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EFFECT OF INTERMITTENT FASTING ON CARDIOMETABOLIC HEALTH IN OBESE PERSONS WITH METABOLIC SYNDROME COMPARED TO CONTINUOUS CALORIC RESTRICTION

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Abstract. The prevalence of metabolic syndrome is increasing due to overeating and sedentary lifestyles. It is a risk factor for the development of diabetes mellitus II and cardiovascular disease. Effective and long-lasting weight loss involving lifestyle changes is necessary for its treatment. Continuous calorie restriction is the most commonly prescribed method of weight loss. However, people often regain the weight lost. Intermittent fasting protocols are being investigated as a safe and effective treatment for weight loss and improvement of cardiometabolic health, therefore, the aim of this research is to define the effects of intermittent fasting versus continuous calorie restriction for the control of cardiometabolic parameters in obese adults with metabolic syndrome. A literature review was carried out in which articles from scientific databases were consulted and analysed. Specifically, 10 articles published in the last 10 years belonging to PubMed were analysed. Intermittent fasting induces a weight loss equivalent to continuous calorie restriction; however, the loss of fat mass is greater when intermittent calorie restriction is performed. Changes in glucoregulatory markers are contradictory and inconclusive. Regarding the lipid profile LDL-cholesterol and triglycerides decrease equivalently with both interventions, not affecting HDL-cholesterol levels. Intermittent fasting and continuous calorie restriction protocols have similar effects on cardiometabolic health. Intermittent fasting is a safe intervention nevertheless, there is a risk of hypoglycaemia in people treated with antidiabetics.

Keywords: “obesity”, “cardiometabolic”, “health”, “periodic fasting”, “alternate day fasting”, “weight loss” and “overweight”.

EFECTO DEL AYUNO INTERMITENTE SOBRE LA SALUD CARDIOMETABÓLICA DE PERSONAS OBESAS CON

SÍNDROME METABÓLICO EN COMPARACIÓN CON UNA RESTRICCIÓN CALÓRICA CONTINUA

Resumen. La prevalencia de síndrome metabólico está aumentando debido a la sobrealimentación y sedentarismo. Es un factor de riesgo para el desarrollo de diabetes mellitus II y enfermedades cardiovasculares. Para su tratamiento es necesaria una pérdida de peso efectiva y duradera que englobe cambios en el estilo de vida. La restricción calórica continua es el método de pérdida de peso más prescrito, sin embargo, las personas suelen recuperar el peso perdido. Los protocolos de ayuno intermitente se están investigando como un tratamiento seguro y eficaz para la pérdida de peso y mejora de la salud cardiometabólica, por tanto, el objetivo de esta investigación es definir cuáles son los efectos de realizar ayuno intermitente frente a una restricción calórica continua para el control de los parámetros cardiometabólicos en adultos obesos con síndrome metabólico. Material y métodos pertenecientes a bases de datos científicas. Se analizaron concretamente 9 artículos publicados en los últimos 10 años registrados en PubMed. El ayuno intermitente induce una pérdida de peso equivalente a la restricción calórica continua, no obstante, la pérdida de masa grasa es mayor cuando se realiza restricción calórica intermitente. Los cambios en los marcadores glucoreguladores son contradictorios y poco concluyentes. Respecto a el perfil lipídico el colesterol LDL y triglicéridos disminuyen de forma equivalente con ambas intervenciones, sin modificaciones en el colesterol HDL. Los protocolos de ayuno intermitente y restricción calórica continua tienen efectos similares sobre la salud cardiometabólica. El ayuno intermitente se trata de una intervención segura, pero existe riesgo de hipoglucemia en personas tratadas con antidiabéticos.

Palabras clave: “obesity”, “cardiometabolic health”, “periodic fasting”, “alternate day fasting”y “weight loss”.

Introduction

There is currently a high and increasing prevalence of overweight and obesity worldwide. In public health, many resources are allocated to the treatment of noncommunicable diseases derived, in part, from overeating and sedentary lifestyles [1,2].

