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Intermittent fasting – a novel approach to treating overweight and obesity? – meta-analysis and literature review

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ABSTRACT

Introduction

Intermittent fasting (IF) is a form of dietary intervention that includes periods of regular calorie intake alternated with periods of fasting. IF has gained a lot of attention as a potential approach to treating metabolic syndrome-related diseases. Therefore, health care professionals need to be able to provide their patients with evidence-based information on IF. The aim of this article is to review data on effectiveness of IF in weight loss, especially in comparison with calorie restriction.

Methods

PubMed and Google Scholar databases were searched for studies published from 1.01.2017 to 31.12.2022 that included phrases “intermittent fasting” or “alternate day fasting”, “intermittent fasting obesity”, “alternate day fasting obesity”. Intervention studies on obese or overweight patients were included. We excluded studies of short duration and studies that focused on intercurrent medical conditions. In total, 14 articles that suited those criteria were identified.

Results

Intermittent fasting induces pronounced metabolic changes in the body due to strict and time-limited restriction of calorie intake and in animal models was proved to prolong lifespan and modulate tumorigenesis and aging. It is a proposed new approach to treating obesity, which is a a major risk factor for cardiovascular diseases and diabetes.

Conclusions

In our study, IF was found as effective, but not superior to calorie restriction in reducing body mass, improving body composition and reducing other cardiometabolic risk factors. Our findings are consistent with other recent systematic reviews. Further research is needed to directly compare various IF regimens and determine patients’ characteristics that may be associated with more successful implementation of intermittent fasting regimens.

Keywords: intermittent fasting, alternate day fasting, time-restricted eating, calorie restriction, weight loss, obesity

INTRODUCTION

Intermittent fasting (IF) is a form of dietary intervention that includes periods of regular calorie intake alternated with periods of fasting [1]. IF has recently gained a lot of public attention as a potential nutrition approach to treating metabolic syndrome-related diseases such as obesity, insulin resistance and diabetes mellitus [2]. Furthermore, IF has been proposed as a way to promote longevity through anti-aging mechanisms [3]. Some studies suggest that as a potential nutrition approach against obesity and metabolic disease IF may be as effective as a more traditional dietary approach, calorie restriction (CR). Nevertheless, the effects of IF in the general population remain to be fully evaluated [4]. Given that IF is currently a controversial subject of public debate, healthcare professionals need to be able to provide their patients with evidence-based information on its effectiveness and applicability in treating overweight and obesity.

AIM OF STUDY

The aim of this article is to provide information on intermittent fasting as a novel dietary approach. Furthermore, we sought to review data on effectiveness of intermittent fasting in treating overweight and obesity, especially in comparison with a more traditional dietary approach, calorie restriction.

REVIEW METHODS

In January 2023, PubMed and Google Scholar databases were searched for studies published from 1.01.2017 to 31.12.2022 that included phrases “intermittent fasting” or “alternate day fasting”, “intermittent fasting obesity”, “alternate fasting obesity”. In the review, only intervention studies on obese or overweight (body mass index [BMI] of ≥ 25 kg/m²) patients were included. We excluded studies of short duration (<3 weeks) and studies that focused on intercurrent medical conditions. In total, 14 articles that suited those criteria were identified.

STATE OF KNOWLEDGE

Intermittent fasting. The term “intermittent fasting” includes a wide variety of nutrition patterns that differ both in length and strictness of the fasting periods. Three main types of IF are: alternate day fasting, complete alternate day fasting and time-restricted fasting. Main differences between those nutrition protocols are summarized in Table 1. [5,6,7,8].

Table 1. Main intermittent fasting protocols

IF protocol	Description
Complete alternate day fasting	24-hour periods of unlimited* food intake alternated with 24-hour periods of strict fasting, that can be repeated during the week in a pre-established proportion.
Alternate day fasting (ADF)	24-hour periods of unlimited* food intake alternated with 24-hour periods during which 20-25% of daily energy demand may be consumed in one meal.
Time-restricted fasting (TRF)	Diurnal alterations of fasting and normal calorie intake, such as 20-hour fast followed by 4 hours of eating or 16-hour fasting followed by a 8-hour period of regular calorie intake.

* Depending on the protocol used, calorie intake may be ad libitum or designed to reach a certain goal, for example 125% daily calorie demand [9].

