HHS Public Access

Author manuscript

J Physiol. Author manuscript; available in PMC 2022 February 16.

Published in final edited form as:

J Physiol. 2022 February ; 600(4): 699–700. doi:10.1113/JP281358.

Time Restricted Feeding Plus Exercise, Could Two Be Better than One for Metabolic Health?

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Daily coordinated rhythms in the metabolic activity of various organs are in part controlled by the circadian clock system comprised of a central clock in the hypothalamus and secondary clocks in peripheral tissues. Functionally, the circadian system allows organisms to anticipate events from one day to the next and maintain temporal separation of incompatible processes (e.g., anabolic and catabolic processes). A combination of living mostly indoors, nighttime illumination, expanded work hours, and 24h food availability has weakened the relationship of the internal circadian system to the external environment leading to delayed and dampened rhythms. As a result, many adults are going to bed later, sleeping shorter, and have adopted an erratic eating pattern where energy is consumed across most clock hours; behaviors that are linked to the development of obesity and diabetes.

One strategy to compensate for a compromised circadian rhythm is to impose time-restricted feeding (**TRF**), a dietary paradigm in which access to food is limited to an 8–10-hour period during the active phase leading to a prolonged fasting period (e.g., > 14h per 24h). Pre-clinical studies have demonstrated that TRF prevents the adverse effects of high fat diet-induced metabolic diseases independent of caloric intake and macronutrient composition, (Chaix *et al.*, 2019b) even in rodents lacking a functional circadian system.(Chaix *et al.*, 2019a) Findings from these studies have led to an explosion in efforts to translate TRF interventions (or more appropriately, time-restricted eating interventions in humans; **TRE**) to clinical populations. As of this publication, there are > 30 studies of TRF/TRE registered on clinicaltrials.gov that are actively recruiting. Conditions under investigation are diverse, ranging from obesity to cancer.

In practice, diet interventions are rarely prescribed in isolation, rather they are almost always combined with recommendations for physical activity. In this issue of the *Journal of Physiology*, Vieira *et al.*,(Vieira *et al.*, 2021) take the first steps towards understanding how the TRF paradigm interacts with combined exercise training, a cornerstone therapy

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AUTHOR CONTRIBUTIONS: A.C. and C.A.R. drafted the manuscript and approved the final version.

DISCLOSURE: No conflicts of interest, financial or otherwise, are declared by the authors.

for the treatment of lifestyle-related diseases. Specifically, Vieira *et al.* aimed to tease out differences in metabolic outcomes and mechanistic underpinnings among TRF alone and TRF combined with exercise in a rodent model, a topic that to our knowledge has not been addressed by any prior pre-clinical study.

Both TRF and exercise have pleiotropic effects on nearly all organs systems, likely with some overlapping mechanisms.(Piercy *et al.*, 2018; Chaix *et al.*, 2019b) Yet, it is tempting to speculate that they also each have tissue-specific and pathway-specific mechanisms of action (e.g., stimulation of mitochondrial biogenesis would be stronger with exercise) that could convey additive benefits and would lead to a more robust therapeutic response when combined. Perhaps, TRF and exercise can even potentiate each other leading to synergistic benefits.

The study conducted by Vieira *et al.*, consisted of a 10-week experiment in which 4-week-old male Swiss mice were divided into four groups, 1) a standard chow diet *ad libitum* group, 2) a high-fat diet *ad libitum* group, 3) a high-fat diet group on 8h TRF during the dark/active phase, and 4) a group of mice on 8h TRF plus aerobic exercise training at the end of the feeding period [between 30–60min of treadmill exercise at 60% of baseline exhaustion velocity, performed 7d/week between zeitgeber time 0 (lights on) and zeitgeber time 1]. At the conclusion of the 10-week intervention, measures of insulin sensitivity, energy expenditure, and markers of liver metabolism were compared among the groups. Similar to previous studies, the authors report attenuated weight gain, increased fat oxidation, and decreased markers of fatty liver in mice receiving TRF alone compared to the control groups. The authors go on to report that TRF combined with exercise training led to a slightly less weight gain and potentially additive benefits to insulin sensitivity and liver metabolism, although adequately powered studies are needed to clarify these findings.

The pilot study by Vieira *et al.*, establishes a foundation for future investigation into many outstanding and interesting questions. For example, what are the specific independent and combined benefits of TRF alone, exercise alone or TRF plus exercise on the prevention of weight gain and metabolic disorders? Will the combination of TRF and exercise be superior for the therapeutic management of established obesity and metabolic disease? What are the organs at play and the molecular drivers of these benefits? In addition, what is the optimal timing of a combined TRF and exercise intervention for maximal benefits?

Vieira *et al.*, are to be applauded for breaking ground on this important topic, but there is still much work ahead on both the pre-clinical and clinical fronts. Adequately powered studies in rodents are needed to understand both the convergent and divergent pathways across relevant organ systems affected by TRF and exercise, respectively. While the study by Vieira focused primarily on liver metabolism and glucose homeostasis, future studies should consider other outcomes such as those relevant to cancer, aging, etc. Considerable thought should also be given to study designs that can help to inform the development of future clinical studies. Pre-clinical efforts should address potential sex-differences by repeating studies in female rodents. Finally, clinical researchers already conducting TRE studies should start to collect pilot data on the exercise behaviors (e.g., duration, intensity, and timing) of participants to begin to understand how a future TRE plus exercise intervention might be tolerated

over the long term. This is especially important since many indicators of a viable lifestyle intervention (e.g., tolerance and compliance) can only be evaluated in clinical studies.

In conclusion, we are enthusiastic about the potential health benefits of combining TRF and exercise since at the very least one strategy might be able to compensate for occasional non-compliance in the other. At the very best, the two strategies will have complementary and perhaps even synergistic benefits.

GRANTS:

This work was supported by grants from the National Institutes of Health (NIH) K01 DK113063 to CAR and R01 AG065993 to AC and from the American Heart Association (AHA) 18CDA34110292 to AC.

REFERENCES:

Chaix A, Lin T, Le HD, Chang MW & Panda S (2019a). Time-Restricted Feeding Prevents Obesity and Metabolic Syndrome in Mice Lacking a Circadian Clock. Cell Metab 29, 303–319.e304. [PubMed: 30174302]

Chaix A, Manoogian ENC, Melkani GC & Panda S (2019b). Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases. Annu Rev Nutr 39, 291–315. [PubMed: 31180809]

Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM & Olson RD (2018). The Physical Activity Guidelines for Americans. JAMA 320, 2020–2028. [PubMed: 30418471]

Vieira R, Munoz V, Junqueira F, Gaspar R, Nakandakari S, Costa S, Torsoni M, da Silva A, Cintra D, de Moura L, Ropelle E, Zaghloul I, Mekary R & Pauli J (2021). Time-restricted feeding combined with aerobic exercise training can prevent weight gain and improve metabolic disorders in mice fed a high-fat diet. J Physiol.