ARCHIVOS LATINOAMERICANOS DE NUTRICIÓN
Revista de la Sociedad Latinoamericana de Nutrición
https://doi.org/10.37527/2023.73.1.006

Vol. 73 N° 1; enero - marzo 2023
Artículo de Revisión

Intermittent fasting for health care, a review

Valentina, Espinoza[1], Carolina, Alarcón[1], Yaroleth, Contreras[1], Fabiana, Sepúlveda[1], Emilia, Bustos[2], Angelica Palisi[3], Sharon, Viscardi[4,5].

Abstract: Intermittent fasting for health care, a review. The incidence of obesity and overweight in the world has been increasing in recent years due to poor diet and lack of physical activity; people suffering obesity and overweight, related with malnutrition due to excess, often resort to calorie restriction diets that are usually not very effective. In this context, intermittent fasting (IF) has become popular due to the possibilities for weight loss that it offers. This diet consists of alternating periods of fasting with unrestricted eating; however, its effectiveness and consequences are unknown to most users. This narrative review analyzes whether intermittent fasting contributes to the improvement of body and metabolic composition. The purpose of the review was to examine the available data on the contribution of intermittent fasting to the improvement of body and metabolic composition, in order to provide information and to define the parameters that condition safe achievement of its benefits. IF dieting triggers adaptive cell responses that cause a decrease in lipid oxidative stress markers in individuals with obesity and prediabetes. Metabolic alterations have been found to go hand in hand with the alteration of circadian rhythms; if IF contributes to this effect, it may assist in treating and preventing obesity and associated diseases. However, there are also disadvantages, such as the loss of lean muscle mass by wasting, and increased hypoglycemia. **Arch Latinoam Nutr 2023; 73(1): 60-73.**

Keywords: Intermittent fasting, calorie restriction, time-restricted fasting.

Resumen: El ayuno intermitente, ¿un éxito o una desventaja para el cuidado de la salud?. La incidencia de obesidad y sobrepeso en el mundo ha ido en aumento en los últimos años debido a la mala alimentación y la falta de actividad física; Las personas que padecen obesidad y sobrepeso, relacionadas con la desnutrición por exceso, suelen recurrir a dietas de restricción calórica que suelen ser poco efectivas. En este contexto, el ayuno intermitente (AI) se ha popularizado debido a las posibilidades de pérdida de peso que ofrece. Esta dieta consiste en alternar períodos de ayuno con alimentación sin restricciones; sin embargo, su eficacia y consecuencias son desconocidas para la mayoría de los usuarios. Esta revisión narrativa analiza si el ayuno intermitente contribuye a la mejora de la composición corporal y metabólica. El objetivo de la revisión fue examinar los datos disponibles sobre la contribución del ayuno intermitente a la mejora de la composición corporal y metabólica, con el fin de aportar información y definir los parámetros que condicionan la consecución segura de sus beneficios. Se ha encontrado que las alteraciones metabólicas van de la mano con la alteración de los ritmos circadianos; si AI contribuye a este efecto, puede ayudar a tratar y prevenir la obesidad y las enfermedades asociadas. Sin embargo, también existen desventajas, como la pérdida de masa muscular magra por atrofia y el aumento de la hipoglucemia. **Arch Latinoam Nutr 2023; 73(1): 60-73.**

Palabras clave: ayuno intermitente, restricción calórica, ayuno con restricción de tiempo.

Introduction

Obesity and overweight have increased in Chile in recent years, due to the greater availability of food and the lack of physical activity. In 2010, the overweight and obese population was 64 %, while in 2020 the estimate gives a figure of 74.2 % (1). Malnutrition due to excess and associated unhealthy lifestyles are the main causes of chronic diseases in Chile, representing the highest and fastest-growing health risk (2,3). Weight loss and improving body composition have formed the

[1]Departamento de Procesos Diagnósticos y Evaluación, Facultad de Ciencias de la Salud, Universidad Católica de Temuco, Temuco, La Araucanía, Chile. [2]Escuela de medicina, Facultad de Ciencias, Universidad Mayor, Avenida Alemania 281, Temuco, La Araucanía, Chile. [3]Ministry of Education, Universities and Research (MIUR), Italy. [4]Núcleo de Investigación en Producción Alimentaria, Facultad de Recursos Naturales, Universidad Católica de Temuco, P.O. Box 15-D, Temuco, Chile. [5]Functional Foods Laboratory, Camino Sanquilco, Parcela 18, Padre Las Casas, La Araucanía, Chile.
Autor para la correspondencia: Dr. Sharon Viscardi, E-mail: sviscardi@uct.cl

mainstay of the treatment of malnutrition due to excess, based on providing education about healthy lifestyles and the implementation of diets based on calorie restriction. Unfortunately, these methods do not achieve the necessary adherence, which normally falls off within 1-4 months, resulting in significant weight recovery within one year (4). In this context, a new method of calorie restriction known as intermittent fasting (IF) has emerged, this promises better adherence and quicker results.

IF is a type of calorie-restricted eating protocol that focuses on when meals can be consumed (5), a practice that has in fact existed for a long time, mostly associated with religious and cultural traditions (6). This is the case of the Ramadan Fast, a form of intermittent fasting adhered to by adult Muslims throughout the world every year, when they modify their habits to eat exclusively at night for an entire lunar month (7).

Two other variations of fasting are well known: alternate-day fasting and early time-restricted fasting. Alternate day fasting consists of 24-hour fasts followed by a 24-hour eating period, and can be practiced several times a week, while time-restricted or early time-restricted fasting are programs that include variations of fasting periods that can last 16, 18 or 20 hours, with eating limited to the remaining time (5). Partial results from short-term studies concerning IF indicate that participants lose 3% to 7% of body weight after 2 to 3 months of alternate-day fasting, and experience improvements in metabolic parameters (8). One of the most important metabolic changes that occur during fasting periods is the depletion of glucose as a fuel source and the shift to the use of fatty acids and ketone bodies for energy; the latter acquire vital importance since they regulate the expression and activity of many proteins and molecules that influence health and aging (9). Most studies of IF have focused on weight loss as the primary goal, under the conception that the primary health benefit arises from this change (8); however, while this new eating protocol has many benefits, its drawbacks are not insignificant, as it is not recommended for everyone and can be dangerous (10). Among its drawbacks, this change in eating pattern is usually accompanied in its initial stages by problems such as bad mood, fatigue or dizziness, since the body needs to adapt to the use of ketones. Moreover, this type of diet is contraindicated in people with hypoglycemia or who are undergoing hypoglycemic treatments since it can generate severe hypoglycemia, incidence of which increases with age and can even result in death (10).

