effects [9,10].

Cumulatively, emerging human research suggests both a restriction on eating duration and the timing of food intake, with potentially preferential effects to earlier distribution of a larger proportion of total daily energy, may benefit metabolic health. The degree to which these effects occur independent of weight loss is less clear.

The Study

8 overweight men [mean BMI 32] with prediabetes [mean fasting blood glucose of 102mg/dL] completed a randomised, controlled feeding, crossover trial where subjects underwent 5-weeks on an early time-restricted feeding [eTRF] protocol which confined 3 meals daily to a 6-hour eating window between 6.30am-1pm. Thus, breakfast at 7am was followed by 'lunch' at 10am and 'dinner' at 1pm. The eTRF intervention was followed by a 7-week washout, before subjects crossed over to a 12-hour daily eating period for a further 5-weeks which served as the control eating schedule, where breakfast time remained constant and lunch and dinner consumed at 1pm and 7pm, respectively.

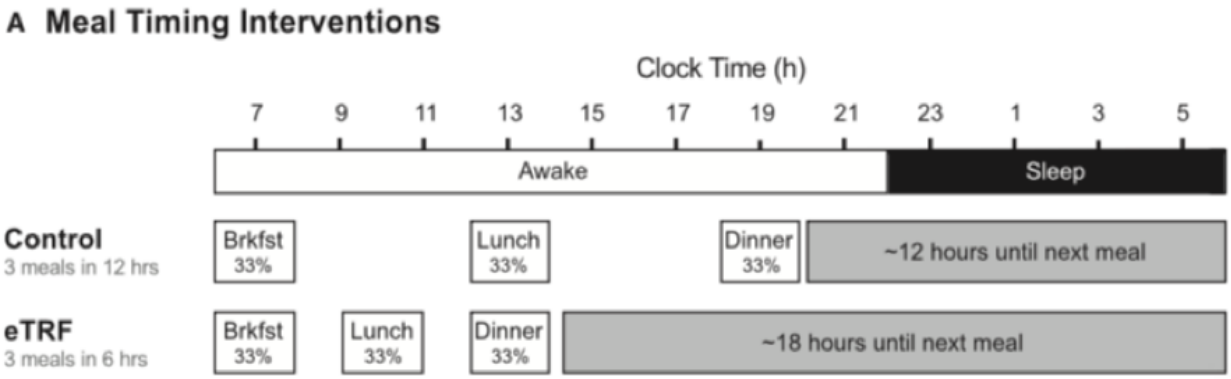

Figure *from paper illustrating study design.*

The three meals each contained 33% daily energy [see above illustration], and the macronutrient composition of the diets were 50% carbohydrate, 35% fat, and 15% protein. The outcome measures included glycaemic control [including fasting blood glucose, post-prandial glucose, insulin, and beta-cell function*], lipids, blood pressure, arterial stiffness, oxidative stress, inflammation, and subjective appetite.

*Geek Box: Beta-Cells and Diabetes

Beta-cells of the pancreas release insulin in response to increases in blood glucose after a meal. Although insulin resistance, i.e., the diminished capacity of peripheral tissues to take in glucose, occurs early in the progression of glucose intolerant states, it is eventual failure of beta-cells that is considered the crux of type-2 diabetes as once beta-cells have failed, the ability to generate healthy insulin responses is lost (whereas factors like physical activity and pharmacotherapy can increase glucose uptake and improve insulin resistance). Dietary interventions may therefore improve glycaemic control, like low-carb diets, but may not restore beta-cell function. To date, the only interventions that restore beta-cell function involve massive weight loss – circa.15kg – with some promising emerging research on the use of very-low calorie liquid diets for 8-weeks achieving this effect. However, measuring beta-cell function is not easily achieved by using simple blood glucose regulation tests. This is just something to bear in mind when a study purports to find improved beta-cell function: the method used to quantify this will be important. More on this below...

Results: The most significant findings - statistically and clinically - were lowered insulin levels both in a fasted state and after meals [measured via Oral Glucose Tolerance Test, where 75g pure glucose is provided in a fasted state, and blood measures taken after] conditions. Post-prandial insulin levels were lower at 60min, 120min, and 180min with eTRF compared to the control diet. The mean reduction of 29mU/L could translate to significant reductions in metabolic disease risk over time, given the associations between fasting and post-prandial insulin as predictors of progression for cardiometabolic disease [11,12]. Larger studies would be needed confirm the reliability of the effect size in this respect. While the magnitude of this effect appeared to be driven by subjects with higher insulin levels at baseline, 7/8 subjects had at least a 5uM/L reduction in mean post-prandial insulin. There was no difference in fasting or post-prandial glucose levels.

There was also a significant reduction in blood pressure, with an 11mmHg and 10mmHg reduction in systolic and diastolic blood pressure, respectively. This could be mediated by the reduction in insulin, given associations between high insulin levels and high blood pressure [13]. The authors also suggest that coinciding salt intake with peak circadian sodium excretion in the daytime may have been a variable, however, no details are presented regarding the sodium content of the intervention diets.

Oxidative stress* was also significantly reduced, which is an important finding given the role of oxidative stress interacting with high post-prandial blood glucose levels to influence endothelial dysfunction [14]. Given the very short 6hr eating window in this study, it is possible that the reduced daily post-prandial duration may be the factor underscoring reductions in oxidative stress.

There were also significant reductions in subjective appetite, and increases in circulating triglycerides, both of which are discussed below. There was no difference in blood cholesterol [although subjects had normal levels at baseline], arterial stiffness, or inflammatory markers.

