MLS - HEALTH & NUTRITION RESEARCH

https://www.mlsjournals.com/MLS-Health-Nutrition

Health & Nutrition Research

Como citar este artículo:

Eguren, G.I. (2022). Nuevos tratamientos dietético-nutricionales en diabetes mellitus tipo 2: una revisión narrativa. *MLS Health & Nutrition Research, 1*(1), 7-22.

NEW DIETARY-NUTRITIONAL TREATMENTS IN TYPE 2 DIABETES MELLITUS: A NARRATIVE REVIEW

Imanol Eguren García
Universidad Europea del Atlántico (España)
imanoleguren7@gmail.com · https://orcid.org/0000-0003-1179-6764

Abstract. Introduction: The increase in the prevalence of type 2 Diabetes Mellitus is closely related to current bad eating and lifestyle habits. Dietary-Nutritional strategies, such as intermittent fasting or high protein diet, could be new treatment options effective and safe in order to improve glycaemic control in people with type 2 Diabetes Mellitus. Objective: Assess the effectivity and safety of intermittent fasting and high protein diet as new dietary-nutritional strategies in the treatment of type 2 Diabetes Mellitus. Method: A bibliographic review was carried out, for which 12 scientific articles from the Pubmed database published in the last 5 years (from April 2015 to April 2020) were selected and analysed, 6 referring to intermittent fasting and 6 to high protein diet. Results and discussion: Both intermittent fasting and high protein diet, with a hypocaloric approach, are dietary-nutritional strategies effective and safe for glycaemic control in adults with type 2 Diabetes Mellitus due to the fact that they cause weight loss which reduces insulin resistance. In the case of intermittent fasting, it is advisable to adjust the medication at the time of intakes to improve its safety, while high protein diet is safe as long as there is no previous kidney damage. Future research is needed to show that both strategies have effects on glycaemic control independent of weight loss.

Keywords: Type 2 Diabetes Mellitus, intermittent fasting, high-protein diet, glycaemic control, weight loss.

NUEVOS TRATAMIENTOS DIETÉTICO-NUTRICIONALES EN DIABETES MELLITUS TIPO 2: UNA REVISIÓN NARRATIVA

Resumen. Introducción: El aumento de la prevalencia de Diabetes Mellitus tipo 2 está muy relacionada con los hábitos actuales de alimentación y vida poco saludables. Estrategias dietético-nutricionales como el ayuno intermitente y la dieta hiperproteica, podrían ser nuevas opciones de tratamiento efectivas y seguras para mejorar el control glucémico en personas con Diabetes Mellitus tipo 2. Objetivo: Evaluar la efectividad y seguridad del ayuno intermitente y la dieta hiperproteica como nuevas estrategias dietético-nutricionales en el tratamiento de la Diabetes Mellitus Tipo 2. Método: Se realizó una revisión bibliográfica, donde se analizaron un total de 12 artículos científicos de la base de datos Pubmed publicados en los últimos 5 años (de abril 2015 a abril 2020), 6 referentes a ayuno intermitente y 6 a dieta hiperproteica. Resultados y discusión: Tanto el ayuno intermitente como la dieta hiperproteica, con un enfoque hipocalórico, son estrategias dietético-nutricionales efectivas y seguras para el control glucémico en adultos con Diabetes Mellitus tipo 2, debido al hecho de que provocan una bajada de peso la cual disminuye la resistencia a la insulina. En el caso del ayuno intermitente es recomendable ajustar la medicación a la hora de las ingestas para mejorar su seguridad, mientras que la dieta hiperproteica es segura siempre y cuando no exista daño renal previo. Se necesita futura investigación para demostrar que ambas estrategias tienen efectos sobre el control glucémico independientemente de la pérdida de peso.

Palabras clave: Diabetes Mellitus tipo 2, ayuno intermitente, dieta hiperproteica, control glucémico, pérdida de peso.

Introduction

The term Diabetes Mellitus (DM) encompasses a group of chronic diseases whose common characteristic is hyperglycemia due to a defect in insulin production, in its action, or in both. Ninety percent of the total diagnosed cases of DM belong to type 2 (DM2), although it is worth noting that a large percentage of cases are undiagnosed (1).

Prevalence and incidence rates have increased in recent years worldwide, especially among young people as reflected by the International Diabetes Federation in its 2019 atlas (2). In Spain, the results of the first part of the study di@bet.es (3) reported a prevalence of DM2 of 13.8% in 2010, implying that more than 4.5 million Spaniards were diagnosed with this disease. In the second part of the study (4) carried out in 2015, the incidence of DM2 in Spanish population was analyzed, being 11.6 cases/1000 persons/year.

The increase in the number of cases of DM2 worldwide seems to be caused by the aging of the population, the increase in sedentary behavior, and the increase in the consumption of unhealthy foods, factors that have been related to the development of obesity and insulin resistance in peripheral tissues (1,5).

DM2 is a major public health problem due to the high human, social, and economic costs derived from medical treatment, in addition to the need to treat the acute and chronic complications generated. Among the acute complications is the appearance of hypo- and hyperglycemia, where the latter can lead to the appearance of diabetic hyperosmolar hyperglycemic syndrome (HHS). Chronic complications include microvascular complications (diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy) as well as macrovascular complications (arterial hypertension, dyslipidemia, cardiovascular disease, and diabetic arteriopathy). DM2 is considered the main cause of cardiovascular disease, blindness, non-traumatic amputations, and renal failure in developed countries (1).