Metabolic syndrome (MS) is a group of disorders that include high blood glucose levels, arterial hypertension (AHT), obesity, hypertriglyceridemia and low levels of HDL cholesterol. Thus, MS is a key factor in the development of cardiovascular disease and type II diabetes. The etiology is widely debated, however, obesity plays an important role in the development of this set of anomalies [1,3].

The use of drugs to control hyperglycemia, dyslipidemia and hypertension is justified as a treatment, but it is crucial to implement lifestyle changes that lead to a sustained weight loss over time together with healthy hygienic and dietary habits [4]. Continuous caloric restriction of energy (CCER) is the most prescribed weight loss method in obese people. The aim is to induce a caloric deficit of approximately 500-700 Kcal/day to reduce weight. The change in body composition over time is not affected by changes in macronutrient ratios, thus subjects often gain the weight they lost through nutritional intervention [5,6].

The Adult Treatment Panel III (ATPIII) proposed a definition that takes into account as diagnostic criteria the presence of 3 of the following factors; fasting hyperglycemia, elevated waist circumference, hypertriglyceridemia, decreased HDL cholesterol and AHT [1].

On the other hand, there is a current definition coined by the International Diabetes Federation (IDF) which proposes that the person with metabolic syndrome is

characterized by central or abdominal obesity together with 2 or more of the following factors: hypertriglyceridemia, decreased HDL cholesterol, hypertension or fasting hyperglycemia. In any case, the difference between the various definitions centers on whether the common factor is insulin resistance or central obesity [(3)].

Table 1

Comparison of the different diagnostic criteria set forth by the WHO, ATPIII and FDI [(8)]

	WHO	ATPIII	FDI
Definition	Glucose intolerance or DMTII and/or insulin resistance with two or more of the following components	Have more than 3 of the following components	Central obesity plus any two of the following four components
		Components	
Central obesity	Waist/hip ratio >0.9 men and >0.85 women and/or BMI > 30kg/m2	Waist circumference ≥ 102 in men and ≥ 88 in women	Increased waist circumference according to race- and sex-specific limits
Blood pressure	≥ 140/90 mmHg o antihypertensive treatment	> 130/85 mmHg or antihypertensive therapy	> 130/85 mmHg or antihypertensive therapy

Lipid profile	Triglycerides ≥ 150 mg/dl and/or HDL cholesterol < 35 mg/dl for men and < 39 mg/dl for women	Triglycerides ≥ 150 mg/dl and/or HDL cholesterol < 40 mg/dl for men and < 50 mg/dl for women	Triglycerides ≥ 150 mg/dl and/or HDL cholesterol < 40 mg/dl for men and < 50 mg/dl for women
Glucose	Impaired glucose tolerance or DMTII or insulin resistance	< 11mg/dl or DMTII	≥ 100 mg/dl or DMTII
Microalbuminuria	Urinary excretion rate > 20 mg/min or albumin/creatine > 30 mg/g	-	-

1.1. Etiology

The etiology of MS is still unclear and many triggers have been proposed that may contribute to its onset, including insulin resistance, dysfunction of insulin-producing cells in the pancreas, malfunction of protein kinases and phosphatases, non-expression of IRS1 and IRS2 genes due to epigenetic factors, obesity and lipotoxicity, glucotoxicity and elevated oxidative stress, chronic inflammation, intestinal microbiome and dietary effects [(7)].

MS is also well known as insulin resistance syndrome because of the role insulin plays in its development [(1,7)]. In a properly functioning organism, the increase in blood glucose stimulates the B-pancreatic cells that release insulin. On the other hand, the release of insulin together with the increase in blood glucose stimulates the uptake of glucose by the hepatic cells that will carry out glycolysis or glycogenogenesis, or its uptake by the adipose tissue. All this suppresses the production of new glucose by the liver so that all these physiological processes contribute to maintaining glucose within its homeostatic range. The most important glucose transporter is GLUT4 expressed mainly in adipose tissue and muscle. GLUT4 is stimulated by insulin and its activation is necessary for the passage of glucose into the cell [(7)].