This narrative review analyzes whether intermittent fasting contributes to the improvement of body and metabolic composition. The purpose of the review was to examine the available data on the contribution of intermittent fasting to the improvement of body and metabolic composition, in order to provide information and to define the parameters that condition safe achievement of its benefits.

Material and methods

A review of the available literature on the different types of existing intermittent fasting methods and their general effects on health was carried out, analyzing their metabolic benefits, effectiveness in weight loss and possible contraindications. To limit the scope of this research, data on pregnant adults, infants and growing children were omitted.

Literature Search Strategies

Databases such as PubMed and Google Scholar were used in the search, and randomized controlled trials, published reviews and meta-analyses were included. The search was restricted to publications in English, using search terms such as intermittent fasting, calorie restriction, adult obesity, time-restricted fasting, fasting calorie restriction, eating times, among others. The initial search date was March 2021 and the last update was added on October 27, 2021.

Inclusion and exclusion criteria

The included studies were review articles and randomized controlled trials with the following characteristics: (1) Population: adults aged 18 years or older; (2) Interventions and publications: daily fasting periods from 12 to 20 hours; (3) Results: data on change in at least one of the following parameters: weight, blood pressure, insulin, glucose, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol; (4) Nutritional status: Overweight or obesity; (5) Language of publication: English.

Studies with the following characteristics were excluded: (1) articles on animal studies or *in vitro* experiments; (2) studies with a population of pregnant and/or lactating adults; (3) subjects under 18 years of age.

Intermittent fasting and body weight loss

Intermittent Fasting (IF) is an eating pattern that involves eating during 'windows' separated by defined fasting periods (greater than 12 to 48 hours or more) (11). Many people consider this a less restrictive method than traditional calorie restriction (CR) methods, as it involves alternating normal daily calorie intake with brief periods of strict calorie restriction (10). There are several methods of IF, in which the day or week is divided into eating periods and fasting periods (12). A frequent pattern within this classification is 5:2 intermittent fasting, which consists in choosing 2 days of the week (which may be consecutive or not) with a strictly restricted calorie diet, or complete fasting for 24 hours/day, leaving the remaining 5 days to eat at will (12).

Another recently developed IF regimen focused on weight loss is Time-Restricted Eating (TRE), which is characterized by specified periods of fasting and eating within a 24-hour cycle (13). One of the characteristics of this pattern is that it establishes that all meals are to be consumed during a defined period of time, followed by a fasting period that can range from 16 to 24 hours, prolonging the physiological night-time fast. Because the eating window is short, total calorie intake is less than normal (14).

The mechanism of action of IF that induces a metabolic shift with the potential to positively alter body composition typically occurs in the third phase of fasting, when the first time exceeds 12 to 16 hours (14). The key mechanism responsible for these effects seems to be the "metabolic switch change", which is the change of glucose utilization from glycogenolysis to depletion. This change is represented by the activation of lipolysis, a process that triggers the mobilization of lipids from adipose tissues. The lipids are metabolized, producing an increase in blood plasma levels of free fatty acids (FFA), which are then transported to the hepatocytes, where they are metabolized to produce B-HB ketones and acetoacetate. The ketones are transported to cells with high metabolic activity where they are further metabolized to generate ATP. These physiological processes allow ketones to serve as an energy source to maintain muscle and brain cell functions during fasting and prolonged periods of physical exertion (15,16). By involving these processes, which are independent of the energy balance, intermittent fasting may constitute an effective strategy for weight loss and act as a regulator of metabolic disorders associated with excess adiposity (17).

IF studies vary considerably depending on the fasting regimen employed and its duration; however, most of the independent studies reviewed report a reduction in body weight (11,18–21). In the studies analyzed, changes in body weight are evidenced after a period of 8 weeks or more with an eating time of 10 hours/day. Changes are also observed in studies that contemplate 8 hours of free eating and alternate day fasting (ADF), suggesting that the IF feeding protocol has an inversely proportional relationship, given that when the hours of fasting increase, weight-related variables tend to decrease as a consequence of the reduction in energy intake (Table 1).

Specifically, TRE studies reported effects of weight reduction while maintaining muscle mass, which is of special interest among physically active people because it helps to achieve a desired body mass for a specific sport category, thus confirming that this new method can produce changes in body composition (10).

Benefits of intermittent fasting

Benefits of the different IF methods have been established. One study reported improvements in insulin levels and sensitivity; increased β-cell responsiveness; and positive effects on diabetes mellitus, obesity, sleep quality, stress levels and oxidative stress in men with prediabetes (6). Another work found that extending the metabolic fast to 12 to 14 h each day may produce greater reductions in body weight and fasting blood glucose levels (19).

Table 1: Effects of intermittent fasting interventions in selected trials

Type of fast	Type of study	Sample	Period	Mealtime	Time- frame	Anthropometric parameters	Body mass	Metabolic parameters	Blood pressure	Metabolic costs	Reference
Time Restricted Eating (TRE) 16:8 and Constant Meal Time (CMT)	Prospective randomized clinical trial (RCT)	105 full cut Adults with overweight and obesity	12 weeks	8 hrs	12:00 pm to 20:00 pm- Constant hours	**Body weight** -0.94 kg TRE -0.68 kg CMT	----	----		No changes	(11)
		"46 Face-to-face sessions lasting 12 weeks Adults with overweight and obesity "	12 weeks	8 hrs	"12:00 pm to 20:00 pm CG: Constant time "	**Body weight** -1.70kg TRE -0..57 kg CMT	**FM** -0.51kg TRE -0.03 kg CMT **MM** -1.10 Kg TRE -0.35 Kg CMT **AFM** -0.64 Kg TRE -0.17 kg CMT **TLM** -0.47 Kg TRE -0.15 kg CMT	**FG** NS **Fasting insulin** NS **HOMA-IR** NS **HbA1c** NS **CT** NS **TG** NS **C-LDL** NS **C-HDL** NS	**SBP** -1.96 mmHg TRE - 3.86 mmHg CMT **DBP** -4.08 mmHg TRE -3.01 mmHg CMT	**RMR** - 28.1 kcal/day TRE -43.15 kcal/day CMT * no changes between groups. **TEE** - 177.9 Kcal/day **TRE** 127.3 Kcal/day CMT *no changes between groups.	
"Modified Alternate Day Fasting (ADF) and Calorie Restriction (CR) "	Randomized clinical trial	"69 participants full cut adults with Overweight and obesity "	8 weeks		ADF: 1 day of fasting and one day of eating. CR < 75% EN	**Body weight** - 4.1 kg ADF -1.7 kg RC **BMI** - 1.6 kg/mt^2 ADF -0.8 kg/mt^2 RC **WC** - 4 cm ADF -1 cm RC	Not measured	**FG** - 5 mg/dl ADF **Fasting insulin** - 2.41 uU/ml ADF - 1.56 uU/ml RC **HOMA-IR** ADF: - 0.72 RC: - 0.39 **C-Total** -11 mg/dl ADF 8 mg/dl CR **TG** 52 mg/dl ADF 40 mg/dl RCR **C-LDL** -5 mg/dl ADF RC: NS **C-HDL** -5 mg/dl ADF **RC: NS** -1 mg/dl ADF RC: NS	**SBP** - 13 mmHg ADF -1 mmHg RC **DBP**	Not measured	(19)
"Eating with time restriction TRE 14:10 hrs. with a fasting ketogenic snack TRE 12:12 hrs *No fasting snack. "	Randomized clinical trial	60 Adults with Obesity		10 hrs	Fasting between 5:00 p.m. and 8:00 p.m.	**Body weight** -10.7 Kg TRE 14:10	Not measured	**FG** -7.6 mg/dl TRE 14.10	Not measured	Not measured	(46)
		"24 participants with obesity and high glucose blood level "		12 hrs		-8.9 kg TRE 12:12 *There was a significant change between groups.		-3.1 mg/dl TRE 12:12 *Both interventions resulted in greater reduction of fasting blood glucose in impaired FG patient.			