Despite these data, there are several publications that affirm that the establishment of good lifestyle habits by following a healthy, adapted, varied, and balanced diet, together with the practice of regular physical activity, they play a key role in preventing the development of DM2, as well as in controlling its signs and symptoms and the appearance of associated complications. It can be stated that the development and progression of DM2 is strongly influenced by dietary and nutritional habits (6). However, the American Diabetes Association (ADA) has not established a consensus on the most appropriate nutritional treatment to apply in DM2, with special emphasis on the importance of individualizing dietary patterns (7).

Several meta-analyses, literature reviews, and studies (8-10) have shown that following a Mediterranean-type diet, characterized by a high consumption of plant-based foods and quality fats, can act as a protective factor against the main chronometabolic diseases that affect our society today, including DM2 (8). Following this dietary pattern has been shown to improve the cardiometabolic profile (9), reduce blood pressure levels, normalize blood glucose, and reduce body mass index (BMI) in people with DM2 (10).

The effectiveness of a dietary pattern in the treatment of a disease lies in the capacity of adherence and adaptation that the affected person generates on it. Currently, different research groups are increasing their interest in the search for new dietary patterns, different from following a conventional Mediterranean diet, to help control chronic diseases related to diet, including DM2. Within these new dietary-nutritional patterns, intermittent fasting (11) and the hyperproteic diet (12) are currently being strongly investigated and discussed within the scientific community as possible treatments in DM2 due to the potential benefits found in both types of dietary patterns.

The main objective of this review is to evaluate the effectiveness and safety of following an intermittent fasting or a hyperproteic diet as a dietary-nutritional treatment in people with DM2.

Method

A search for scientific articles related to the topic was conducted, giving priority to human clinical trials, review articles, and meta-analyses using the Pubmed database. The search for articles began in January 2020 and ended in April 2020.

To locate articles relating intermittent fasting and DM2 we applied the 5 years old filter and used the different search strategies: ("Fasting" [MeSH] or "Intermittent Fasting" [in title and abstract]) AND ("Diabetes Mellitus type 2" [MeSH], or "Diabetes Mellitus type 2" [in title and abstract], or "Glycemic Control" [in title and abstract], or "Hypoglycemia" [in title and abstract], or "Insulin Resistance" [in title and abstract], or "Weight Control" [in title and abstract]).

To locate articles relating Hyperproteic Diet and DM2, the 5 years old filter was applied and the following search strategies were used: ("Hyperproteic Diet" [MeSH] or "Hyperproteic Diet" [in title and abstract] AND ("Diabetes Mellitus type 2" [MeSH], or "Diabetes Mellitus type 2" [in title and abstract], or "Glycemic Control" [in title and abstract], or "Hypoglycemia"

[in title and abstract], or "Insulin Resistance" [in title and abstract], or "Weight Control" [in title and abstract]).

Once the titles and summaries of the different articles were obtained, the inclusion criteria were observational studies, clinical trials, reviews, or meta-analyses in which an intermittent fasting protocol or a high-protein diet was applied in persons diagnosed with DM2 or pre-diabetes, with or without overweight/obesity, and interventions of at least 1 month's duration.

The exclusion criteria were articles that did not fit the topic were carried out in cellular models, animal models; the sample that was not diagnosed with DM2 or pre-diabetes, the interventions were of very short duration or it was impossible to read beyond the title/abstract.

Finally, a total of 12 articles were selected and included in the review; 6 related to Intermittent Fasting and DM2 and 6 related to Hyperproteic Diet and DM2, which were analyzed in depth.

Results

Intermittent Fasting

Intermittent fasting is understood as the alternation of periods of voluntary abstention from food intake with periods of free intake for a certain period of time (11).

Fasting is a practice that has been used since ancient times, due to the religious and medical properties that have been attributed to it (11). Currently, the interest of the world population in this practice has increased in recent years, producing an exponential increase in internet searches (13). This fact has led numerous lines of research to focus on investigating the health effects of intermittent fasting and its use as a possible medical treatment (14).

Intermittent fasting is not a dietary plan per se, so the type of food consumed during the period of intake and its quality are not taken into account (13). Depending on the duration of the period of intake restriction, a classification of different types of intermittent fasting is established (13,16-19). The main types of fasting and their description, assuming that there are many possible variants, are summarized in Table 1. It should be emphasized that it is difficult to make a classification since there is no consensus on the part of any national or international scientific body.

Table 1. Summary of the main types of feeding patterns in intermittent fasting (11, 13-17).

Name	Abbreviation	Description
Food restricted time	TRF	Fasting 16 h - Feeding 8 h Fasting 12h - Feeding 12h
Early restricted time feeding	eTRF	Feeding allowed from 6:30-8:00h until 14:00-15:00 h.
Fasting alternate days	ADF	Alternates: 1 full day fasting - 1 day normal food intake
Modified alternate-day fasting	ADMF	Alternates: 1 day intake of 20-25% Total Energy Expenditure (TEE) - 1 day total intake of TEE
Periodic fasting	PF	Alternates: 2 non-consecutive days per week intake 20-25% of GET - remaining days of the week total intake of GET

TRF: Time-Restricted Feeding; eTRF: Early-Time Restricted Feeding; ADF: Alternated-Day Fasting; ADMF: Alternated-Day Modified Fasting; PF: Periodic Fasting.

