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REVIEW ARTICLE

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Efficacy of Diabetes-Specific Formulas as Meal Replacements in Diabetic Patients: An Overview

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Abstract

Diabetes-specific formulas have shown to be effective at improving glucose control with additional nutritional benefits. The aim of this review is to assess the current knowledge on the different types of DSF (Diabetes-Specific Formulas) and how they affect the weight, HbA1c (glycosylated hemoglobin), glucose, insulin and lipid profiles. Database research was made with diabetes and nutritional formulas as keywords. From over 60,000 titles retrieved from 2005 to 2020, only 34 were chosen based mainly on their methodology and results. Results show that for glycemia control, high fiber carbohydrates are more effective as well as high protein formulas. For HbA1c, oat seemed to be less effective than Meal Replacement (MR) and a protein-rich formula proved to be effective in the long-term. One of the most researched benefits in MR plans is weight loss, evidences show up to a 5-10% decrease in interventions with DSF formulas. Other advantages of this approach include greater glycemic control, insulin sensitivity and lower postprandial secretion, which consequently lead to a decrease in morbidity and mortality associated with cardiovascular causes. About lipid profile values; HDL, LDL and Total cholesterol, existing evidence differ from one another, so it is necessary to investigate further to reach a consensus.

Introduction

Worldwide prevalence of diabetes has increased over the last 40 years from 4.7% to 8.5% of the adult population, especially those in 2016, around 1.6 million deaths occurred as a direct consequence of diabetes, making it the 7th leading cause of death in that same year [1]. Poor glycemic control and dyslipidemia are very important aspects of the type 2 diabetic patient follow up, mainly because of the systemic consequences high blood glucose and dyslipidemia have proven to promote [2]. Many comorbidities such as hypertension, which affects at least 65% of diabetic patients, is also linked to other fatalities like coronary artery disease, myocardial infarction, stroke and congestive heart failure [3].

Additionally, microvascular complications as neuropathy, retinopathy and nephropathy play an important role in advanced diabetes mellitus. This is all possible because hyperglycemia promotes irregularities in the protein kinase C, polyol and hexosamine pathways, along with the free radical damage from Reactive Oxygen Species (ROS) and glycated end products which can produce endothelial dysfunction. Because of all this, the therapeutic target of diabetes is to keep blood glucose levels as low and as stable as possible, so that damage can be partially, if not completely, prevented [4]. DSF formulas have shown to help maintain glucose and lipid profiles at adequate levels when used for short periods of time [5].

Nevertheless, not all DSF formulas are created equal, nor is their effectiveness at short and long term. That is why the aim of this review is to give an overlook of the effects of DSF formulas (as meal replacements) on blood glucose, insulin, HbA1c, lipid profile and weight of these patients [6].

Methods

Search terms

Databases used for searching titles included Google Scholar, PubMed, SciELo and Ebsco. Keywords or search terms varied among the phrases: "diabetes and polymeric formulas", "diabetes and nutritional formulas and "diabetes and nutrition". Filters were applied when possible, such as "humans". Year range went from 2005 to 2020, English and Spanish language articles were allowed only.

Selection criteria

Inclusion criteria for the articles included the following: those studies related to humans, English and Spanish language publications, relevant results for the aim of this review, full-text article availability. On the other hand, texts with redundant results, different target populations, tube feeding, diet plans, poor methodology and grey literature were not considered for the writing of this review [Figure 1].