Intermittent fasting differs from CR, as the main goal of IF is not decreased calorie intake [5]. Recent research has been mainly focused on examining pleiotropic effects of IF on metabolic health [2,10].

Physiology of intermittent fasting. Intermittent fasting regimen is known to induce pronounced metabolic changes in the body due to strict and time-limited restriction of calorie intake [11]. Most data on metabolic effects of IF is derived from studies on animal models, in which prolonged lifespan was mainly associated with long (24-hour) periods of fasting [12]. Shifts in metabolic patterns during the fasting periods are often described as “metabolic switch” [13]. Various studies have shown that the “metabolic switch” induced by IF may have a positive impact on metabolism and longevity [7,14]. Glucose, which normally is a main energy source for most tissues of the body, in IF is elevated only a few hours after the end of food intake, and remains low during fasting periods. Refraining from eating leads to the consumption of glycogen reserves and activates gluconeogenesis. Insulin is a leading hormone during the fed time, as it allows the body to use absorbed glucose as a source of energy. In fasting periods of IF insulin and insulin-like growth hormone-1 levels remain low and glucagon level is elevated [15].

The aforementioned “metabolic switch” occurs typically 12 hours after last calorie intake and is characterized by negative energy balance due to the depletion of glycogen reserves in the liver. This leads to the rise of ketone body levels as energy is derived from

transformation of triglycerides to fatty acids and glycerol [9]. An example of ketone body is beta-hydroxybutyrate, which is a signaling metabolite known to elicit several direct and indirect molecular responses, such as reduction of oxidative stress, inflammation, tumorigenesis and aging [16,17].

Multiple pathways are advocated to mediate those effects, for example activation of AMP-activated protein kinase (AMPK) and decrease of cellular levels of ATP, which lead to inhibition of anabolic pathways and stimulation of catabolic autophagy [14]. Other possible mechanisms include inhibition of mTOR pathway due to a decrease in circulating levels of glucose and amino acids, as well as elevated levels of ketone bodies. mTOR pathway inhibition leads to prolonged lifespan in experimental animals, as it increases mitochondrial biogenesis and autophagy and reduces sympathetic tone [9, 14]. Increased autophagy is an especially important mechanism, as the removal of damaged cells is associated with prolonged longevity and anti-aging in animal models [18]. Catabolic state that occurs during fasting time in IF is advocated to be crucial for effective autophagy as opposed to anabolic post-prandial state that is associated with regular calorie intake [19].

Anton et al. suggest that fatty acids and ketones, which are a main source of energy during fasting time, may promote multiple positive effects on various body tissues by inducing synthesis of fibroblast growth factor 21 (FGF21). Metabolic switching may also result in the more pronounced expression of other factors, such as brain-derived neurotrophic factor (BDNF), nuclear factor κ B (NF- κ B) and cyclic AMP response element-binding protein (CREB). Those cellular pathways are associated with reduced inflammation, increased autophagy and reduced aging [14]. Thus, diseases associated with aging, inflammation and abnormal cellular proliferation such as cardiovascular diseases, cancer, type 2 diabetes mellitus, dementia and autoimmune diseases may be alleviated by ketogenesis and the activation of above mentioned ketone-induced pathways. Furthermore, ketone body production is also associated with more immediate effects such as decreased appetite, augmentation of lipolysis and improved physical and mental performance [20].

What is important, evolution mechanisms that adapt the human body to periods of fasting preserve muscle mass and function and energy is derived from fat tissue. Ketones may promote conservation of proteins by inhibition of oxidation of branched chain amino acids, mainly in individuals with increased amount of fat tissue [21]. Thus, IF regimens that lead to metabolic switch may lead to the improvement of body composition, especially in overweight and obese patients [14].

To conclude, research that has been mainly conducted on animal models, shows that catabolic state that occurs during fasting time may prove beneficial not only in treating obesity, but also in autoimmune diseases, neoplasms, diabetes mellitus and dementia. Further research in humans is needed to prove this data. As this article focuses mainly on IF's applicability in treating overweight and obesity, it is important to note that weight loss is usually achieved not only by dietary intervention, but with a multi-focal approach that consists also of psychological support and increased physical activity [22].