In the following sections we will analyze different mechanisms through which following different intermittent fasting strategies can produce beneficial effects on the control of DM2, the most significant of which are efficacy in weight loss, improvements in markers of glycemic control, and reduction of insulin resistance. At the same time, the risks and contraindications of following an intermittent fasting protocol in people with DM2 will be presented.

Intermittent fasting and weight loss

As previously mentioned, one of the main risk factors for the development of DM2 is being overweight or obese (1). It has been shown that a reduction in body weight can improve and even reverse DM2 in a large percentage of diagnosed individuals (6), so that a main objective in the treatment of DM2 is to reduce body weight, especially in those individuals who, in addition to DM2, are also overweight or obese.

The hourly restriction of food intake can facilitate the consumption of fewer calories at the end of the day (11). For this reason, several professionals prescribe a hypocaloric diet within an intermittent fasting protocol, with the aim of creating an energy deficit in a simpler way that favors weight loss. However, several studies have been carried out which reject this belief that intermittent energy restriction favors weight loss more than a continuous hypocaloric diet (13,16,18,19).

In 2018, Harris L et al. (16) performed a meta-analysis where they analyzed a total of 6 clinical trials, which evaluated the efficacy of following different intermittent energy restriction protocols in reducing body weight during a time period of 3-12 months in different samples of

people older than 18 years with BMI ≥ 25 kg/m^2. In 4 of the trials, the control groups performed a continuous hypocaloric diet during the same time periods. The results obtained were that intermittent energy restriction and continuous energy restriction resulted in weight loss without significant differences (-1.03 (-2.46, -0.40) kg; 95% CI; p = 0.156).

In the review by Seimon RV et al. (18), they reached the same conclusion as the previous meta-analysis. After analyzing a total of 40 clinical trials evaluating the effectiveness of following different intermittent fasting protocols (specifically different ADF protocols) to reduce body weight and control blood glucose for a mean of 12 weeks, they stated that different intermittent fasting protocols produce similar effects to continuous energy restriction in reducing body weight and glucose metabolism.

Intermittent fasting and glycemic control

In humans, the main mechanism by which intermittent fasting improves glycemia is the reduction of insulin resistance in peripheral tissues; this mechanism being dependent on weight loss, which means that continuous energy restriction, when also producing weight loss, achieves the same effects on glycemia. Few studies have directly evaluated the effect of intermittent fasting on glycemic control in humans (20-22).

A randomized clinical trial by Carter S et al. (20) addressed this relationship. A total of 137 individuals aged 61 ± 9.1 years with obesity (BMI of 36.0 ± 5.8 kg/m^2) and DM2 (HbA_{1c} 7.3 ± 1.3%) participated. The objective was to compare the effects of following an intermittent energy restriction protocol with continuous energy restriction on glycemic control and weight loss in individuals with DM2 for 12 months. The intervention group was subjected to a 5:2 FP (on fasting days the number of calories was 500 - 600 kcal), while the control group followed a continuous hypocaloric diet (1200 - 1500 kcal/day), both diets had the same foods and were elaborated by dieticians-nutritionists, who offered advice to both study groups. During the one-year follow-up of the study, no significant differences were found between the control group and the intervention group in the decrease of HbA_{1c} levels (- 0.5 ± 0.2% vs - 0.3 ± 0.1%; 90% CI; p = 0.65) and weight loss (-5.0 ± 0.8 kg vs - 6.8 ± 0.8 kg; 90% CI; p = 0.25) between both groups.

One year after the end of the intervention, the same authors (21) measured the same variables again in both groups one year after the end of the intervention. As results they found that HbA_{1c} levels increased in both the control group (0.4 ± 0.3%) and the intervention group (0.1 ± 0.2%) although without significant differences between the two groups (CI 90%; p = 0.32). Weight loss was maintained at -3.9 ± 1.1 kg in both groups, with a difference between the two groups of 0.07 (-2.5, 2.6) kg; 90% CI).

Cho Y et al. (22) pooled in a meta-analysis, 12 clinical trials (a total of 545 participants with DM2) comparing the effectiveness of different intermittent calorie restriction protocols (TRF, ADF, ADMF and PF) in reducing BMI and improving glycemic metabolism with a continuous hypocaloric diet. After the end of the intervention periods of the different studies, which ranged from 4 to 24 months, it was found that there was a significant decrease in fasting glucose levels in those groups that followed an intermittent fasting protocol compared to the control groups (-4.16 (-6.92, -1.40) mg/dL; 95% CI; p = 0.003). A significant decrease in BMI was also observed in the intervention group compared to the control group (-0.75 (-1.44, -0.06) kg/m^2; 95% CI; p = 0.033). In this investigation, variation in insulin resistance levels was also assessed in 6 of the studies using the homeostatic model assessment marker of insulin resistance

(HOMA-IR). The decrease in mean insulin resistance was significantly greater in the groups following an intermittent energy restriction protocol (0.54 (-1.05, -0.03) %; 95% CI; p = 0.038).