In the first phase of insulin resistance, there is a decrease in insulin secretion, resulting in hyperglycemia after ingestion. The second phase is a chronic

hyperinsulinemia that does not resolve the previous situation since the tissues do not respond efficiently to insulin. This situation, maintained over time, leads to apoptosis of the B-pancreatic cells, which eventually lose their functionality. Therefore, insulin resistance would largely explain the existing complications in the glycolytic pathways that generate the components contemplated in MS [7,8].

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The mechanism by which insulin resistance occurs is still unclear, but it appears that protein kinases and phosphatases may play a crucial role in its development. In addition, insulin receptor proteins -1 (IRS1) and -2 (IRS2) also play key roles in the insulin signaling cascade, therefore, a suppression in the function or gene inactivation of these proteins has also been linked to insulin resistance. Moreover, studies in animal models suggest that chronodisruption negatively influences insulin signaling pathways [7,8].

It is clear that an extra energy intake combined with a sedentary lifestyle contributes to an excess in the energy balance which results in the accumulation of excessive fat. There are differences between subcutaneous and visceral fat deposits, such that visceral fat deposits associated with MS have different gene expression mechanisms and are associated with increased insulin resistance, lower HDL cholesterol and increased LDL cholesterol. In those individuals in whom there is a deficit of insulin produced by resistance or dysfunction of the B-pancreatic cells, an increase in lipase occurs [2].

The increase in free fatty acids (FFA) in turn stimulates hepatic production of VLDL triggering hypertriglyceridemia. On the other hand, an exchange of triglycerides from VLDL proteins for cholesteryl esters from HDL-C takes place resulting in a rapid clearance of HDL-C. Excess triglycerides are also transferred to LDL which will be catabolized by hepatic lipase generating smaller and denser LDL particles. These particles are more atherogenic than large LDL, as they are more susceptible to oxidation and absorption in the arterial wall. All this explains clinical signs such as hypertriglyceridemia, increased LDL levels and low HDL levels [2].

AHT appears to have a multifactorial cause mediated by endothelial dysfunction, hyperactivation of the sympathetic nervous system, inhibition of nitric oxide synthase, and the effects of cytokines released by fat tissue. In addition, obesity is associated with an increase in the renin-angiotensin-aldosterone system [2,7].

On the other hand, fat tissue has endocrine and autocrine functions. Among the adipokines secreted is adiponectin, which is related to lower systemic inflammation and higher insulin sensitivity, thus having a positive effect. In addition, obese individuals with

metabolic complications have elevated levels of C-reactive protein, interleukin-6 (IL-6) and tumor necrosis factor a (TNF-a) that contribute to macrophage infiltration of adipose tissue causing inflammation and downstream insulin receptor resistance [2, 8].

Inflammation is not only caused by macrophage infiltration and cytokine release, but has also been linked to alterations in the intestinal microbiome. Studies using experimental models suggest that a diet high in fat and low in soluble fiber (inulin) may alter the intestinal microbiome causing inflammation, an important component in the development of MS [7].

Risk factors for the development of MS include family history of MS, smoking, advanced age, obesity, low socioeconomic status, Mexican-American ethnicity, climacteric status, lack of physical activity, inappropriate intake of sugary beverages, alcoholism and Western diet, medications used in HIV or those used as antipsychotics [1].

1.2. Metabolic syndrome and other associations

Although MS was originally defined to predict the risk of cardiovascular disease (CVD), its ability to predict the risk of IMTD has been investigated. Finally, through various investigations it was concluded that early diagnosis of MS predicts incident diabetes in individuals from numerous backgrounds. The greater the number of MS components, the greater the risk of suffering IMTD, with fasting glucose and glucose intolerance being the most important determinants. A diagnosis of MS increases the risk of developing T1DMD by a factor of 5 [2].