Weight loss and obesity. Obesity, defined as body mass index greater than or equal 30 ($BMI \geq 30 \text{ kg/m}^2$), is a major risk factor for cardiovascular diseases and diabetes [23] and

is associated with increased risk of death due to COVID-19 infection [24]. Obesity is a result of excessive calorie intake, which is not balanced by physical activity and leads to the accumulation of fat tissue [25]. Multiple factors contribute to the development of obesity: eating patterns, level of physical activity, genetics, environmental factors and socioeconomic statute [26]. Recently, a study on a representative sample of adult inhabitants of Poland was conducted to determine the prevalence of overweight and obesity in the Polish population. Of 1831 adults included in the study, 42.2% were overweight, whereas 16.4% were obese [27]. Results of this study indicate a high incidence of overweight and obesity in the Polish population. Therefore, health care professionals should be aware of possible ways to effectively reduce body weight.

Most common approach to treating obesity is increased physical activity combined with the restriction of calorie intake (CR) [22]. CR is an established intervention in treating obesity and prolonged CR is proven to induce not only weight loss, but also to reduce various cardiovascular risk factors and improve insulin sensitivity [28]. Nevertheless, as adherence to CR decreases over time, weight regain is a common problem [28,29]. Thus IF, which is a novel dietary approach, is an incentive alternative to CR, as the intermittent nature of fasting may be better tolerated than constant hunger associated with caloric restriction. Moreover, according to some studies, adherence to IF may be better than to CR as IF does not necessarily demand counting and restricting calories everyday [30].

REVIEW

Study characteristics. Recently a few studies have been conducted to evaluate the effectiveness of intermittent fasting on body weight reduction. Authors identified 14 articles that compared various IF regimens to either CR or to no intervention group or other IF protocol. Analysis included studies of duration from 4 to 26 weeks (median= 12 weeks). Number of participants who completed the studies ranged from 15 to 144 (n=843). Mean age of participants ranged from 34.5 to 56 years. Studies on overweight and obese participants were included in the analysis, with BMI range from 27.8 to 37.1 kg/m². Various IF protocols were applied in the studies. 10 studies used alternate day fasting protocols, with the number of fasting days per week ranging from 2 to 3 and 20-25% of estimated daily calorie requirement allowed on fast days [31-40]. Of 10 studies that used ADF protocol, we identified nine [31,32;33-40] that used calorie restriction (CR) as a comparator diet to ADF. One study compared ADF to ADF combined with exercise and exercise without dietary regimen [35]. No studies included complete alternate day fasting protocols. Of 4 studies that used time-restricted fasting protocols, 1 study compared 8-hour feast 16-hour fast diet [41] to no restriction eating, 1 study compared 8-hour feast 12-hour fast diet to consistent meal timing [42] and 2 studies used other TRF protocols as comparator [43,44]. High-protein diet was implemented in one study [32]. Main characteristics of reviewed articles are summarized in Table 2.

Table 2. Main characteristics of reviewed articles.

Study identification	Number of participants	Mean BMI (kg/m ²)	Mean age	Duration of the study	IF protocol; study design
Antoni et al., 2018 [31]	15 (7 male, 8 female)	29.8±0.9 (IF) 30.8±1.1 (CR)	42±4 (IF) 48±3 (CR)	Until 5% weight loss is reached	ADF (25% of caloric need 2d/w and no calorie restriction 5d/w) vs. CR
Browen et al., 2018 [32]	135	36.0±6.0	40±8	16 weeks	High-protein ADF (600 kcal 3 d/w + 1200 kcal 3 d/w + no calorie intake restriction 1d/w) vs. high-protein meal replacement diet with CR
Cho et al., 2019 [33]	31	28.0 (IF+exercise) 27.8 (IF only)	34.5 (IF+exercise) 33.5 (IF only)	8 weeks	ADF and exercise vs. ADF only vs. exercise only vs. no intervention; ADF protocol: 25% of EER* 3d/w
Coutinho et al., 2018 [34]	28 (22 female, 6 male)	36.0±4.0	39±9	12 weeks	ADF (550 to 660 kcal/d 3d/w + no calorie intake restriction 4d/w) vs. CR
Schübel et al., 2018 [35]	114	32.0 (IF) 31.1 (ad libitum)	32.0±3.8 (IF) 31.1±3.6 (ad libitum) 31.2±4.0 (CR)	12 weeks	ADF (25% of EER 2d/w, no calorie restriction 5d/w) vs. CR vs. control group
Sundfør et al., 2018 [36]	112 (56 female, 56 male)	35.2	49.9	26 weeks	ADF (20% of EER 2d/wk, + no calorie restriction 5d/wk) vs CR
Trzepanowski et al., 2017 [37]	69 (57 female, 12 male)	35.0±4.0	44±11	26 weeks	ADF (25% of EER on fast days and 125% of EER on feast days) vs. CR vs. control group
Beaulieu et al., 2021 [38]	46 (all female)	29.1±2.3	35±10	12 weeks	ADF (25% of EER 3d/w + no calorie restriction 4d/w) vs. CR
Steger et al., 2021 [39]	30	31.2±2.4	45.6±10.7	12 weeks	ADF (550 to 800 kcal/d 3d/w + no calorie restriction 4 d/w)
Pinto et al., 2020 [40]	43 (31 female, 12 male)	31.8±4.5 (IF) 31.1±5.7 (CR)	50±12 (IF) 56±8 (CR)	4 weeks	ADF (600 kcal/d 2d/w + no calorie restriction 5d/w) vs. CR
Chow et al., 2020 [41]	20 (17 female, 3 male)	33.8±7.6 (IF) 34.4±7.8 (control)	45.5±12.1	12 weeks	TRF (16-h fasting, 8-h no restriction eating window)