Sutton EF et al. (17) sought to demonstrate that early intermittent fasting (eTRF), in tune with circadian metabolic rhythms, has benefits in improving insulin resistance independent of weight loss. To this end, they conducted a 5-week randomized clinical trial in which they divided the sample of 12 adults aged 56 ± 9 years with obesity (BMI = 32.2 ± 4.4 kg/m^2) and prediabetes (fasting glucose 102 ± 9 mg/dl). Individuals in the intervention group performed an eTRF with 6 hours of early feeding (from 8:00 am until 2:00 pm), and those in the control group a TRF similar to the feeding pattern of the average American citizen with 12 hours of feeding (from 8:00 am until 8:00 pm), 12 hours of fasting, of which only 8 individuals completed the test. The diet in both groups was normocaloric, adjusted to the needs of each individual and was not focused on weight loss. Among the results, it was obtained that the application of an eTRF significantly improved basal insulin levels (3.4 ±1.6 mU/l; p <0.005) and insulin resistance (36 ± 10 U/mg; p <0.005), independently of weight loss. In addition, it was the first intermittent fasting study to show the weekly menu with its respective foods, although not the amounts, since these depended on the energy needs of each individual.

Risks and Contraindications

Following an intermittent fasting protocol is not risk-free, both in the short and long term, and even less so in ill persons, as is the case of patients with DM2 (24).

The most frequent short-term risk in patients with DM2 who practice intermittent fasting is the occurrence of episodes of hypoglycemia (24). The patients most at risk are those under treatment with insulin and/or sulfonylureas (11). Other types of antidiabetic medication are not usually associated with episodes of hypoglycemia (25,26). The results obtained in the clinical trial by Corley BT et al. (27) show that any fasting protocol, whether scheduled or not, increases the risk of hypoglycemia compared to a regular meal schedule in patients with DM2 without other pathologies. However, in those patients who receive more nutritional education and have more frequent blood glucose monitoring, hypoglycemia episodes are lower (28).

Hyperproteic Diet

The recommended daily intake (RDA) of protein for a sedentary adult, regardless of age and sex, is 0.8 g/kg body weight per day, which represents 10-15% of total calories (29). Diets with this protein content are considered normoproteic for adults, although the needs vary with age, physical activity, and state of health (30). This amount is considered the minimum to avoid protein deficiency; however, in recent years it has been proposed that providing higher amounts of protein can be beneficial for the control of metabolic diseases (12,31).

It is difficult to establish the limit for a diet to be considered high-protein. In general, a high-protein or hyperprotein diet is defined as one that provides more than 20% of total calories in the form of protein, which represents an amount of about 1.2 g/kg bw/day, the same as the amount recommended for the elderly (29,30).

The following sections will show the possible beneficial effects of following a high-protein diet in the management of DM2 by aiding weight loss and improving glycemic control. At the same time, the risks and contraindications of following a high protein diet in people with DM2 will be presented.

Hyperproteic diet and weight loss

The use of a high protein diet has been considered an effective protocol for weight loss in cases of overweight and obesity (31).

Wycherley TP et al. (31) evaluated in a meta-analysis 24 clinical trials comparing the differences in weight loss between following a low-fat, high-protein diet, and a diet with the same calories low in fat but normoproteic. Data were collected from a total of 1063 individuals over 18 years of age. The mean duration of the interventions was 12.1 ± 9.3 weeks. Compared with a normal protein diet, the hyperprotein diet produced a significant, albeit moderate, reduction in body weight (-0.79 (-1.50, -0.08) kg; 95% CI; $p < 0.005$).

However, other studies did not reach these results. In a review and meta-analysis of the literature, Zhao T et al. (12) analyzed 18 clinical trials, where they found no significant difference in whether the amount of protein in a normocaloric diet is related to greater or lesser weight loss in adults with DM2 (-0.09 (-0.21, -0.04) kg; 95% CI; $p = 0.17$).

In 2015, Tay J et al. (32) conducted a clinical trial where they evaluated in 115 adults with obesity (BMI 34.6 ± 4.3 kg/m^2 and DM2 (HbA1c 7.3 ± 1.1%) the differences in weight loss between following a hyperproteic hypocaloric diet and a normoproteic hypocaloric diet together with the same physical exercise program. After 52 weeks of intervention, no significant differences were found in the resulting weight loss between the two groups (-9.3 (-10.6, -8.0) kg; 95% CI; $p = 0.18$).

The same results were obtained by Campos-Nonato I et al. (33) where in a sample of 105 adults and after 6 months of intervention they found no significant differences in the percentage of weight lost between following a hypocaloric diet with a standard amount of protein (0.8 g protein / kg weight) and a hypocaloric hyperprotein diet (1.34 g protein / kg weight) -2.1(-7.5-3.2) (95% CI; $p = 0.427$). However, a higher percentage of weight loss was observed in those individuals with high adherence to the prescribed diet (considered those who complied with the prescribed diet at least 75% of the time), being higher in the individuals in the intervention group (-9.5%) than in the individuals in the control group (-5.8%) (99% CI; $p < 0.001$).

