TIME-RESTRICTED NUTRITION AS A NEW STRATEGY FOR THE THERAPY OF OBESITY AND COMORBID CONDITIONS

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ABSTRACT

This manuscript reviews the current literature examining time-restricted eating (TRE) as a tool for treating obesity and comorbid conditions. The search for new nutritional strategies for the treatment of obesity, one of which is POM, is due to the poor adherence of patients to hypocaloric diets in the long term, as well as existing data on the important role of desynchronization of food intake with natural circadian rhythms in the development and progression of obesity and cardiometabolic complications. The article describes the basic mechanisms that regulate circadian rhythms of food intake and nutrient absorption, and substantiates the importance of maintaining a physiological diet to maintain metabolic health. The main part of the review is devoted to the consideration of currently available studies on the effectiveness of various strategies of intermittent energy restriction for reducing body weight and correcting metabolic parameters. Potential mechanisms of the effect of SEM on health are discussed, including those mediated by an unintentional reduction in calorie intake and changes in eating behavior, and differences in the effectiveness of early and late SEM. The article contains an in-depth discussion of the potential problems and controversies associated with the introduction of time-restricted feeding into clinical practice, namely the limited and inconsistent clinical trials available, the lack of data on long-term effectiveness and safety, and the social and psychological limitations that hinder the widespread use of RFE.

Keywords: obesity; time-limited meals; intermittent fasting.

RELEVANCE

Obesity is a disease whose prevalence has now reached epidemic proportions and poses a real threat to public health and public health. The incidence of obesity has been progressively increasing over the past decades: from 1975 to 2016. The proportion of the world's population that is obese has increased from 5 to 13% and amounted to more than 650 million people worldwide [1]. According to WHO forecasts, by 2025 the number of obese patients will double and will account for 30–50% of the population of economically developed countries [1]. Obesity can be defined as a chronic heterogeneous systemic disease that develops as a result of an imbalance in energy intake and expenditure, characterized by excessive accumulation of adipose tissue and accompanied by a high cardiometabolic risk. Adipose tissue, and primarily visceral fat, in addition to its storage function, plays an important role in the regulation of carbohydrate and fat metabolism, as well as the development of cardiometabolic disorders and complications associated with obesity. Adipose tissue is an independent endocrine organ, the dysfunction of which, which occurs in obesity, causes the occurrence of insulin resistance, pro-inflammatory, pro-atherogenic and prothrombogenic conditions, the progression of which leads to an increased risk of developing type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular diseases (CVD). Given the widespread prevalence of obesity and comorbid conditions, it is difficult to overestimate the importance of effective treatment of obesity, the main goal of which is, undoubtedly, to reduce morbidity and mortality from CVD, T2DM and their complications. Since the main causes of obesity are excess caloric intake of food combined with a decrease in energy expenditure, including as a result of insufficient physical activity, the basis of treatment is a balanced anti-atherogenic hypocaloric diet. Moderate caloric restriction (15–30% of baseline) is the most common approach recommended to combat obesity [2]. There is no doubt that lifestyle modification, including a healthy diet, is an integral part of the treatment of obesity. However, low patient adherence to recommendations aimed at changing the quality and calorie content of the diet using hypocaloric diets causes the low effectiveness of the measures taken [3, 4]. Moreover, these strategies are difficult to maintain over the long term, so their effectiveness in reducing cardiometabolic risks in obese patients is limited. In recent years, evidence has been accumulating that, in addition to the total calorie intake of the diet, adherence to a diet is important in regulating energy metabolism, reducing and maintaining body weight, and improving cardiometabolic parameters. In the modern world, irregular nutrition, and eating throughout most of the day (eating window greater than 14–15 h) are common [5, 6] and may be associated with obesity, T2DM, metabolic syndrome, and CVD [7, 8]. It has been shown that more than 50% of people eat for a period of >15 h each day and only about 10% of

adults typically fast for ≥12 h during the day [6]. In an American population of patients with metabolic syndrome, the eating window, defined as the time interval during which 95% of all food-related events occur, was approximately 15 hours [9]. Irregular meal times have also been demonstrated to negatively impact cardiometabolic health [7]. A discrepancy between diet and natural circadian rhythm leads to metabolic dysregulation and increased cardiometabolic risks [10–13]. Thus, the search for new effective nutritional strategies aimed at treating obesity, metabolic syndrome and related diseases remains relevant. Some of the dietary approaches that have become increasingly popular in recent years deserve special attention given the accumulating evidence base for their positive effects on body weight and cardiometabolic parameters. In particular, strategies of interest are those that focus not on the type, quality, or quantity of foods, but primarily on the timing of meals and the length of the fasting period: so-called intermittent fasting and time-restricted eating (TRE). These approaches, aimed at normalizing circadian rhythms by changing the timing and duration of daily meals, may represent a promising strategy for patients with obesity and metabolic syndrome [14–18]. CIRCADIAN REGULATION OF FOOD EATING AND METABOLISM Circadian rhythms are periodic fluctuations in the internal biological mechanisms that determine behavior and metabolic processes, such as sleep and wakefulness, performance, hormonal signals, body temperature, nutrient intake and absorption [19]. Regulation of circadian rhythms is carried out by a system of central and peripheral mechanisms. The central component of regulation includes the suprachiasmatic nucleus of the hypothalamus (SCN), which acts as the main stimulator of the synthesis and maintenance of the body's circadian rhythm. The most powerful regulator of circadian rhythms under central control is light. The retina detects photonic inputs and converts them into the SCN, allowing the activity and metabolism of tissues and organs to be synchronized with the day/night cycle. These circadian oscillations are generated by proteins encoded by a set of genes (e.g., Clock, Bmal1, Per, and Cry) that constitute a transcriptional-translational feedback loop [20]. One cycle of this feedback loop takes approximately 24 hours and is the basis of circadian rhythms in many organisms, including humans. In addition to the central clock, circadian rhythms are influenced by peripheral clocks (such as those of the liver, pancreas, adipocytes, etc.), which are not directly stimulated by light [19]. Unlike the SCN, the peripheral clock is extremely sensitive to the food/fast cycle and can be desynchronized with the central clock as a result of changes in feeding patterns. For example, restricting food access to the light phase in mice, when these nocturnal animals typically sleep, completely alters the phase of the circadian clock in the liver, stomach, intestines, heart, pancreas, and kidneys without affecting the SCN [21]. Simply delaying food intake for 4 hours also results in a phase shift of the circadian clock in the mouse liver of a similar

duration [22]. Conversely, studies have shown that rhythmic feeding is sufficient to maintain circadian rhythms of clock genes in peripheral tissues during periods of constant light or darkness or after SCN lesions [23, 24].

CONCLUSION

The growing pandemic of obesity and related cardiovascular diseases dictates the need to search for new modern, effective and safe tools for reducing body weight, incl. nutritional strategies. In recent years, more and more attention has been paid to intermittent energy restriction (IER), which is being studied as an effective measure to combat obesity and comorbid conditions, including in comparison with the traditional approach involving a healthy hypocaloric diet. Studies in animal models and trials in humans show that POM can have beneficial effects on body weight, body composition, cardiovascular parameters and, in some cases, eating behavior. However, the studies available to date are characterized by small size and significant heterogeneity of samples, short duration of observations, vary greatly in the nutritional protocols used and the duration of periods of fasting/feeding, and generally show mixed results. In particular, it cannot be denied that the positive effects of SOM can be mediated by a decrease in calorie intake against the background of these nutritional patterns.

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