					daily) vs. no restriction (non-time restricted eating)
Lowe et al., 2020 [42]	116 (46 female, 70 male)	32.7±4.2	46.5±10.5	12 weeks	TRF (8-h no caloric restriction and 12-h fast) vs. consistent meal timing (3 meals/d + snacks allowed)
Cienfuegos et al., 2020 [43]	49	37.0±1.0 (IF) 36.0± (control)	47±3 (IF) 45±2(control)	8 weeks	TRF (18-h fasting + 6-h eating window) vs. ADF (20-h fasting and 4-h eating window) vs. no intervention
Peeke et al., 2021 [44]	60	33.5±5.2	44±11	8 weeks	TRF (14-h fasting and a snack of 200 kcal + 10-h eating window) vs. TRF (12-h fast and 12-h eating window)

*EER- estimated energy requirement

Weight loss. The percentage of weight loss observed in the reviewed studies varied depending on duration of the study and applied ADF/TRF protocols. No statistical difference in the percentage of weight loss was found in any of the studies that compared IF to CR regimen [31-32; 34-40] ($p>0.05$). Hence, ADF was proved as efficient, but not superior to CR protocols as a dietary regimen for weight loss in overweight and obese patients. ADF combined with physical exercise was proved more effective than physical exercise without dietary intervention in reducing body mass [33] which indicates that ADF is an effective dietary protocol that may be combined with other weight loss interventions. Of 10 studies that applied alternate day fasting protocols, Coutinho et al. [34] observed highest percentage of weight loss both in participants randomized to ADF (12.97%) and to CR (12.10%) dietary regimens, whereas Pinto et al. [40] reported lowest percentage of weight loss in ADF and CR groups (2.05 and 3.36%, respectively). In this case, more pronounced weight loss was reported in the study of longer duration. We identified four studies of 12-week duration that compared ADF to CR. The percentage of weight loss in those studies varied from 6.03 to 12.97% and 5.2 to 12.10% in the ADF and CR groups respectively [34,35,38,39]. Mean weight loss observed in those interventions was $9.02\% \pm 2.7$ and $8.69\% \pm 3.29$ in the ADF and CR groups respectively. Similar ADF and CR protocols were used in the 12-week studies that observed highest [34] and lowest [38] weight loss in the ADF group in the 12-week intervention. In those studies, more pronounced weight loss was observed in the study on participants with higher initial BMI. Of two 26-week studies that used ADF protocols, one observed 8.4% and 8.6% weight loss in ADF and CR groups respectively [36], and the other 5.81 and 4.83% weight loss in ADF and CR groups respectively [37]. Mean weight loss observed in those studies was $7.11 \pm 1.3\%$ and $6.72 \pm 1.9\%$ in ADF and CR groups respectively. In

this case, the difference in weight loss was not associated with higher initial BMI of the participants. Four studies that applied various time-restricted feeding protocols reported weight loss percentages that ranged from 0.95% to 8.5% in participants randomized to TRF regimen (mean=4.63±2.83%) [41-44]. Of those studies, Peeke et al. reported highest percentage of weight loss in both studied TRF protocols (8.5 and 7.34% in 10:14 and 12:12 regimens respectively) and statistically important superiority of 10:14 regiment in weight reduction [44], whereas Lowe et al. reported lowest percentage of weight loss in the intervention group (0.95%) [42]. Of the studies that applied TRF protocols, least pronounced weight loss was obtained by using a protocol that allowed 8 hours of no restriction calorie intake alternated with 12-hour fast [42] and 10-hour feast 14-hour fast diet was most effective in weight reduction [44].