High-protein diet and glycemic control

Different systematic reviews and meta-analyses have analyzed different clinical trials studying the effects of following a high-protein diet on glycemic control in people with DM2 (12,34,35).

In the meta-analysis of clinical trials presented above, Zhao T et al. (12) also collected data on different markers of glycemic metabolism. No significant differences were found between following a hyperprotein and a normal protein diet in changes in fasting glucose (-0.08 (-0.21, -0.06); 95% CI; $p = 0.25$), fasting insulin (-0.04 (-0.24, 0.17); 95% CI; $p = 0.71$), and HbA1c (-0.07 (-0.20, 0.06); 95% CI; $p = 0.27$), suggesting that the amount of protein present in the diet does not affect long-term glycemic control in adults with DM2.

In another meta-analysis, Yu Z et al. (34) analyzed 13 clinical trials studying the effect of following a high-protein diet on glycemic control in different samples with a total of 1138 adults with DM2. The results showed no significant differences in changes in fasting glucose (-0.13 (-0.46, 0.19); 95% CI; p = 0.43) and HbA1c (-0.05 (-0.18, 0.08); 95% CI; p = 0.92) between following a high-protein diet and a normal protein diet. However, significant differences were observed in the reduction of insulin resistance, measured by the HOMA-IR marker (-0.27 (-0.47, -0.06); 95% CI; p = 0.01).

The results of the two previous publications also correlate with the conclusions obtained in the systematic review recently carried out by Malaeb S et al. (35), where after analyzing a total of 21 clinical trials they concluded that, in randomized studies with a large number of participants and long term, following a high-protein diet does not provide greater benefits in glycemic control in patients with DM2 than a diet with a normal protein content associated with abandonment or non-follow-up of the diet.

Risks and Contraindications

As previously mentioned, a protein intake above the RDA may be beneficial for the control of metabolic diseases (12,31). However, excessive intake is not without risk (36-39).

First, it has been postulated that long-term consumption of a high-protein diet can produce a series of alterations in renal function that can lead to the development of renal diseases (36-38). The potential renal damage associated with a high protein diet appears to be glomerular hyperfiltration, proteinuria, nephrolithiasis, increased renal acid load, and decreased long-term glomerular filtration rate (38).

Diabetic nephropathy is a frequent complication in DM2, mainly caused by poor long-term control of blood glucose and blood pressure (36). In turn, it has been proposed that a high protein diet, by causing glomerular hyperfiltration, can lead to damage in the structure of the glomerulus, deteriorating renal function, so that for years it has been advised against following a high protein diet in persons with DM2 to avoid deterioration of renal function (37).

However, more recent studies suggest that following a high-protein diet does not adversely affect long-term renal structure and function in patients with DM2 (32,40). Tay J et al. (32) also studied the effects of following a high-protein diet for 52 weeks on renal function markers in subjects with obesity and DM2. They concluded that, performing a long-term hyperproteic diet does not worsen renal function in subjects with DM2 without previous renal disease.

On the other hand, in a retrospective cohort study, Kaji A et al. (40) analyzed the association between protein intake and changes in urinary albumin levels and glomerular filtration rate, observing no significant differences between the amount of protein in the diet and the changes produced in renal function markers in persons with DM2 without macroalbuminuria.

Second, a cross-sectional study suggested an association between consumption of a high-protein diet and an increased risk of hypertension (OR = 1.16 (1.02-1.30); CI:95%; p = 0.02) since some foods containing high protein are also high in sodium (41). However, in three recent systematic reviews and meta-analyses presented above, the authors observed no significant differences between the amount of dietary protein and increased blood pressure in patients with DM2 (12,34,35).

Discussion

The effectiveness of a feeding protocol on glycemic control in people with DM2 can be achieved directly through a decrease in body weight or through mechanisms independent of this weight loss by decreasing markers such as insulin resistance (1).

In reference to intermittent fasting, 6 of the articles included in this review directly address the relationship between following an intermittent fasting protocol and its effects on weight or glycemic control in adults with DM2 (16-18,20-22).

In relation to weight loss, most evidence shows that following intermittent fasting strategies with a hypocaloric approach does not offer greater weight loss compared to other protocols with longer feeding periods (16,18,18,20,21). Several authors state that other factors are more influential in weight loss than feeding schedules, such as adherence to a healthy diet and the type of foods that are part of the diet (11,13,15,16). Cho Y et al. (22) did demonstrate that intermittent energy restriction is more effective as a strategy to reduce BMI in people with DM2 than a continuous hypocaloric diet. The authors state that this is due to the fact that during a period of fasting lipolysis processes are stimulated, stimulating the use of fat deposits as the main source of energy, added to the fact that, by concentrating the diet in a diurnal time slot, the activity of the circadian rhythms of the organism is improved, having a positive impact on body weight loss (22).

Some authors argue that this weight loss is the direct cause of the improvement in glycemic control in people with DM2 who are overweight or obese (20-22). Weight loss reduces inflammation in peripheral tissues decreasing insulin resistance. These effects do not seem to be shown in individuals with DM2 and normal weight (14-16). The favorable results of intermittent fasting on glycemic control, independently of weight loss, seem to occur only in animal studies (42,43) or in interventions with a very small population sample and short duration (17).