Table 1: [continued] Effects of intermittent fasting interventions in selected trials

Type of fast	Type of study	Sample	Period	Mealtime	Time-frame	Anthropometric parameters	Body mass	Metabolic parameters	Blood pressure	Metabolic costs	Reference
Eating with a time restriction of 16:8 hours and a control group that maintains its eating habits	Non-randomized controlled clinical trial	"32 participants TRE 8:16 hrs "	3 months	8 hrs	Fasting from 8:00 p.m. to 12:00 p.m. and eating from 12:00 p.m. to 8:00 p.m.	**Body weight** **-3.38 Kg TRE** **+1.32 kg Control Group**	**FM** -2.17 kg TRE + 0.85 kg Control group	FG +1.8 mg/dl TRE +2 mg/dl Control group	**SBP** "TRE: -5.4 mmHg " Control group: - 6.8 mmHg	Not measured	(11)
"Modified Alternate Day Fasting (ADF) and Calorie Restriction (CR) "		12 Control Group. women with obesity				**BMI** "- 1.34 Kg/mt^2 TRE " + 0.85 kg/mt^2 Control Group **WC** -3.98 cm TRE +1.27cm Control Group	**%GC** - 0.9 % TRE + 0.35% Control group **MM** -0.68 kg TRE + 0.19 kg Control Group	**Insulin** -0.1 mU/L TRE "+ 3.5 mU/L Control Group " **C-Total** +8.8 mg/dl TRE -6.6 mg/dl Control Group **TG** -12.1 mg/dl TRE -17.2 mg/dl. Control Group **C-LDL** +7.4 mg/dl TRE -1.7 mg/dl Control Group **C- HDL** +0.6 mg/dl TRE -2.9 mg/dl Control Group	**DBP** TRE: -3.4 mmHg Control Group: - 4.8 mmHg		(19)
"Early Time-Restricted Feeding (eTRF) 6:18 a.m. vs. a control group (CG) with a feeding period of 12 hours "	Randomized controlled clinical trial	"8 participants " Men with prediabetes	5 weeks	6 hrs 12 hrs	eTRF: dinner before 15:00 pm	**Body weight** 1.4 +1.3 kg eTRF 1.0 +1.1 kg Control Group * Body weight was stable and changes in body weight were similar between groups	Not measured NS: eTRF	**FG** "eTRF: 11 + 4 mmHg " NS: Control **Fasting Insulin** 3.4 + 1.6 mU/L eTRF "in the insulinogenic index and decreased resistance to insulin eTRF. " **Cholesterol** C-HDL: 0.6+09 mg/dl. C-LDL: 2+6 mg/dl eTRF: NS "TG: 57+13mg/dl CT:13+5 mg/dL eTRF"	**SBP** **DBP** "eTRF: 10 + 4 mmHg "	Does not affect energy expenditure	(21)

FM: fat mass; FFM: lean mass or fat-free mass; AFM: appendicular fat mass; TLM: trunk lean mass; FG: fasting glucose; NS: Not significant. RMR: Resting Metabolic Rate. TEE: Total Energy Expenditure; EN: Energy needs. WC: Waist circumference. MM: Muscle mass; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TG: Triglycerides.

A 5-week early time-restricted feeding (eTRF) protocol is reported to improve insulin sensitivity, β-cell responsiveness, blood pressure, oxidative stress and appetite compared to the 12-hour feeding control group (CG) (22). A similar protocol was reported to improve glucose metabolism and increase tissue sensitivity to insulin by increasing pancreatic islet β cells (10).

A study of orthodox religious fasting highlights the finding that eating time restrictions could be associated with a better metabolic and glycemic profile (23).

Long-term benefits have also been shown. The cell mechanisms by which IF improves health and counteracts pathological processes are due to the activation of adaptive cellular stress-response signaling pathways, improving mitochondrial health, DNA repair and autophagy (10).

Moreover, there is a general consensus that IF improves cardiovascular health in humans as a result of improvements in the profile of inflammatory markers and plasma lipids (24). At a physiological level, the IF eating pattern has effects on the inflammatory state, in particular by decreasing the levels of CRP (C-reactive protein, which is released into the bloodstream in response to inflammation); however, no changes are observed in TNF-a and IL-6 levels (25). There is also evidence that IF inhibits the development of atherosclerotic plaque by reducing the concentration of inflammatory markers such as IL-6, homocysteine and CRP. It also causes an increase in brain-derived neurotrophic factor (BDNF), resulting in a drop in systolic and diastolic blood pressure by activating the parasympathetic system. BDNF causes the vagus nerve to release acetylcholine, which reduces the frequency of heart contractions, lowering the likelihood of developing cardiac hypertrophy. This positive effect of IF has also been documented in people with obesity and diabetes (10).

Alternate-day fasting (ADF), TRE and intermittent energy restriction (IER) are all reported to have beneficial regulatory effects on gut microbial compositions in various animal models and human trials (26). The gut microbiome is remodeled during intermittent fasting, contributing to the cyclical nature of the gut microbiome, as reflected by improved fluctuations in bacterial abundance and function (21). This new composition of the microbiome may result in increased production or conversion of metabolites, including tryptophan and its derivatives, short-chain fatty acids and bile acids, along with decreased expression of lipopolysaccharides in the outer membrane of gram-negative bacteria (27).

Intermittent fasting and its role in oxidative stress

The generation of molecular oxygen in the form of reactive oxygen species (ROS) is a natural part of aerobic life. Basal levels of ROS are essential for the manifestation of various cell functions, such as signal transduction pathways, defense against microorganisms, gene expression and promotion of cell growth or death (28).