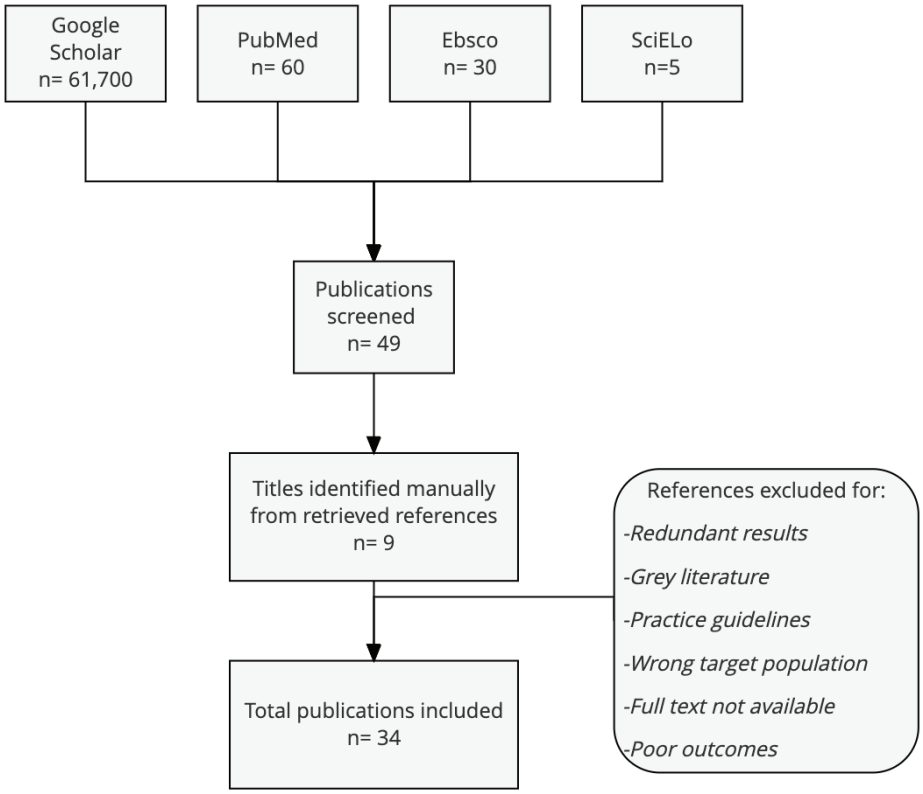

Figure 1: Flow chart of the review literature.

Results and Discussion

Effect of meal replacements on blood glucose

When replacing one meal, a lower glycemic index has been linked with the consumption of DSF formulas with extended-release carbohydrates, if compared with the same amount of carbohydrates from a reference food, such as bread or glucose. This means that a lower glycemia was observed in subjects consuming DSF formulas [7,8]. Something similar happened when patients were given an oral nutritional formula based on a protein blend, fiber and a fat blend high on oleic oil. Researchers compared it with those receiving a cornflakes and milk isocaloric meal and found that the area under the curve for post-meal glycemia was significantly lower in the experimental group at 30 min (p=0.003), 60 min (p=0.0001), 120 min (p=0.0001), and 180 min (p 0.0001) [9].

Likewise, postprandial glycemia was also significantly lower and got back to baseline faster when experimenting with two DSF formulas versus an isocaloric amount of oatmeal for breakfast. This could be explained by the low glycemic index of the formulas and macronutrient composition [10]. Another study compared two DSF formulas *vs.* a standard control formula for a two-year follow-up period, results in plasma glucose levels showed that compared with the standard control formula, both DSF lowered insulin requirements, improving capillary glycemia (146.1 ± 45.8 mg/dL, p<0.001) [11].

Taking a high-energy, high-protein DSF formula and substituting the maltodextrin for isomaltose from an oral nutrition supplement resulted in an attenuated postprandial glucose level. However, postprandial peak glucose concentration in both formulas did not differ significantly (p=0.107) [12]. Another hyper-protein but very low-carbohydrate nutrition formula was tested against a standard protein formula. The first one showed to keep blood glucose concentrations within very small variations when followed up from 30 to 150 min. These could be very helpful in malnourished patients suffering from muscle wasting or sarcopenia, given the fact that most DSF formulas tend have a higher lipid content and normoprotein distribution [13].

A higher fat and fiber content, as well as lower carbohydrate and the presence of fructose in DSF oral nutritional formulas has shown to contribute to a significantly lower glycemic index and glycemic control when compared to standard nutritional formulas. Although, it is important to note that a high-fat content meal could promote weight gain and lipid distortions among diabetic patients despite of its effects on blood glucose. In the Look AHEAD study, findings showed significant reduction in weight and blood glucose levels on those type-2 diabetes patients under MR plans with DSF in comparison to others carrying on standard diets with equal caloric count [14].