In human clinical trials using intermittent fasting as a strategy to improve glycemic control, a variety of results were found (20-22). Carter S et al. (20) showed that there are no significant differences in glycemic control in patients with DM2 and overweight or obesity between any diet focused on weight loss, either intermittent energy restriction or continuous hypocaloric diet. However, after one year after discontinuation of intermittent fasting, HbA_{1c} increased again in both groups, despite the fact that the patients did not regain the lost weight (21). On the other hand, Cho Y et al. (22) did find a significant reduction in fasting glucose levels among the group that performed intermittent energy restriction versus the group that followed a continuous hypocaloric diet. Even so, in both groups this reduction in blood glucose was attributed to weight loss by reducing central adiposity and improving insulin resistance. Further research in humans is needed to determine whether the use of any of the different variants of intermittent fasting may have additional effects on glycemic control beyond weight loss in patients with DM2.

Regarding the safety of intermittent fasting, although no study directly confirms it, experts suggest that any fasting practice increases the risk of suffering hypoglycemia, both in patients without any pathology and in patients with DM2, by increasing the number of hours

spent without ingesting food (26). However, adequate nutritional education and medication readjustment seem to significantly reduce the occurrence of hypoglycemia episodes in patients with DM2 who practice intermittent fasting (11,24,25,27).

Regarding the high protein diet, 6 articles were reviewed that directly related the effects of a high protein diet on weight (12,31-33) and/or glycemic control in adults with DM2 (12,34,35).

In relation to weight loss, most authors state that a hypocaloric hyperproteic diet is as effective as a hypocaloric normoproteic diet for long-term weight loss. Therefore, the protein content of the diet would not be related to weight loss and the number of total calories in the diet would (12,32). On the other hand, Wycherley TP et al. (31) found a greater weight loss in the group that followed a high protein diet, which was attributed, among other causes, to a greater feeling of satiety (44). Campos-Nonato I et al. (33) found that, although weight loss was similar in both groups, individuals with high adherence to the hyperprotein diet experienced greater weight loss than individuals with high adherence to the normoproteic diet, pointing once again to the importance of good adherence to any dietary protocol.

In relation to the hyperprotein diet and glycemic control in persons with DM2, no additional benefits have been found in the reduction of glucose or HbA_{1c} levels other than those directly caused by weight loss (33). However, Yu Z et al. (34) did observe a greater reduction in insulin resistance by following a hyperprotein diet. They attribute this result to a lower insulin release by increasing the amount of protein in the diet and reducing the amount of carbohydrate (34). The increase in the amount of protein seems to cause greater weight loss at the beginning of its follow-up, but in the long term its effect seems to be similar to that of other diets with a lower amount of protein.

Traditionally, a high protein diet has been associated with the occurrence of renal damage (37,41). However, both Tay J et al. (32) and Kaji A et al. (40) did not find that a high protein diet is associated with greater renal damage in patients with DM2 as long as there are no previous renal pathologies. Several authors are of the opinion that other factors, such as failure to maintain an adequate weight or high blood pressure are more important for the development of renal disease (38,39).

Regarding the limitations of the study since there is no consensus on the definition of intermittent fasting, each research group defines its own protocol, making it difficult to compare results between different publications. In addition, each research group uses one or more different markers to assess glycemic control (glucose levels, insulin, HbA1c, insulin resistance, etc.), which makes it difficult to compare results. Finally, no clinical trials of sufficient duration have been carried out to evaluate the long-term safety of following an intermittent fasting protocol and/or a high-protein diet in people with DM2.

With a view to future studies, we recommend that food professionals prepare a document containing the definition and characteristics of the main intermittent fasting protocols, which would allow standardization and comparison of results between different research groups. Finally, we propose the elaboration of a long-term clinical trial to study the effects of following an intermittent fasting protocol and/or a high-protein diet on glycemic control in patients with DM2, using HbA1c as the standard marker of effectiveness since it is the only indicator of long-term glycemic control.

Conclusions

On the basis of the review carried out, we conclude that both intermittent fasting and a high-protein diet with energy restriction, adequately planned and monitored by a health and nutrition professional, can be effective dietary-nutritional strategies for weight loss. It is this weight loss that directly results in improvements in glycemic control in people with DM2 by decreasing inflammation and thus insulin resistance in peripheral tissues. Further research is needed to determine whether both feeding protocols exert an effect on improving glycemic control in people with DM2 independent of weight loss.

Intermittent fasting protocols have not been shown to cause a greater number of episodes of hypoglycemia compared to continuous feeding. Nor has it been shown that a high-protein diet increases the risk of developing renal disease in persons with DM2 as long as there is no previous renal damage.

Therefore, any variant of intermittent fasting or following a hyperproteic diet are safe dietary-nutritional strategies to be applied in people with DM2 as long as they are monitored by a health professional who applies nutritional education strategies and a readjustment in medication, especially in the distribution of fast-acting insulin in the case of practicing an intermittent fasting protocol.

References

(1) Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239-2251. doi:10.1016/S0140-6736(17)30058-2.

(2) Federación Internacional de Diabetes (FID). Atlas de la Diabetes de la FID. 9ª ed [Internet]. 2019 [Citado el 7 de abril de 2021]. Disponible en: https://diabetesatlas.org/upload/resources/material/20200302_133352_2406-IDF-ATLAS-SPAN-BOOK.pdf

(3) Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. Diabetologia. 2012;55(1):88-93. doi:10.1007/s00125-011-2336-9.