An imbalance in the production of these reactive oxygen species, and the body's inability to detoxify these reactive products, is defined as oxidative stress (22). When ROS production is not controlled and circulating levels of these markers accumulate, this can lead to the development of metabolic syndromes and the progression of atherosclerotic disease (29).

Short-term trial data suggest that TRE may produce consistent reductions in markers of oxidative stress. For example, 8-isoprostane (a marker of lipid oxidative stress) was reduced by 14% in the 6-hour TRE study in obese men with prediabetes (22). Similarly, there was a change in the plasma levels of 8-isoprostane at week 8 in groups that adhered to TRE for 4 hours and TRE for 6 hours, obtaining reductions of 37% in the first group and 43% in the second, versus controls without mealtime restrictions. In contrast, none of the interventions had any impact on levels of inflammatory markers such as tumor necrosis factor alpha (TNF-alpha) and plasma interleukin-6 (IL-6) (9). It has also been shown that TRE plays a protective role against oxidative stress, since it is aligned with circadian time, regulating the production of various signaling molecules, maintaining mitochondrial homeostasis and reducing oxidative stress (30).

Intermittent fasting elicits adaptive cell responses that are preserved by the body through evolution and are integrated within the organs in a way that results in improved glucose regulation, increased resistance to stress and suppressed inflammation, through the activation in cells of pathways that enhance intrinsic defenses against oxidative and metabolic stress, and pathways that eliminate and repair damaged molecules (9). These promising preliminary findings show that TRE may offer some benefit in helping to regulate ROS production in humans.

Disadvantages of intermittent fasting

Intermittent fasting can be dangerous and is not recommended for people with hormonal imbalances, pregnant or lactating women, people with diabetes or eating disorders such as anorexia or bulimia, or who have a BMI of less than 18.5 kg/m² (underweight) (10), as it could lead to serious vitamin deficiencies as well as loss of fat-free mass (31). Current evidence suggests that IF may represent a counterproductive strategy for optimizing muscle mass, as protein turnover may remodel old/damaged proteins (32).

A significant reduction in lean mass in the TRE group is reported in one study, where the average weight loss in the group was 1.70 kg, of which 1.10 kg was lean mass and 0.51 kg fat mass; however, the lean mass loss in this study far exceeds the normal range (11). TRE has been shown to lead to a reduction in calorie intake and may also reduce protein intake; these data highlight the importance of adequate protein intake while adhering to a TRE diet (11).

On the other hand, it was observed that diabetics who consume hypoglycemia-inducing medication, and who are classified as high-risk patients, should not follow an IF diet due to the likelihood of hypoglycemia, hyperglycemia, and ketoacidosis. In the case of diabetic patients who decide to adhere to IF, monitoring of the blood glucose level at least twice a day during fasting is essential, requiring interruption of the diet if dangerously low glycemic levels occur (31).

Other minor physical symptoms have been reported, such as hunger, lack of energy, headache, dizziness, constipation, bad breath and feeling cold, along with minor adverse cognitive effects, including poor concentration, for 1 to 6 months as a result of daily IF or CR (28). Temporary sleep disturbances have also been reported during the first month of intervention in groups adhering to IF (33).

Moreover, it is reported that daily fasting periods lasting 14 hours or more may be associated with increased gallstone formation, and weight loss benefits from TRE may be similar to those achieved by following a consistent eating schedule (12). Another aspect that has been highlighted is that TRE has the potential to reduce systemic inflammation and autoimmune-related diseases, but at the same time it can weaken the immune system and increase susceptibility to infections and cancer (12,34).

In the follow-up of patients who participated in a study with 5:2 fasting and CR, it was reported that both groups recovered the lost weight (22% in the 5:2 group and 42.6% in the CR group) within 12 to 24 months. Furthermore, the subjects in the 5:2 group lost more lean mass during this follow-up period, losing 2.2 kg as compared to 0.8 kg in the CR group (35).

Finally, it should be mentioned that excessive calorie restriction has been reported to cause dysregulation of hormonal management, which can lead to menstrual cycle disorders in women and decreased testosterone in men (10).

Intermittent fasting and its effect on reducing cardiovascular disease risk factors

Lifestyle choices, including diet and physical exercise, have a major impact on CVD (cardiovascular disease) risk. Among the most common risk factors are diabetes and obesity (12), and one of the ways to reduce the risk of vascular diseases is through weight loss (29).

The evidence suggests that IF could be a safe dietary intervention with broad cardiometabolic health benefits against aging, obesity, diabetes mellitus and cardiovascular diseases, since it has been described that calorie restriction brings a decrease in circulating lipids, such as triglycerides, low- and very-low-density lipoproteins (LDL and VLDL cholesterol, respectively), but no change in plasma levels of high-density lipoproteins (HDL) (36). Time-restricted fasting has also been reported to effectively improve the cardiometabolic risk profile, in addition to inducing weight loss in prediabetic subjects (37).

In a study of 60 overweight and obese adults who underwent a 75% calorie restriction period every other day, the subjects experienced a reduction in LDL cholesterol and triglyceride levels after 12 weeks. However, these changes could also be explained by the weight loss observed (5).

Furthermore, epidemiological evidence suggests that IF may help lower blood pressure. These findings are consistent with a study in which an improvement in systolic and diastolic blood pressure values was observed in the population after fasting, IER and CR (38). Similarly, reductions in systolic and diastolic blood pressure have been reported during TRE, with blood pressure decreases noted more frequently in studies in which participants lost at least 3% of baseline body weight (29).

Thus IF has the ability to reduce blood pressure, due to a decrease in sympathetic tone and an increase in parasympathetic tone, which could improve CVD mortality (5).

Intermittent fasting and its role in circadian rhythms

Organisms have adapted to the changing light-dark cycle that makes up a day, distributing their performance of functions such as eating and sleeping, which are crucial to survival, over time. There are several physiological pathways that display the same behavior, known as circadian rhythms (39). Molecular circadian clocks regulate daily behavioral and metabolic rhythms with the external day-night cycle. Alterations in these rhythms are usually accompanied by metabolic alterations, ranging from overweight and type II diabetes mellitus to the development of metabolic syndrome (40).

The general dietary trend today has changed from the classic consumption of 3 meals a day to consuming 45% of daily energy levels in the evening meal and night-time snacks. This eating pattern contributes to the misalignment of circadian rhythms and the disruption of metabolic processes, resulting in excessive energy consumption and impaired metabolic health (41).