MS is also associated with non-alcoholic fatty liver disease so that it has sometimes been referred to as the "metabolic liver syndrome". It appears that non-alcoholic fatty liver disease is associated with the components of MS such as; elevated waist circumference, AHT, elevated fasting glucose, insulin resistance and other components. The higher the number of SM components, the higher the risk of nonalcoholic fatty liver disease [2].

On the other hand, it has also been associated with the risk of cancer, however, this association is more closely related to the obesity component. It appears that inflammation of adipose tissue, hyperglycemia, hyperinsulinemia and/or insulin-like growth factor promote the development of cancer [2].

In any case, the importance of the diagnosis of MS lies in the impact it has on the probability of suffering CVD, as well as T1DM, taking into account that the main cause of death in the world is acute myocardial infarction, the prevalence of which continues to increase according to the United Nations (UN) [4]. There are also alarming data on the prevalence of MS, such as those presented by the National Health and Nutrition Examination and Surveys (NHANES), which determine its presence in 35% of U.S. adults [1]. It seems that cases of MS will increase in parallel with obesity and overweight, a fundamental factor in its development [2].

1.3. Treatment of metabolic syndrome

Treatment of MS is applied in order to reduce CVD and T1DMD. Lifestyle change strategies should be integrated with nutritional treatment and exercise [7].

Treatment of dyslipidemia and hypertension with drugs should also be considered. Among the drugs widely used for the treatment of dyslipidemias are statins that can be used together with cholesterol absorption inhibitors or bile acid sequestrants. After lowering LDL cholesterol with the drugs mentioned above, there is still some risk of CVD due to low HDL cholesterol levels. It seems that niacin increases HDL cholesterol levels, so that the combination of both treatments could be useful in some patients; however, there are no significantly superior benefits in those patients already treated with statins [2].

A meta-analysis comparing the efficacy of various interventions for SM reversal assumed that the likelihood of reversal was higher when lifestyle changes were applied compared to pharmacological treatments [15].

Finally, we must take into account the progress of nutrigenomics, a science that studies the mediated interactions between genes and nutrition. Thus a recent study has observed how women with the IRS-1 rs2943641 TT genotype have a lower insulin resistance and thus risk of TIDD when their circulating Vitamin 25(OH)D levels were higher, however, the beneficial effect was not as strong for carriers of another allele [7]. This is an example of how gene therapies can be applied in this field, however, it is still a science of lifestyle changes should lead to a loss of 7-10% of body weight, addressed through a caloric deficit of 500-1000 kcal/day to induce such a loss over a period of 6-12 months in order to improve MS symptoms and CVD risk [5].

The Mediterranean diet can be prescribed together with caloric restriction or not to all people with MS. Olive oil is an essential component of the Mediterranean diet, and studies that have evaluated its use in the treatment of MS conclude that replacing fats used with olive oil may have a beneficial effect in the treatment of MS [14]. The lipid content of the diet should be between 25-35% of total calories, since values outside this range can worsen atherogenic dyslipidemia. Fats should come primarily from polyunsaturated and monounsaturated fatty acids (olive oil) that have cardioprotective benefits against CVD and AHT in humans [5,7].

Regarding alcohol consumption, a review study shows that people who have a moderate consumption of wine or beer are less likely to develop MS, with beer being less preventive than wine, compared to those who do not drink alcohol or drink it in large quantities [14].

There are other dietary patterns that may be beneficial in the treatment of MS such as the DASH diet that has been shown to improve the symptoms of the syndrome, also the new Nordic diet and vegetarian diets (Table 2) [14,15]. It is worth noting the benefit of accompanying the above changes with a physical exercise program that includes 30 to 60 minutes of moderate physical activity for the control and treatment of MS development that needs a research trajectory [5,14].

Table 2.