(4) Rojo-Martínez G, Valdés S, Soriguer F, Vendrell J, Urrutia I, Pérez V, et al. Incidence of diabetes mellitus in Spain as results of the nation-wide cohort di@bet.es study. Sci Rep. 2020;10(2765). doi:https://doi.org/10.1038/s41598-020-59643-7.

(5) Halim M, Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). Diabetes Metab Syndr. 2019;13(2):1165-1172. doi:101016/j.dsx.2019.01.040.

(6) Pan B, Wu Y, Yang Q, Long G, Caiyun G, Xun Y, et al. The impact of major dietary patterns on glycemic control, weight loss in patients with type 2 diabetes: a network meta-analysis. J Evid Based Med. 2019;12(1):29-39. doi:10.1111/jebm.12312.

(7) Evert AB, Dennison M, Gardner CD, et al. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. Diabetes Care. 2019;42(5):731-754. doi:https://doi.org/10.2337/dci19-0014.

(8) Schwingshackl L, Missbach B, König J, Hoffman G. Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis. Public Health Nutr. 2015;18(7):1292-1299. doi:10.1017/S1368980014001542.

(9) Esposito K, Maiorino MI, Bellastella G, Panagiotakos DB, Giugliano D. Mediterranean diet for type 2 diabetes: cardiometabólico benefits. Endocrine. 2017; 56(1):27-32. doi:10.1007/s12020-016-1018-2.

(10) Vitale M, Masulli M, Calabrese I, Rivellese AA, Bonora E, Signorini S, et al. Impact of a Mediterranean dietary pattern and its components on cardiovascular risk factors, glucose control and body weight in people with type 2 diabetes: a real-life study. Nutrients. 2018;10(8). doi:10.3390/nu10081067.

(11) Grajower MM, Horne BD. Clinical management of intermittent fasting in patients with diabetes mellitus. Nutrients. 2019;11(4):873. doi:10.3390/nu11040873.

(12) Zhao WT, Luo Y, Zhang Y, Zhou Y, Zhao TT. High protein diet is of benefit for patients with type 2 diabetes: an updated meta-analysis. Medicine (Baltimore): 2018; 97(46):13149. doi:10.1097/MD.0000000000013149.

(13) Johnstone A. Fasting for weight loss: an effective strategy or latest dieting trend? Int J Obes. 2015;39:727-733. doi:https://doi.org/10.1038/ijo.2014.214.

(14) Anton SD, Moehl K, Donahoo WT, Marosi K, Lee S, Mainous AG, et al. Flipping the metabolic switch: understanding and applying health benefits of fasting. Obesity (Silver Spring). 2018;26(2): 54-268. doi:10.1002/oby.22065.

(15) Patterson RE, Laughlin GA, Sears DD, LaCroix AZ, Marinac C, Gallo LC, et al. Intermittent fasting and human metabolic health. J Acad Nutr Diet. 2015;115(8):1203-1212. doi:10.1016/j.jand.2015.02.018.

(16) Harris L, Hamilton S, Azevedo LB, Olajide J, De Brún C, Waller G, et al. Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis. JBI Datadase System Rev Implement Rep. 2018;16(2):507-547. doi:10.11124/JBISRIR-2016-003248.

(17) 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. doi:10.1016/j.cmet.2018.04.010.

(18) Seimon RV, Roekens JA, Zibellini J, Zhu B, Gibson AA, Hills AP. Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials. Mol Cell Endocrinol. 2015;418(2):153-172. doi:10.1016/j.mce.2015.09.014.

(19) Obert J, Pearlman M, Obert L, Chapin S. Popular weight loss strategies: a review of four weight loss techniques. Curr Gastroenterol Rep. 2017;19(61). doi:10.1007/s11894-017-0603-8.

(20) Carter S, Clifton PM, Keogh JB. The effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: a randomized non-inferiority trial. JAMA Netw Open. 2018;1(3). doi:10.1001/jamanetworkopen.2018.0756.

(21) Carter S, Clifton PM, Keogh JB. The effect of intermittent compared with continuous energy restricted diet on glycemic control in patients with type 2 diabetes: 24-month follow-up of a randomized non-inferiority trial. Diabetes Res Clin Pract. 2019;151:11-19. doi:10.1016/j.diabres.2019.03.022.

(22) Cho Y, Hong N, Kim KW, Cho SJ, Lee M, Lee YH, 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. doi:10.3390/jcm8101645.

(23) Gutiérrez-Rodelo C, Rousa-Guiberna A, Olivares-Reyes JA. Mecanismos moleculares de la resistencia a la insulina: una actualización. Gac Med Mex. 2017;153:214-228.

(24) Horne BD, Muhlestein JB, Anderson JL. Health effects of intermittent fasting: hormesis or harm? A systematic review. AM J Clin Nutr. 2015;102(2):464-470. doi:10.3945/ajcn.115.109553.

(25) Silbert R, Salcido-Montenegro A, Rodriguez-Gutiérrez R, Katabi A, McCoy RG. Hypoglucemia among patients with type 2 diabetes: Epidemiology, risk factors, and prevention strategies. Curr Diab Rep. 2018;18(8):53. doi:10.1007/s11892-018-1018-0.