*Geek Box: Oxidative Stress

You've likely heard this term, and you've definitely heard the term 'antioxidant' but what do they really mean? In order to live, we breathe oxygen, eat food, convert that food into fuels (requires oxygen), do physical activities (requires oxygen), and use up energy in these processes (did I mention these processes require oxygen?!). However, all of these processes come at some cost insofar as they create waste products, known as reactive ***oxygen*** *species (ROS), which are 'pro-oxidants'. Thankfully, evolution didn't leave us hanging, and developed internal systems to neutralise these compounds: our 'anti-oxidant' defence systems, a network of inbuilt factors coupled with external compounds – like vitamins E and C – obtained from the diet. The production of pro-oxidants is a fact of life: literally life is not possible without generating them. In normal, healthy individuals, these products will be neutralised and eliminated by our anti-oxidant systems. However, 'oxidative stress' occurs where the capacities of these anti-oxidant systems are exceeded by the production of pro-oxidants. For example, poor diet quality – specifically low fruit and vegetable intake – smoking, and inactivity, may all exacerbate pro-oxidant levels while also failing to provide appropriate support to internal anti-oxidant defences. Oxidative stress is emerging as a characteristic of major disease progression.*

The Critical Breakdown

Pros: Compliance both with eating the provided meals and timing of meals was as good as it gets in a nutrition intervention. The meals were prepared in a research kitchen, provided and consumed while monitored by study staff. Energy intake was matched across meals and diets, minimising any confounding effect of meal size and second-meal metabolism effects [i.e., the influence of size and composition of a preceding meal on responses to subsequent meals]. Despite the small sample size, the study retained statistical power.

Cons: Although a positive result in the trial, the improvement in pancreatic beta-cell function may be interpreted with some caution, as beta-cell responsiveness was determined by an Oral Glucose Tolerance Test. While this method is a more convenient and easier to administer test, it is not a robust a measure of beta-cell function [compared to, for example, a hyperglycaemic clamp] [15]. Thus, it is difficult to have full confidence in the finding regarding beta-cell function. The study itself was very small, in an all-male sample. While not a 'con' per se, studies of such methodological rigour may have little practical application in free-living conditions. The testing did not match fasting duration between intervention and control, meaning the intervention phase had fasted for 18-hours prior to testing, compared to 12-hours in the control phase, which may have influenced the results in relation to glucose regulation and triglycerides.

Key Characteristic

The key feature of this study's design was the maintenance of energy balance in subjects, to prevent weight loss, and energy intake over the course of the study was adjusted to maintain weight. In this respect, the study is the strongest controlled trial thus far examining whether benefits to Time Restricted Feeding - and earlier timing of food intake - occur in humans independent of weight loss. Watch this space!

Interesting Finding

The reduction in appetite in the evening in the eTRF group may seem counterintuitive given the last meal was consumed at 1pm. This seems even more counterintuitive when we consider the circadian rhythm of ghrelin, which is the gut-derived hormone with a role in hunger signalling, which peaks in the evening corresponding to around 7pm [16]. This fact has been used in support of suggestions that humans are predisposed to consume more energy in the evening.

However, a couple of trials in humans have found that greater energy intake earlier in the day reduces ghrelin levels [17], including the present study. This suggests the behavioural distribution of energy to the early part of the day may influence the circadian rhythm in ghrelin, and reduce hunger later in the day.

The other interesting finding was the significant increase in circulating triglycerides in the eTRF condition. This may not necessarily be pathological, as circulating free fatty acids and triglycerides both exhibit circadian rhythmicity, peaking during the biological night [18]. Given the extended fasting duration from earlier in the day, the elevation in TG's observed from testing could reflect increased substrate availability from fat breakdown and mobilisation. It could also be a reflection of the different time in a fasted state prior to testing on the intervention [18hrs] compared to the control [12hrs].

Relevance

The eTRF intervention had no effect on body weight, confirming we are not mice: energy balance remains fundamental. However, the timing of food intake does appear to influence metabolic health, observed in this study of prediabetic men and in another RCT in metabolically healthy, lean women comparing an earlier [1.30pm] to later [4pm] timing of lunch [9]. This is important given the habitual pattern of energy consumption in the UK population has up to 46% of daily energy consumed in the evening [19].

The macronutrient profile in this study reflects current UK National Diet and Nutrition Survey data, indicating that modification of food timing may yield beneficial results without significant dietary composition overhaul (often difficult in the real world). We don' t know whether there would have been any material difference to a larger window, for example 10hrs. This is something to be addressed in future research.

Application to Practice

The design itself is clearly of limited real-world application given the rigorous control. It should also be noted that subjects found the 6-hour window difficult [although did not find the 18-hour fast difficult]. However, there are some principles which can be applied in a more general context:

1. Distributing a greater proportion of daily energy to the early part of the day may be beneficial, particularly in subjects with metabolic risk factors. Encouraging more substantial breakfasts and lunches may reduce appetite in the evening, facilitating lower overall evening energy consumption.

2. The time-restricted period in this study is unlikely to be 'user friendly' in free-living conditions. However, advice to follow a more achievable 10-hour or 11-hour window may be effective, particularly if the net effect is an earlier timing of dinner and a reduction in late-night snacking.

In sum, more daily energy earlier in the day coupled with a slight reduction in eating duration may be a more applicable interpretation and application of this interesting, methodologically rigorous study.

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