Dietary patterns and potential benefits in the control of MS (15)

Dietary pattern	Nutritional distribution	Improvements in the SM components
Mediterranean Diet	· 35.45% kcal/day of lipids (mainly monounsaturated and polyunsaturated from olive oil and nuts) · 35-45% kcal/day of carbohydrates · 15-18% kcal/day of protein	Decreases; CVD, hypertension, mortality, dyslipidemia, and IIDM
Vegetarian diet	· Restriction of foods of animal origin · High intake of plant foods · Rich in polyunsaturated fats	Decreases; HTA, body weight, CVD, mortality and DMII
Nordic diet	· High in fiber-rich whole foods · Few meat and processed foods	Decreases HTA and increases HDL cholesterol levels
DASH diet	· Low in fat (27% kcal/day), especially saturated fat (6% kcal/day) and cholesterol · Sodium reduction to 1500- 2300 mg/day · Rich in fiber (>30 g/day), potassium, magnesium and calcium	Decreases; HTA, CVD, cancer, DMII, body weight and adiposity

1.4. Continued caloric restriction (CCR)

CCR is the most prescribed weight loss method in obese adults and also in those with MS. The objective of the treatment is to induce a daily caloric deficit of about 25-30% (500 - 750 kcal) of total calories without lack of essential nutrients in order to achieve a significant weight loss that can be maintained over time. There is evidence that adherence to treatment is lost or decreases after 1 to 4 months and is inefficient when the lost weight is regained [6,17]. For this reason, it is necessary to address new nutritional treatments in the control of MS that improve follow-up and long-term success in weight loss and control of metabolic parameters [6,16].

In general, it can be said that CCR has benefits on life expectancy and health. There are four mechanisms through which CCR increases cellular longevity and lifespan; adaptations of the neuroendocrine system, prevention of inflammation, hormonal response and protection against oxidative stress [10].

The adaptations of the neuroendocrine system have their benefit in a reduction of anabolic hormones, insulin resistance and hormones that promote thermogenesis, as well as an increase in anti-inflammatory hormones. It has been demonstrated in experimental animal models that CCR is able to delay diseases such as cancer, cardiomyopathy, neurodegenerative diseases, diabetes, kidney disease and arteriosclerosis [10].

It has been established that RCC is capable of resolving errors produced in DNA and promoting the elimination of damaged proteins and lipids, as well as playing an antioxidant role by activating endogenous enzymatic and non-enzymatic mechanisms. It also triggers processes such as enhanced apoptosis, autophagy and decreased oxidative stress. It is able to reduce fasting insulin levels and some growth factors and cytokines such as tumor necrosis factor α (TNFα) which causes inflammation and is elevated in MS. Studies with primates have also observed how a 30% CCR can decrease glucose intolerance, CVD and cancer [10].

1.5. Intermittent caloric restriction (ICR)

Among the dietary strategies currently being investigated are intermittent fasting or intermittent calorie restriction (ICR) which appears to have benefits on CVD, T2DM, metabolic disorders and cancer due to the caloric restriction it entails. The main cardiometabolic benefits when ICR strategies are applied are decreases in insulin resistance, body weight, blood pressure, dyslipidemia and inflammation in general terms [9]. RCI generally refers to the intake of a very low calorie diet (VLCD) 500-700 kcal for approximately 2 to 4 days a week. These types of interventions are more commonly accepted by people, as strict caloric restriction is only done on specific days of the week. It is therefore interesting to evaluate the benefits of these regimens for obese individuals with MS [9].

A limitation in the field of intermittent fasting is the lack of clear terminology defining the different regimens of IFN. In general, dietary patterns in which prolonged periods of reduced or no intake are included with those in which the person eats normally are referred to as RCI [6]. The characteristics of the different ICR regimens known as; alternate day complete fasting (ADA) or consecutive (2:5 diet), alternate day modified fasting (AMDA) and time-restricted feeding (ART) are detailed below [12,13].

In alternate day complete fasting (ADA), fasting days in which no caloric intake is performed alternate with feeding days in which food and beverages are consumed ad libitum [18]. In the two-day-a-week (2DS) fasting, also known as the 5:2 diet, the fast is prolonged for two days and then food is consumed ad libitum for the rest of the week. [6,19].

