Editorial Commentary

Time-restricted feeding: what we have done and what more we can do?

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Obesity and other metabolic syndromes such as hypertension, type 2 diabetes, and hyperlipidemia remain a major public health burden worldwide. Apart from higher incidence of cardiovascular diseases, obesity and other abnormal metabolic status also promote cancer development and poor prognosis of cancer patients (1-3). In addition to using different surgical modalities (4), weight management through lifestyle changes has proven to be a more economical and low-risk approach. For obese patients, whether daily caloric intake can be reasonably restricted is recognized as an important strategy for solving their problem. In the past few years, intermittent fasting (IF), especially time-restricted feeding (TRF), has shown good clinical weight loss effect (>5% loss from baseline) (5). Moreover, people who participate in IF or TRF can often show good compliance, because compared with traditional dieting, IF or TRF does not require participants to record the specific calories of each meal in detail, participants only need to eat within the specified time period and not have any caloric intake at any other time. Moreover, the time period of eating can also be flexibly controlled by the participants, which is more in line with the living habits of different participants. Therefore, dietary modification is a more effective and promising approach to deal with the current overall global burden of metabolic syndrome.

Although IF and TRF are becoming increasingly popular, even many people who are not obese choose to use these diets to maintain their body weight, there are currently still few studies that have investigated the benefits and risks of these diets in humans. Moreover, the specific mechanism by which IF and TRF affect body weight is still unclear. Whether TRF readjusts the patient's biological rhythm and whether this effect is beneficial or harmful is still controversial.

Regardless of the controversy, it has been widely demonstrated that IF and TRF can reduce patient body weight and improve related metabolic markers such as Hb1Ac, HOMA-IR and serum cholesterol. Chow *et al.* demonstrated that TRF can effectively reduce the weight of obese and overweight people within 8–12 weeks, and reduced approximately 0.2–0.5 kg of body weight per week. The application of TRF in insulin-resistant people showed similar effect of weight loss (6-8). However, the weight loss through IF and TRF is mainly fat weight, lean body weight only accounts for about 25% of total weight loss.

Although IF and TRF for a short period of time can significantly reduce body weight in obese and overweight patients, whether the same effect can be maintained for a longer period of time has been debated for some time. A single-center, double-blind, randomized controlled study by Liu *et al.* evaluated the effect of TRF on long-term (12 months) weight loss and effects of metabolic risk factors. The findings suggest that for obese patients, TRF can maintain weight loss over a longer period of time (9).

The effects of TRF on blood pressure, blood lipids, and glucose metabolism indicators have not been consistent in different studies. Some studies showed a reduction in blood pressure compared to baseline (10), but several other studies did not see similar effects (6,11). However, trials showing blood pressure reduction involved participants with elevated baseline blood pressure. Therefore, TRF may only help lower blood pressure in hypertensive or borderline hypertensive patients at the beginning of treatment. Changes in LDL cholesterol levels also had conflict results in different studies, some studies showed a reduction in LDL compared to baseline levels (12), but others showed no change. Due to the limited number of relevant studies to date, it is difficult to determine whether and to what extent lipid lowering varies by patient baseline body mass index (BMI) and serum lipid level or duration of intervention (6,10). In most studies of TRF, participants with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) were not involved, and no significant changes in fasting glucose levels were seen in these studies (6-8,10,11). However, fasting insulin levels were significantly lower than baseline in most studies. Additionally, the effects of TRF on insulin resistance and insulin sensitivity vary widely, with some studies showing improvements but most showing no effects.

Considering that many healthy people would also use TRF for body weight controlling, the effectiveness and safety in healthy population is another important issue, Xie *et al.* carried out a 5-week TRF study involving 90 healthy volunteers (13) showed that TRF do not result in an increased frequency of constipation, diarrhoea, nausea, irritability, fatigue or dizziness, nor cause digestive system diseases such as peptic ulcer and gallstones. The only side effect observed in the experiment is that participants will feel unbearable hunger in the early stage of the experiment, but it can disappear after 1–2 weeks of adaptation.

Although there was no significant difference in weight loss between TRF and calorie control alone during a long period of follow-up (9), the regulation and impact of TRF on circadian rhythm still needs further elucidation. In previous studies, mice with rhythm gene defects showed obvious obesity and gene-specific metabolic abnormalities, but TRF feeding can effectively improve the metabolic state of rhythm gene-deficient mice (14). In the study of healthy people, it was also found that TRF can significantly affect BMAL1, PER1, PER2, SIRT1 gene expression rhythm (13). Deota *et al.* recently conducted single-cell sequencing by collecting different tissues (stomach, small intestine, muscle, heart, brain, liver, etc.) of mice fed with TRF, and found that TRF profoundly affects the rhythm gene expression of different tissues of mice. Nearly 80% of genes showed differential expression or rhythmicity in at least one tissue (15). The function of these changes reveals tissue- and pathway-specific effects of TRF and indirectly explains those conflicting results shown in human trials.

In conclusion, IF and TRF have obvious effects in reducing body weight and improving metabolic status, with the advantages of good compliance and easy implementation and management. However, more clinical trials are needed to verify the safety and effectiveness of T1DM and T2DM patients. At present, single-cell sequencing technology has initially revealed the specific influence of TRF on biological rhythms, and more in-depth mechanism exploration is one of the future directions. Finally, energy metabolism not only affects metabolic syndrome, but for patients with acute pancreatitis, sepsis, and cancer, reasonable energy supply will have a favorable impact on their prognosis. Therefore, can TRF bring profit to these patients is the direction worthy of attention in the future.

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Footnote

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