When the period of food intake is aligned with the central circadian clock, it can cause changes in the metabolism of lipids, proteins and carbohydrates (42). Consequently, intermittent fasting regimens may be a promising intervention strategy through which disordered circadian rhythms can be realigned and obesity and its associated metabolic diseases can be treated or even prevented (27). Time-restricted eating (TRE), where food is specified to be consumed within a constant interval of 8 to 12 hours, appears to be the IF variable that maintains optimal nutrient utilization and promotes health, as it is in synchrony with the circadian rhythm (43).

Another important factor is the production of melatonin, since it has effects on glucose homeostasis through the attenuation of glucose-stimulated insulin release, producing a reduced insulin response to late-night meals. This would justify the notion that it is best to avoid ingesting food 2 to 3 hours before bedtime and for one hour after waking up. It should also be noted that the release of insulin from the pancreas decreases near the resting phase, thus late-night meals lead to an increase in prolonged serum glucose levels that are likely to be stored as triglycerides (TG) in adipose tissue (42).

In a study of overweight and obese women following a TRE protocol with a shorter feeding period of less than 11 hours for eating, and beginning their fast 2 hours before bedtime, the results reported lower energy intake, glycemic load and eating frequency (41).

As reported in table 2, early time-restricted feeding (eTRF) is thought to improve mean glucose levels over a 24-hour period, to alter lipid metabolism and oxidation and the gene expression of the circadian clock, to stimulate autophagy and to have anti-aging effects (6). In a study in 119 prediabetic adults, a longer feeding window of 12 hours or more was associated with a higher percentage of body fat (44). In another study in overweight and obese women that compared an interval of 12 hours or less with one of more than 12 hours, a significant decrease in calories was found in the group with the shorter eating window, which is consistent with the TRE pattern (41).

These findings support the notion that limiting all calorie intake to a defined time interval, separated by a few hours from the daily sleep interval, has multiple health benefits (43,45,46).

Table 2: Metabolic, hormonal and genetic results associated with different times of feeding

Eating time	Study description	Metabolic Results	Gene and hormone expression	Reference
eTRF 6: 18 hrs	Full cut 11 Adults	eTRF Glucose 24h: 4 +1mg/dl.	Cortisol (am): 1.5 + 0.9 ug/dl	(57)
	BMI: > 25 kg/m^2	Fasting Glucose: 2 +1mg/dl.	Cortisol (pm) :1.4 +0.6 ug/dl	
CG: 12: 12 hrs	Age: > 32 years	Fasting Insulin: 2.9+0.4 mU/l	BDNF: 2.46 + 1.34 ng/ml	
	Duration 4 days	C-LDL: 9 + 4 mg/dl	BMAL1: 8+3%	
		C-HDL: 3+1 mg/dl.	CRY1: 14+ 2%	
		TG: NS	CRY2: 8+4%	
		C-Total: 10+4 mg/dl	REV-ERBA:12+6% RORA:13+4%	
			CLOCK and PER2: NS	
			SIRT1: 10+3%	
			LC3A: 22+5%	
			MTOR:9+3%	
Eating window	119 adults full cut	Late eating was associated with % body fat.		(44)
< 10 h/d	BMI:>25 kg/m^2			
>12 h/d	Age: >30 a<70 years	Daily eating window and percentage of CG:NA.		
>14 h/d				
TRE 11:13 hrs. Daily Eating Interval (DEI) >12 hours	229 full cut Women	TRE: 140 kcal.		(17)
	BMI: >25 kg/m^2	CG: 15 units. Intake frequency.		
	Age: > 40 years	DEI: 53 kcal		
		CG: +6 units higher. Intake frequency		

GL: glycemic load; DEI: daily eating interval; eTRF: early time-restricted feeding; TRE: time-restricted eating; NS: not significant; NA: no association.

Discussion

Intermittent fasting (IF) is a popular alternative, in which fasting is alternated with periods of unrestricted eating. This appears to be an approach equivalent to calorie restriction (CR) for inducing weight loss, although there is limited evidence so far regarding long term results. The purpose of this study was to review the available data on intermittent fasting and its contribution to the improvement of body and metabolic composition, and to define the parameters that condition the safety of its benefits.

IF has been found to be as effective as CER for losing weight and fat mass, suggesting that this type of fasting could be considered a valid alternative to calorie restriction (47,48). Although TRE does not place emphasis on calorie restriction, controlled eating times do in fact reduce calorie intake. This pattern appears to generate greater adherence than CER, making TRE a safe and well-tolerated intervention in the short term. Recent studies of TRE with a daily feeding window of 8 to 10 h reported dropout rates of less than 10%; however, these tended to increase to 20% with a shorter feeding window, suggesting that TRE may be an effective strategy to promote weight loss in users who have difficulty adhering to diets that alter the entire nutritional pattern of the individual's daily food intake. This is the case of alternate day fasting (ADF), for example, which the data show to be associated with a higher dropout rate (40%), suggesting that it may not be a feasible weight loss alternative for many people (49).

The metabolic switch involved in prolonged fasting of more than 12 hours consists of a marked reduction in liver glycogen, leading to the mobilization of fatty acids from adipose tissue and their metabolism by the liver. Increased β-oxidation of fatty acids leads to excess formation of β-hydroxybutyrate and acetoacetate (50). These are transported to cells where they are further metabolized to generate ATP, which maintains muscle and brain cell function during fasting. With these processes involved, it can be an effective strategy for weight loss and can also act as a regulator of metabolic disorders associated with excess adiposity.

When contrasting IF with calorie restriction, IF exhibits superior benefits because it produces a series of changes that contribute to the improvement of parameters affecting heart health. Along the same lines, studies conclude that TRE improves blood glucose levels and insulin sensitivity, in addition to having an effect on the composition of the intestinal microbiota (51).

Oxidative stress is understood to be the result of imbalance in the production of reactive oxygen species (ROS) and the inability of the body to detoxify them. IF causes an improvement in ROS regulation through adaptive cell responses, increasing resistance to stress. There are data indicating that TRE decreases lipid oxidative stress markers in individuals with obesity and prediabetes.

It is widely proven that dietary restriction prolongs the lifespan of many species, including mammals; among other beneficial effects on cells, it lowers ROS production and thus decreases oxidative stress and oxidative damage to biomolecules (52). These findings show that TRE may offer benefits in regulating ROS production in humans.

Turning to the disadvantages of IF, it should be noted that most of the studies analyzed were conducted with small sample sizes and short-term interventions. It was shown that although IF can be beneficial to people with diabetes mellitus II, it effectively increases hypoglycemia and can lead to decompensation. Dietary plans that involve intermittent fasting have also reported side effects such as cramps, headache, cardiac arrhythmias, menstrual irregularities, gout, etc., although these effects have been associated mainly with people suffering from chronic diseases, and it is estimated that they could be controlled with the assistance of a nutrition expert. In addition, this method has been noted to produce muscle wasting reflected in the loss of lean mass, making it advisable to ensure adequate replacement of proteins (48).