Method

The literature review was carried out by analyzing the scientific evidence on ICR protocols in the treatment of MS, in addition to their application compared to classic CCR for the control of the syndrome.

It was carried out through the initial selection of 8577 articles, 1634 were eliminated for not being original or duplicates, 6849 for not meeting the inclusion criteria and 85 for not fitting the subject matter. The literature search was initiated in January 2022 and completed in April 2022.

The search was carried out in Pubmed, Cocharane, Google Scholar and Clinical Trials databases. The key words used were "obesity", "cardiometabolic health", "periodic fasting", "alternate day fasting", "weightloss" and "overweight". The inclusion criteria for the selection of articles were those published since 2012, indexed in scientific journals with an impact factor greater than 1.5 and dealing with topics related to ICR, SM and CCR. The exclusion criteria were articles published more than 10 years ago, in non-indexed journals and those published in journals with an impact factor of less than 1.5. In addition, articles were excluded if the sample included persons with normal weight and preserved cardiometabolic health. Finally, most of the selected articles were found in Pubmed belonging to scientific journals.

Results

In relation to the effectiveness of ICR as an alternative treatment to CCR in people with MS, 3 articles were included, 2 of which were randomized clinical trials and 1 a systematic review. Table 3.1 details the characteristics and results found in each study [18,19,22].

Regarding weight loss two of the articles [18,19] concluded that weight loss is greater when performing RCI protocols compared to RCC, however, Kunduraci et al. [22] found no significant differences, but significant weight loss in both groups. In this same study, improvements in waist/hip ratio, fat mass, total body water and BMI were observed in participants who performed ICR compared to CCR, therefore, although ICR does not offer advantages over weight loss, it does result in a greater decrease in fat mass and contributes to maintaining lean mass (20). Also Parvaresh et al. [17] reported a greater reduction in waist-to-hip ratio in the RCI group.

Various glucoregulatory markers were analyzed; two of the studies showed significant reductions in fasting glucose [19,22] when comparing both groups, whereas Wang et al. [18] did not find the same results. Regarding fasting insulin concentrations,

HbA1c and HOMA-IR there were no differences between the intervention arms in two of the articles [18,19], however, significant differences were found in HOMA-IR in the study by Kunduraci et al. [22].

Regarding the changes in the lipid profile of the participants, all the studies state that the reductions in total cholesterol, LDL and triglycerides were similar in the RCI and RCC groups. HDL cholesterol remained unchanged in both intervention arms [18,19,22].

Some caution should be exercised in interpreting the above findings since the randomized clinical trials conducted by Parvaresh et al. [19] and Kunduraci et al. [22] are of short duration (8-12 weeks) and a small sample (70 participants). In addition, it should be noted that the RCI regimens applied in each trial were different, Kunduraci et al. used ART regimens while Parvaresh et al. studied ADF regimens. Studies with a larger number of participants with MS are needed to corroborate the results and have clinical relevance to ensure that RCI is an alternative to RCC for this type of profile.

There are few studies that compare the efficacy of ICR with CCR in people with MS, since most of them use overweight and obese people as a sample. As a result of the above, 6 articles have been included that directly analyze the benefits of performing ICR with respect to CCR in overweight and obese individuals, since obesity itself is a key factor in the development of MS. Depending on the type of study, 1 literature review [6], 1 systematic review [11] and 4 randomized clinical trials [20,21,23,25]were included.

Regarding the changes produced in body composition, all articles endorse a significant and similar weight loss when performing CCR or ICR [6,11,20,21,21,23,25]. Also Cioffi et al. [17] corroborate these results in their meta-analysis. In this aspect it does not coincide with 2 of the articles whose results in people with MS approve a greater weight loss with RCI regimens [16,19].