Other parameters. Besides weight loss, other indicators of metabolic health were analyzed in the revised studies. Antoni et al. reported that intermittent fasting was statistically more effective in reduction of postprandial lipaemia than CR [31]. Aside from that, IF was comparably efficient in reduction of cardiometabolic risk factors and improvement of body composition [31,32;34-36;39-44] (for detailed information see Table 3. below). Coutinho et al. reported that compensatory mechanisms induced by weight loss did not differ between IF and CR group [34]. Schübel et al. and Sundfør et al. reported similar weight loss maintenance in both studied dietary regimens [35,36]. Trepanowski et al. described higher rate of attrition and weaker adherence to predetermined calorie intake in the participants randomized to ADF regimen compared to CR regimen [37], whereas Steger et al. reported similar adherence and retention in both studied groups [39]. Sundfør et al. and Beaulieu et al. reported that IF may be a less favorable dietary pattern in patients with more pronounced hunger and poor control of food cravings [36, 38] Percentage of obtained weight loss and key results of the revised studies are summarized in Table 3.

Table 3. Main results of the revised articles.

Study identification	Weight loss (%)	Weight loss in the control group (CR/no intervention, %)	Key results
Antoni et al., 2018 [31]	-5.30% (median time to 5% weight loss: 59d)	-5.01% (CR; 2510 kJ below EER)(median time to 5% weight loss:73 d)	1. No statistical difference in: body composition, postprandial glycaemia, comparable reduction of insulinemia, time to reach 5% weight loss in both groups. 2. IF is superior in reducing postprandial lipaemia.
Browen et al., 2018 [32]	-10.64%	-11.24%	1. High protein diets combined with CR and IF+CR are equally effective in body weight reduction. 2. Improvement of metabolic and

			nutritional markers and sustained 10% weight loss to six months did not differ statistically in both groups.
Cho et al., 2019 [33]	-5.00%	-2.1 (exercise only, no dietary intervention)	<p>1. Physical exercise has a more pronounced effect on cholesterol metabolism than weight reduction or calorie restriction</p> <p>2. Exercise with or without ADF improves cholesterol metabolism.</p> <p>3. IF combined with exercise is associated with greater weight loss than exercise without dietary intervention.</p>
Coutinho et al., 2018 [34]	-12.97%	-12.10% (CR: 33% energy restriction basen on EER)	<p>1. IF and CR lead to comparable weight loss and fat reduction</p> <p>2. Compensatory mechanisms induced by weight loss (for example reduced resting metabolic rate and increased appetite) did not differ between IF and CR groups.</p>
Schübel et al., 2018 [35]	-7.10%	-5.20% (CR:80% of estimated energy requirement)	<p>1. Weight loss and maintenance is similar in IF and CR.</p> <p>2. IF may be equivalent, but not superior, to CR in weight loss and prevention of metabolic diseases.</p>
Sundfør et al., 2018 [36]	-8.4%	-8.6% (CR)	<p>1. IF and CR resulted in comparable weight loss, weight loss maintenance and improvement of cardiovascular risk factors at 1-year follow up.</p> <p>2. IF may be associated with a more pronounced feeling of hunger.</p>
Trzepanowski et al., 2017 [37]	-5.81%	-4.83% (CR:75% of estimated energy requirement)	<p>1. IF promotes weight loss and weight maintenance similar to CR.</p> <p>2. Adherence to predetermined calorie intake was weaker in ADF group than in CR group.</p> <p>3. The rate of attrition was significantly higher in ADF group as compared to CR group.</p>
Beaulieu et al., 2021 [38]	-6.03%	-5.60% (CR: 25% energy restriction)	<p>1. Weight loss was comparable in CR and IF group.</p>