It has been pointed out that IF could be a safe dietary intervention with broad cardiometabolic benefits, given the observed decrease in circulating lipids. Humans adhering to IF exhibit lower circulating levels of TG, while ADF helps to further improve predictive markers of cardiometabolic health, including a reduction in cholesterol and inflammation (53). It is also noted that IF may help lower blood pressure: a recent series of clinical studies of overweight and obese adults adhering to TRE, with an eating range of 6, 8 or 10 hours for a period equal to or greater than 12 weeks, reflected a decrease in blood pressure (53,54), indicating that IF can modify cardiovascular risk factors.

Alterations in circadian rhythms go hand in hand with metabolic alterations such as overweight, type II diabetes mellitus and the development of metabolic syndrome, where the current diet contributes to the misalignment of these rhythms. IF regimens may help to restore their alignment, treating and preventing obesity and associated diseases as a collateral effect.

It is noted that TRE where food is consumed over a constant interval of 8 to 12 hours maintains optimal nutrient utilization and is in synchrony with the circadian rhythm. Both prolonging daily fasting and shifting food intake to earlier in the day contribute to metabolic improvements after early time-restricted feeding (eTRF). Daytime metabolic responses to nutrients are influenced by the circadian system and glucose tolerance is higher earlier in the day;

thus shifting nutrient intake to earlier hours of the day may have beneficial effects on the metabolism (55). An example of this is that insulin release from the pancreas decreases during the resting phase, so late night ingestion of food leads to increased serum glucose, which is likely to be stored as triglycerides in adipose tissue.

Early time-restricted feeding (eTRF) has been shown to improve 24-hour glucose levels, to alter lipid metabolism and oxidation and the gene expression of the circadian clock, to stimulate autophagy and to have anti-aging effects. It is also important to note that recurrent eating patterns with IF confer a health benefit by delaying many age-related diseases and helping to improve metabolic markers, which are independent of weight loss (53).

Thus aligning food intake with circadian rhythms can be a powerful strategy for reducing appetite and losing weight; the subset of meal-timing interventions involving intermittent fasting, such as TRE, may confer additional benefits by improving metabolic flexibility and increasing 24-hour fat oxidation (56). The notion of limiting all calorie intake to a defined time interval, separated by a few hours from the daily sleep interval, is thus supported. In sum, intermittent fasting provides multiple health benefits to individuals; however, long-term studies are needed to assess the continuity of these benefits over time (31).

TRE is a simple and well-tolerated diet, implemented also as Ramadan in Islamic culture (36) that generates many beneficial health effects based on chrononutrition principles which may protect cardiovascular health by improving the lipid profile and raising the sub-optimal HDL and may provide a significant metabolic benefit by improving glycemic control, insulin resistance, and adipokine concentration with a reduction of BMI in adults (6,25,39,45,47,51). Even if time-restricted eating, in the absence of other interventions, is not more effective in weight loss than eating throughout the day (11). In participants with obesity who completed 8 weeks of the 14:10 TRE schedule combined with a commercial weight loss program, there was statistically significant and clinically meaningful weight loss and improvements in fasting blood glucose (46), showing an effect also in waist circumference, systolic blood pressure (19).

In patients with multiple sclerosis, the data available are too scarce to draw any firm conclusions, but it does appear that intermittent fasting may be a safe and feasible intervention (31). Neither dietary model affected the concentrations of tumor necrosis factor-α or interleukin-6 (32).

Conclusions

The growing prevalence of malnutrition due to excess throughout the world demands nutritional treatment methods that are adapted to current lifestyles and that ensure their effectiveness in reducing both body weight and the incidence of disorders associated with obesity. IF interventions are currently emerging as a tool for weight loss and to combat the development of many age-related diseases derived from metabolic dysfunctions.

Despite the multiple benefits indicated, there is some controversy regarding the safety and viability of this new food protocol, because IF encompasses different regimens that are not yet regulated; in addition, long-term adherence represents a challenge. TRE is a simple and well-tolerated diet, implemented also as Ramadan in Islamic culture (MIRMIRAN P, BARDORAN) that generates many beneficial health effects based on chrononutrition principles which may protect cardiovascular health by improving the lipid profile and raising the sub-optimal HDL and may provide a significant metabolic benefit by improving glycemic control, insulin resistance, and adipokine concentration with a reduction of BMI in adults . Finally, it should be noted that the discrepancy between the available studies may be due to heterogeneity in the design of the IF protocols, suggesting that more research is required in this regard.

Conflicts of Interest:

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Funding: This research was supported by Projects number VIPUCT2019PROSV05 and VIPUCT2021PROWB01, funded by Universidad Católica de Temuco, Chile, and MINEDUC UCT21102, Government of Chile.