Several glucoregulatory markers were analyzed; fasting glucose, HOMA-IR, HbA1c, fasting insulin, insulin sensitivity and insulin resistance. In the case of fasting glucose showed similar reductions in both intervention arms in 4 of the studies [6,11,20,25], Sutton et al. [23] reported that there were no reductions in fasting glucose concentrations during the study in the RCI group. On the other hand, 2 of the studies [11,21] showed that the reductions in fasting glucose and HbA1c were greater in the group that underwent ICR; however, Welton et al. warned of the risk of hypoglycemia that exists in those treated with oral antidiabetics or insulin, for which reason caution should be exercised when implementing this type of dietary treatment.

Regarding sensitivity, insulin resistance, as well as fasting insulin and pancreatic B-cell responsiveness, 3 of the studies [6,20,24] reported that there were no additional advantages of performing ICR versus CCR. In addition, Pinto AM et al. [20] added that the reductions produced had no therapeutic relevance. On the other hand, 3 of the studies [11,21,23] did find improvements in fasting insulin, insulin resistance, insulin sensitivity and pancreatic B-cell responsiveness.

Regarding improvements in lipid profile, 2 of the studies [21,24] report improvements in HDL cholesterol when RCI protocols are carried out, in contrast to the results found by Sutton et al. [23] who found no changes in HDL cholesterol during the study. Moreover, there were also no changes in HDL in studies performed in people with MS [16,19,22]. LDL cholesterol was not affected either in the study by Sutton et al. [23]. The TG results were significantly increased in the RCI group in 2 of the studies [20,23], contrasting with the improvements found in the study by Sundfor et al. [21].

In a study by Trepanowski et al. [24] reported a high dropout rate in the ADA group. For this reason, they decided to conduct a secondary study [25] in order to clarify the reasons why they had dropped out of the study. The null hypothesis was that ADA regimens could lower leptin and other adipokines in such a way that adherence to the dietary regimen would be difficult for participants. This hypothesis was not confirmed; it was established that circulating leptin and other adipokine levels increased in both intervention arms during the study.

Table 3.

Articles addressing the effectiveness of intermittent fasting in people diagnosed with metabolic syndrome compared to continuous caloric restriction

Author, year, type of study, sample size and characteristics	Study groups and regimens applied	Body composition	Glucoregulatory markers	Lipids
Kunduraci YE et al. 2020 [22] Randomized Controlled Trial 70 participants with a diagnosis of MS 12 weeks of duration	GI: RCC time-restricted feeding ART (<25% kcal) GC: RCC <25% kcal	Both significantly decreased weight	Fasting glucose, HOMA-IR and HbA1c decreased significantly in both groups	Total cholesterol, triglycerides and LDL in both groups decreased significantly.
Parvaresh A et al. 2019 [19] Randomized clinical trial 69 participants with a diagnosis of MS 8 weeks duration	GI: AFD (alternate day fasting) GC: CCR 25% per day	The ADF protocol showed significant weight reductions compared to the ADF protocol with RCC	The ADF protocol significantly reduced fasting glucose compared to CCR. There were no significant differences in HOMA-IR or fasting insulin concentrations between the two groups.	No significant differences were observed in TG, total cholesterol and HDL between the groups.
Wang X et al. 2021[18] Systematic review and meta-analysis of 4 studies. Participants with SM 8-12 weeks	GI: Different RCI regimes GC: CCR 25% OF kcal/day	ICR was more successful for weight loss than CCR	No significant differences were found in HbA1c or fasting glucose between groups.	There was no statistical difference in total, HDL and LDL cholesterol levels.

Table 4.

Articles addressing the effectiveness of intermittent fasting in overweight and obese individuals compared to continuous caloric restriction

Author, year, type of study, sample size and characteristics	Study groups and applied regimens	Body composition	Glucoregulatory markers	Lipids
Rynders CA et al. [6] 2019 Literature review 11 clinical trials Overweight persons and obesity Duration >= 8 weeks	GC: RCC GI: Different RCI strategies	There are no significant differences in weight loss or in the loss of body fat	There are no advantages in the improvement of cardiometabolic health when comparing both groups.	It was not studied.
Welton S et al. [11] 2020 Systematic review of 41 items Overweight people and obesity Duration between 2 and 26 weeks	QA: following a diet with RCC GI: monitoring of different rCI protocols	Similar weight loss in both groups	Glucose levels in the blood fasting and fasting insulin decrease significantly with rCI protocols, however, may be at risk of hypoglycemia for diabetic people.	It is not rated at the study.