(26) Carter S, Clifton PM, Keogh JB. Intermittent energy restriction in type 2 diabetes: a short discussion of medication management. World J Diabetes. 2016;7(20):627-630. doi:10.4239/wjd.v7.i20.627.

(27) Corley BT, Carroll RW, Weatherall M, Parry-Strong A, Krebs JD. Intermittent fasting in type 2 diabetes mellitus and the risk of hypoglycemia: a randomized controlled trial. Diabet Med. 2018;35(5):588-594. doi:10.1111/dme.13595.

(28) Olansky L. Strategies for management of intermittent fasting in patients with diabetes. Clevel Clin J Med. 2017;84(5):357-358. doi:10.3949/ccjm.84a.16118.

(29) Lonnie M, Hooker E, Brunstrom JM, Corfe BM, Green MA, Watson AW, et al. Protein for life: review of optimal protein intake sustainable dietary sources and the effect on appetite in ageing adults. Nutrients. 2018;10(3):360. doi:10.3390/nu10030360.

(30) Wolfe RR, Cifelli AM, Kostas G, Kim IY. Optimizing protein intake in adults: interpretation and application of the recommended dietary allowance compared with the acceptable macronutrient distribution range. Adv Nutr. 2017;8(2):266-275. doi:10.3945/an.116.013821.

(31) Wycherley TP, Moran LJ, Clifton PM, Manny N, Brinkworth GD. Effects of energy-restricted high-protein, low-fat compared with standard-protein, low-fat diets: a meta-analysis

of randomized controlled trials. Am J Clin Nutr. 2012;96(6):1281-1298. doi:10.3945/ajcn.112.044321.

(32) Tay J, Thompsom CH, Luscombe-Marsh ND, Noakes M, Buckley JD, Wittert GA, et al. Long-term effects of a very low carbohydrate compared with a high carbohydrate diet on renal function in individuals with type 2 diabetes: A randomized trial. Medicine (Baltimore). 2015:94(47):2181. doi:10.1097/MD.0000000000002181.

(33) Campos-Nonato I, Hernandez L, Barquera S. Effect of a high-protein diet versus standard-protein diet on weight loss and biomarkers of metabolic syndrome: a randomized clinical trial. Obes Facts. 2017;10(3):238-251. doi:10.1159/000471485.

(34) Yu Z, Nan F, Wang LY, Jiang H, Chen W, Jiang Y. Effects of high-protein diet on glycemic control, insulin resistance and blood pressure in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Clin Nutr. 2020;39(6):1724-1734. doi:10.1016/j.clnu.2019.08.008.

(35) Malaeb S, Bakker C, Chow LS, Bantle AE. High-protein diets for treatment of type 2 diabetes mellitus: a systematic review. Adv Nutr. 2019;10(4):621-633. doi:10.1093/advances/nmz002.

(36) Cuenca-Sánchez M, Navas-Castillo D, Orenes-Piñero E. Controversies surrounding high-protein diet intake: satiating effect and kidney and bone health. Adv Nutr. 2015;6(3):260-266. doi:10.3945/an.114.007716.

(37) Ko GJ, Obi Y, Tortoricci AR, Kalantar-Zadeh K. Dietary protein intake and chronic kidney disease. Curr Opin Clin Nutr Metab Care. 2017;20(1):77-85. doi:10.1097/MCO.0000000000000342.

(38) Kamper AL, Strandgaard S. Long-term effects of high-protein diets on renal function. Annu Rev Nutr. 2017;37:347-369. doi:10.1146/annurev-nutr-071714-034426.

(39) Rendón-Rodríguez R. Efecto de las dietas hiperproteicas sobre la función renal: una controversia actual. Nutr Clin Med. 2018;12(3):149-162. doi:10.7400/NCM.2018.12.3.5069.

(40) Kaji A, Hashimoto Y, Kobayashi Y, Wada S, Kuwahata M, Yamazaki M, et al. Protein intake is not associated with progression of diabetic kidney disease in patients without macroalbuminuria. Diabetes Metab Res Rev. 2019;35(5):3150. doi:10.1002/dmrr.3150.

(41) Mattos CB, Vianna LC, Paula TP, Sarmento RA, Almeida JC, Gross JL, et al. Increased protein intake is associated with uncontrolled blood pressure by 24-hour ambulatory blood pressure monitoring in patients with type 2 diabetes. J Am Coll Nutr. 2015;34(3):232-239. doi:10.1080/07315724.2014.926155.

(42) Wei S, Zhao J, Bai M, Li C, Zhang L, Chen Y. Comparison of glycemic improvement between intermittent calorie restriction and continuous calorie restriction in diabetic mice. Nutr Metab (Lond). 2019;16:60. doi:10.1186/s12986-019-0388-x.

(43) Muñoz-Hernández L, Márquez-López Ziomara, 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;20(4):13. doi:10.1007/s11892-020-1295-2.

(44) Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care. 2006;29(9):2102-2107. doi:10.2337/dc06-0560.

Receipt date: 11/30/2021
Revision date: 12/02/2021
Acceptance date: 12/20/2021