References

1. de Salud M. Ministerio de Salud 2020.pdf [Internet]. 2020. Available from: https://www.ispandresbello.cl/wp-content/uploads/2020/10/informe-indice-de-salud-2020.pdf
2. Muñoz-Hernández L, Márquez-López Z, Mehta R, Aguilar-Salinas CA. Intermittent Fasting as Part of the Management for T2DM: from Animal Models to Human Clinical Studies. Curr Diab Rep. 2020 12; 20(4):13, 1-10. https//:doi.org/10.1007/s11892-020-1295-2.
3. Aburto S, Cisterna M, Acuña J, Ruíz C, Viscardi S, Márquez JL, *et al*. Obesity as a Risk Factor for Severe COVID-19 in Hospitalized Patients: Epidemiology and Potential Mechanisms. Healthcare 2022; 10(10):1838. https://doi.org/10.3390/healthcare10101838
4. Pureza IROM, Macena ML, da Silva Junior AE, Praxedes DRS, Vasconcelos LGL, Bueno NB. Effect of early time-restricted feeding on the metabolic profile of adults with excess weight: A systematic review with meta-analysis. Clin Nutr. 2021; 40(4):1788-1799. https://doi.org/10.1016/j.clnu.2020.10.031.
5. Dong TA, Sandesara PB, Dhindsa DS. *et al*. Intermittent Fasting: A Heart Healthy Dietary Pattern? Am J Med. 2020;133(8):901–907. https://doi.org/10.1016/j.amjmed.2020.03.030
6. Ahmed N, Farooq J, Siddiqi HS *et al*. Impact of Intermittent Fasting on Lipid Profile–A Quasi-Randomized Clinical Trial. Front Nutr 2021; 7: 596787. https://doi.org/10.3389/fnut.2020.596787
7. Lessan N, Ali T. Energy Metabolism and Intermittent Fasting: The Ramadan Perspective. Nutrients. 2019 27; 11(5):1192. https://doi.org/10.3390/nu11051192.
8. Grajower MM, Horne BD. Clinical Management of Intermittent Fasting in Patients with Diabetes Mellitus. Nutrients. 2019 18;11(4):873. https://doi.org/10.3390/nu11040873.
9. de Cabo R, Mattson MP. Effects of Intermittent Fasting on Health, Aging, and Disease. Longo DL, editor. N Engl J Med. 2019 26;381(26):2541–2551.https://doi.org/10.1056/nejmra1905136
10. Malinowski B, Zalewska K, Węsierska A. *et al*. Intermittent Fasting in Cardiovascular Disorders—An Overview. Nutrients. 2019 20; 11(3):673. https://doi.org/10.3390/nu11030673
11. Lowe DA, Wu N, Rohdin-Bibby L, Moore AH, Kelly N, Liu YE, *et al*. Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity. JAMA Intern Med. 2020; 180(11):1491-1499. https://doi.org/10.1001/jamainternmed.2020.4153.
12. Crupi AN, Haase J, Brandhorst S, Longo VD. Periodic and Intermittent Fasting in Diabetes and Cardiovascular Disease. Curr Diab Rep. 2020 10;20(12):83. https://doi.org/10.1007/s11892-020-01362-4
13. Schroder JD, Falqueto H, Mânica A, Zanini D, de Oliveira T, de Sá CA, *et al*. Effects of time-restricted feeding in weight loss, metabolic syndrome and cardiovascular risk in obese women. J Transl Med. 2021; 19(1):3. https://doi.org/10.1186/s12967-020-02687-0
14. Zhang X, Zou Q, Zhao B, *et al*. Effects of alternate-day fasting, time-restricted fasting and intermittent energy restriction DSS-induced on colitis and behavioral disorders. Redox Biol.2020; 32:101535. https://doi.org/10.1016/j.redox.2020.101535.
15. Anton SD, Moehl K, Donahoo WT, *et al*. Flipping the Metabolic Switch: Understanding and Applying the Health Benefits of Fasting. Obesity (Silver Spring) 2018; 26(2):254–268, https://doi.org/10.1002/oby.22065.
16. Freire R. Scientific evidence of diets for weight loss: Different macronutrient composition, intermittent fasting, and popular diets. Nutrition. 2020; 69:110549. https://doi.org/10.1016/j.nut.2019.07.001
17. Taetzsch A, Roberts SB, Bukhari A. *et al*. Eating Timing: Associations with Dietary Intake and Metabolic Health. J Acad Nutr Diet. 2021;121(4):738–748. https://doi.org/10.1016/j.jand.2020.10.001
18. Centro de Desarrollo de la Organización para la Cooperación y el Desarrollo Económicos, (2017). Perspectivas económicas de América Latina 2017, 1-25. http://dx.doi.org/10.1787/leo-2017-es.
19. Parvaresh A, Razavi R, Abbasi B. *et al*. Modified alternate-day fasting vs. calorie restriction in the treatment of patients with metabolic syndrome: A randomized clinical trial. Complement Ther Med. 2019; 47:102187. https://doi.org/10.1016/j.ctim.2019.08.021
20. Sandoval C, Santibañez S, Villagrán F. Effectiveness of intermittent fasting to potentiate weight loss or muscle gains in humans younger than 60 years old: a systematic review. Int J Food Sci Nutr. 2021;72(6):734–745. https://doi.org/10.1080/09637486.2020.1868412
21. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. Cell Metab. 2018; 27(6):1212–1221.e3. https://doi.org/10.1016/j.cmet.2018.04.010.
22. Senoner T, Dichtl W. Oxidative Stress in Cardiovascular Diseases: Still a Therapeutic Target? Nutrients. 2019; 11(9):2090. https://doi.org/10.3390/nu11092090.
23. Currenti W, Godos J, Castellano S. *et al*. Association between Time Restricted Feeding and Cognitive Status in Older Italian Adults. Nutrients. 2021; 13(1):191. https://doi.org/10.3390/nu13010191.