Pinto AM et al. [20] Randomized clinical trial 43 participants with central obesity 4 weeks duration	GI: diet 5:2 CC: RCC Protocol	Similar weight loss in both intervention groups	It increased insulin sensitivity, decreased insulin resistance, serum insulin and blood glucose in both intervention arms. The magnitude of the change was not relatively therapeutic.	Intervention group increased fasting TG concentrations.
Sundfor et al. [21] 2018 Randomized controlled trial 112 overweight and obese participants Duration 6 months and a further 6-month maintenance phase	GI: ADA fasting (400-600 kcal) every other day GC: RCC Protocol	Similar weight loss in both groups, and recovery at 6 months was also minimal and similar. Decrease in waist circumference with no significant differences among the different groups.	There were improvements in HbCA1 in the ADA group compared to RCC. Insulin sensitivity was also improved.	Improvements in TG and HDL cholesterol were observed in the intervention group.
Sutton E et al. 2018 [23] Randomized controlled trial 8 participants with overweight and obesity 5 weeks duration	GI: ART early feeding restricted in time CC: Normal power supply 12/12 Both performed the intakes under supervision throughout the study	Similar weight loss in both groups.	TRF improved insulin sensitivity, B-cell responsiveness and reduced insulin levels. It did not improve glucose levels.	TRF increased resting heart rate, TG and total cholesterol. HDL and LDL cholesterol were not modified.

Trepanowski J et al. [24] 2017 Randomized clinical trial 100 obese participants 1 year duration (6 months of intervention + 6 months of maintenance)	GI: fasting on alternate days ADA (25% caloric restriction on fasting days) GI: continuous caloric restriction (75% of TSG every day) GC: no intervention	Similar weight loss in the continuous caloric restriction and ADA groups.	There were no significant differences in fasting glucose concentrations, insulin resistance and fasting insulin between the intervention groups, but there were significant differences with respect to the control group.	It increased LDL cholesterol in the group performing ADA at month 6 significantly, but not at month 12 compared to CCR. HDL cholesterol was significantly elevated in the month 12 in the ADA participants compared to the ADA group RCC.

Discussion and conclusions

RCI protocols in people with MS appear to result in greater weight and fat mass loss in the short term than CRS. In the long term there is no evidence of an advantage of RCI over RCC for weight loss in the treatment of obese individuals. On the other hand, the results on the improvement of glucoregulatory parameters with ICR versus CCR are contradictory and inconclusive. As for changes in the lipid profile, there were equivalent reductions in LDL cholesterol and triglycerides without changes in HDL cholesterol.

Therefore, both interventions have similar effects on the control of cardiometabolic parameters; however, it remains to be resolved whether the cardiometabolic effects mediated by RCI are due solely to the caloric deficit generated. ICR is a safe protocol, however, caution should be exercised in those treated with antidiabetics due to the risk of hypoglycemia. It should be noted that all the studies analyzed were of short duration and with a small sample size, so more studies are needed, with a sufficiently large sample size to be extrapolated to all people with MS.

More clinical trials comparing the efficacy of ICR in people with MS vs. CCR are needed, as most studies include overweight and obese people.

The following recommendations are proposed for future studies:

- A consensus document should be drawn up to define the definition and characteristics of ICR regimens so that accurate comparisons can be made between the various studies.
- Studies should include the dietary recommendations and the menu prescribed for each diet, as well as the percentage of macronutrients in the diet, since most of them only mention the daily amount of restricted energy.
- Development of studies that include a large sample of people diagnosed with MS. In addition, it would be advisable for them to be of long duration in order to observe whether there are metabolic changes and good adherence that could be an advantage over CCR.
- Take into account confounding variables in future studies that may affect the results, such as physical activity or adherence to the prescribed diet by the participants.

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