			<p>2. Hunger was more pronounced in IF group and worse control of food cravings was obtained compared to CR. IF may be less favourable than CR to control hunger and food cravings.</p> <p>3. Fast days in IF group were associated with less physical activity.</p>
Steger et al., 2021 [39]	-9.98%	-11.86% (CR: 1200-1600 kcal/d)	<p>1. IF is a feasible alternative to CR for weight loss and improvement of body composition.</p> <p>2. Thorough lifestyle changes and continuous support are indispensable for effective behavior changes.</p> <p>3. Adherence and retention were similar in CR and IF groups.</p>
Pinto et al., 2020 [40]	-2.05%	-3.36% (CR: reduce weekly energy intake by 3500 kcal)	<p>1. Short-term IF and CR diets result in comparable changes in cardiometabolic risk, increased insulin sensitivity and reduction of inflammatory markers, lipids, sympathetic tone and ambulatory blood pressure.</p>
Chow et al., 2020 [41]	-3.18%	-0.79% (no calorie restriction)	<p>1. Time-restricted eating (TRE) led to significantly greater restriction of eating time compared to non-restriction group (9.9 hours in TRE group, 15.1 in non-TRE group).</p> <p>2. TRE led to weight loss, improved body composition and decrease in eating occasions.</p> <p>3. TRE may be a simplified dietary intervention that reduces weight and leads to better food cravings control.</p>
Lowe et al., 2020 [42]	-0.95%	-0.69% (consistent meal timing, CMT: no calorie restriction, 3 structured meals per day, snacks allowed)	<p>1. Weight loss was modest, but statistically important in TRE group.</p> <p>2. There was no statistical difference in weight loss between CMT and IF group.</p> <p>3. TRE, in the absence of other interventions, is not more effective in weight loss than eating throughout a day with 3 structured meals and snacks.</p>

<p>Cienfuegos et al., 2020 [43]</p>	<p>-3.20%</p>	<p>-0.10% (no calorie restriction)</p>	<p>1. Both TRF protocols were comparably effective in the reduction of body weight, insulin resistance and oxidative stress.</p> <p>2. Energy intake was reduced by ~550 kcal/day in both ADF groups.</p>
<p>Peeke et al., 2021 [44]</p>	<p>-8.50%</p>	<p>-7.34% (12:12 ADF)</p>	<p>1. 14:10 TRF group there was a statistically significant weight loss and improvement of fasting blood glucose compared to 12:12 ADF group.</p> <p>2. Both 14:10 and 12:12 TRF programs resulted in statistically important reduction of fasting blood glucose at baseline.</p>

CONCLUSIONS

This study found no statistical difference in the percentage of weight loss obtained with IF regimens as compared to CR. IF was found as effective, but not superior to calorie restriction in reducing body mass, improving body composition and reducing other cardiometabolic risk factors such as glycemia, blood pressure or oxidative stress. Our findings are consistent with other recent systematic reviews [45, 46, 47, 48]. In the revised articles, IF regimens were well-tolerated and no major adverse events were reported. Recent study on safety of intermittent fasting in obese patients reported that IF did not provoke binge-eating patterns or purgative behavior, and improved body image and mood [49]. Furthermore, IF regimens led to overall calorie restriction without calorie counting and reduced eating window [41,43]. To the contrary, in some of the studies more pronounced hunger and food cravings were reported [36,38]. Other possible adverse reactions to fasting included dizziness, feeling of cold, headache, constipation and sleeping problems, but their intensity did not statistically differ from baseline [34,36,38,39,49]. Therefore, IF may be a promising alternative to calorie reduction in a selected group of patients that have good cravings control and do not have time or resources to count calories or depend on commercially-obtained dietary programs. IF is a simplified dietary regimen and, since a wide variety of intermittent fasting protocols is available, it may be a promising new approach in patients who have already tried other weight loss programs and are discouraged from calorie-counting regimens. The heterogeneity of intermittent fasting protocols leaves it an open discussion as to which is most effective, and decisions should be made individually for each patient. Further research is needed to directly compare various IF regimens and determine patients' characteristics that may be associated with more successful implementation of intermittent fasting regimens. Health care professionals should bare in mind that the approach to treating overweight and obesity should be multifocal, with intensive lifestyle changes, increased physical activity and continuous psychological support [50].

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