24. Lee JH, Verma N, Thakkar N, Yeung C, Sung HK. Intermittent Fasting: Physiological Implications on Outcomes in Mice and Men. Physiology 2020; 35(3):185-195. https://doi.org/10.1152/physiol.00030.2019.
25. Waldman HS, Renteria LI, McAllister MJ. Time-restricted feeding for the prevention of cardiometabolic diseases in high-stress occupations: a mechanistic review. Nutr Rev. 2020; 78(6):459-464, https://doi.org/10.1093/nutrit/nuz090.
26. Williamson E, Moore DR. A Muscle-Centric Perspective on Intermittent Fasting: A Suboptimal Dietary Strategy for Supporting Muscle Protein Remodeling and Muscle Mass? Front Nutr 2021; 8: 640621. https://doi.org/10.3389/fnut.2021.640621.
27. Daas MC, de Roos NM. Intermittent fasting contributes to aligned circadian rhythms through interactions with the gut microbiome. Benef Microbes. 2021; 12(2):147-161. https://doi.org/10.3920/bm2020.0149.
28. Liu K, Liu B, Heilbronn LK. Intermittent fasting: What questions should we be asking? Physiol Behav. 2020; 218:112827. https://doi.org/10.1016/j.physbeh.2020.112827.
29. Gabel K, Cienfuegos S, Kalam F, Ezpeleta M, Varady KA. Time-Restricted Eating to Improve Cardiovascular Health. Curr Atheroscler Rep. 2021; 23(5):22. https://doi.org/10.1007/s11883-021-00922-7.
30. Teong XT, Heilbronn LK. Evidence gaps and potential roles of intermittent fasting in the prevention of chronic diseases. Exp Gerontol. 2021; 153:111506. https://doi.org/10.1016/j.exger.2021.111506.
31. Morales-Suarez-Varela M, Collado Sánchez E, Peraita-Costa I, Llopis-Morales A, Soriano JM. Intermittent Fasting and the Possible Benefits in Obesity, Diabetes, and Multiple Sclerosis: A Systematic Review of Randomized Clinical Trials. Nutrients. 2021; 13(9):3179. https://doi.org/10.3390/nu13093179
32. Wang X, Yang Q, Liao Q, *et al*. Effects of intermittent fasting diets on plasma concentrations of inflammatory biomarkers: A systematic review and meta-analysis of randomized controlled trials. Nutrition. 2020; 79-80:110974. https://doi.org/10.1016/j.nut.2020.110974.
33. Templeman I, Gonzalez JT, Thompson D, Betts JA. The role of intermittent fasting and meal timing in weight management and metabolic health. Proc Nutr Soc. 2020 26; 79(1):76–87. https://doi.org/10.1017/s0029665119000636.
34. Gasmi M, Sellami M, Denham J, *et al*. Time-restricted feeding influences immune responses without compromising muscle performance in older men. Nutrition. 2018; 51-52:29–37. https://doi.org/10.1016/j.nut.2017.12.014.
35. Fanti M, Mishra A, Longo VD, Brandhorst S. Time-Restricted Eating, Intermittent Fasting, and Fasting-Mimicking Diets in Weight Loss. Curr Obes Rep. 2021; 10 (2):70–80. https://doi.org/10.1007/s13679-021-00424-2.
36. Mirmiran P, Bahadoran Z, Gaeini Z, Moslehi N, Azizi F. Effects of Ramadan intermittent fasting on lipid and lipoprotein parameters: An updated meta-analysis. Nutr Metab Cardiovasc Dis. 2019; 29 (9):906-915. https://doi.org/10.1016/j.numecd.2019.05.056.
37. Abdellatif M, Sedej S. Cardiovascular benefits of intermittent fasting. Cardiovasc Res. 2020; 116(3):e36-38. https://doi.org/10.1093/cvr/cvaa022.
38. Rynders CA, Thomas EA, Zaman A, Pan Z, Catenacci VA, Melanson EL. Effectiveness of Intermittent Fasting and Time-Restricted Feeding Compared to Continuous Energy Restriction for Weight Loss. Nutrients. 2019; 11(10):2442. https://doi.org/10.3390/nu11102442.
39. Moon S, Kang J, Kim SH, *et al*. Beneficial Effects of Time-Restricted Eating on Metabolic Diseases: A Systemic Review and Meta-Analysis. Nutrients. 2020; 12(5):1267. https://doi.org/10.3390/nu12051267.
40. Kolbe I, Oster H. Chronodisruption, metabolic homeostasis, and the regulation of inflammation in adipose tissues. Yale J Biol Med. 2019; 92(2):317–325.
41. Su J, Wang Y, Zhang X, *et al.* Remodeling of the gut microbiome during Ramadan-associated intermittent fasting. Am J Clin Nutr. 2021; 113(5):1332-1342. https://doi.org/10.1093/ajcn/nqaa388
42. Ravussin E, Beyl RA, Poggiogalle E, Hsia DS, Peterson CM. Early Time-Restricted Feeding Reduces Appetite and Increases Fat Oxidation But Does Not Affect Energy Expenditure in Humans. Obesity. 2019;27(8):1244-1254, https://doi.org/10.1002/oby.22518.
43. Chaix A, Manoogian ENC, Melkani GC, Panda S. Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases. Annu Rev Nutr. 2019; 39(1):291-315. https://doi.org/10.1146/annurev-nutr-082018-124320.
44. Mogensen CS, Færch K, Bruhn L *et. al*. Timing and Frequency of Daily Energy Intake in Adults with Prediabetes and Overweight or Obesity and Their Associations with Body Fat. Nutrients. 2020; 12(11):3484. https://doi.org/10.3390/nu12113484.
45. Adafer R, Messaadi W, Meddahi M, *et al.* Food Timing, Circadian Rhythm and Chrononutrition: A Systematic Review of Time-Restricted Eating's Effects on Human Health. Nutrients. 2020; 12(12):3770. https://doi.org/10.3390/nu12123770
46. Peeke PM, Greenway FL, Billes SK, Zhang D, Fujioka K. Effect of time restricted eating on body weight and fasting glucose in participants with obesity: results of a randomized, controlled, virtual clinical trial. Nutr Diabetes. 2021;11(1):6. https://doi.org/10.1038/s41387-021-00149-0.
47. Enríquez Guerrero A, San Mauro Martín I, Garicano Vilar E, Camina Martín MA. Effectiveness of an intermittent fasting diet versus continuous energy restriction on anthropometric measurements, body composition and lipid profile in overweight and

obese adults: a meta-analysis. Eur J Clin Nutr. 2021 9;75(7):1024–1039, https://doi.org/10.1038/s41430-020-00821-1.

48. Queiroz JDN, Macedo RCO, Tinsley GM, Reischak-Oliveira A. Time-restricted eating and circadian rhythms: the biological clock is ticking. Crit Rev Food Sci Nutr. 2021; 61(17):2863-2875. https://doi.org/10.1080/10408398.2020.1789550.
49. Zubrzycki A, Cierpka-Kmiec K, Kmiec Z, Wronska A. The role of low-calorie diets and intermittent fasting in the treatment of obesity and type-2 diabetes. J Physiol Pharmacol. 2018;69(5):663-683, https://doi.org/10.26402/jpp.2018.5.02.
50. Attinà A, Leggeri C, Paroni R *et al.* Fasting: How to Guide. Nutrients. 2021; 13(5):1570. https://doi.org/10.3390/nu13051570.
51. Cho Y, Hong N, Kim KW *et al.* The Effectiveness of Intermittent Fasting to Reduce Body Mass Index and Glucose Metabolism: A Systematic Review and Meta-Analysis. J Clin Med 2019;8(10):1645. https://doi.org/10.3390/jcm8101645.
52. Mladenovic Djordjevic A, Loncarevic-Vasiljkovic N, Gonos ES. Dietary Restriction and Oxidative Stress: Friends or Enemies? Antioxid Redox Signal. 2021; 34(5):421-438. https://doi.org/10.1089/ars.2019.7959.
53. Duregon E, Pomatto-Watson LCDD, Bernier M, Price NL, de Cabo R. Intermittent fasting: from calories to time restriction. Geroscience. 2021;43(3):1083-1092. https://doi.org/10.1007/s11357-021-00335-z.
54. Andriessen C, Schrauwen P, Hoeks J. The importance of 24-h metabolism in obesity-related metabolic disorders: opportunities for timed interventions. Int J Obes (Lond). 2021; 45(3):479-490. https://doi.org/10.1038/s41366-020-00719-9.
55. Jones R, Pabla P, Mallinson J *et al*. Two weeks of early time-restricted feeding (eTRF) improves skeletal muscle insulin and anabolic sensitivity in healthy men. Am J Clin Nutr. 2020; 112(4):1015–1028. https://doi.org/10.1093/ajcn/nqaa192
56. Rajpal A, Ismail-Beigi F. Intermittent fasting and 'metabolic switch': Effects on metabolic syndrome, prediabetes and type 2 diabetes. Diabetes Obes Metab. 2020; 22(9):1496–510, https://doi.org/10.1111/dom.14080.
57. Jamshed H, Beyl RA, Della Manna DL, Yang ES, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans. Nutrients. 2019; 11(6):1234 https://doi.org/10.3390/nu11061234.

Recibido: 14/11/2022
Aceptado: 01/03/2023