Effect of meal replacements on HbA1c

When diabetic patients were given a high fiber meal replacement for breakfast containing rice, soybean, resistant starch and oat dietary based meal, was measured as a long-term glycemic control variable. For patients who took the oat-based meal, HbA1c increased by 0.3% (95% CI, 0.1% to 0.5%, p=0.005). In contrast to those who took the high fiber breakfast replacement, whose HbA1c diminished by

-0.2% (95% CI, -0.38% to -0.07%, p=0.004). This suggests further consideration when recommending oat-based meals for the long term to these patients [15].

On the other hand, in this 12-week trial, patients replaced three meals a day with a protein-rich formula during week 1. In weeks 2-4, both dinner and breakfast were replaced and finally from week 5 through 12, only dinners were exchanged. After 8 weeks, HbA1c decreased from initially 8.8% to 7.7% (1.1%) (p=0.002). At the end of the study there was a slight increase of HbA1c to 8.1%, which was still statistically significantly lower than the reference [0.8% (1.4%); p=0.048], proving the effectiveness of the protein-rich meal replacement formula in long term control of glycemia [16].

An intervention consisting of a personalized diet, regular motivation and meal replacement with a low carbohydrate formula was able to decrease HbA1c to a mean of [95% confidence interval] -0.97% [-1.21 to -0.74] just as the previous studies demonstrated. Nevertheless, it is difficult to point out which of the elements of the intervention contributed the most to the lowering of HbA1c, which could diminish the clinical significance of the results from this study [17]. Other data demonstrate that three-month interventions following a 1 or 2 meal replacements daily program lead to a great decrease (0.11%) in HbA1c [18]. In the Look AHEAD trial study, individuals exposed to the intervention had better odds to lost >10% of their initial weight after the 1-year period of follow up, at the same time, this group also got lower results in HbA1c (6.1% ± 0.7 men, 6.3% ± 1.0 women) compared to their baseline data (7.0% ± 1.1) ; p (<0.0001) [19].

Effect of meal replacements on weight

Different studies have shown that weight loss of approximately 5-7% is a determining factor in reducing the mortality rate due to cardiovascular reasons; sleep apnea; female sexual dysfunction; hospital stay and urinary symptoms in overweight patients with typess 2 diabetes [20].

The Look AHEAD initiative, focused on Intensive Lifestyle Intervention (ILI), consists of a program that integrates Meal Replacements (MR) with physical activity, and its results reported that after 1 year the experimental group participants lost approximately 8.6 kg (P<0.001) compared to the control group that followed a dietary scheme with the same amount of calories per day. The most relevant data showed a positive correlation between weight loss and the quantity of meals replace by a nutritional formula per day (r=0.32, p<0.001), also, likewise data analysis demonstrated that same candidates were 4 times more likely to achieve a weight loss greater than 10% at the end of the study. Finally, the consumption of meal replacements was the third most influential factor to reach the goal of weight loss, followed by greater self-reported physical activity [21].

Interventions such as; Slim-Fast and Weight Watchers (both dietary plans calculated by energy intake for achieving weight loss), low carb diet and combined diet- exercise plan; have demonstrated effectiveness in decreasing some anthropometric measures of participants, specifically the perimeter of waist and weight [22]. Looking into a short MR intervention performed on 2009, diabetic patients (BMI 33-44 kg/m^2), were randomized in counseling sessions and hypocaloric diet (60%) reduction of subgroups. Those patients treated with the specific formula Glucerna SR developed a greater and sustained weight loss over time. This formula provides 206 calories per serving distributed in 9 g protein, 25 g carbohydrate and 24 other compounds. Specifically, maltodextrin; sunflower oil; soy oil, fructose; minerals (such as potassium, magnesium, sodium, copper, zinc and ferrous sulfate); vitamins B, A, K1, D2, antioxidants, taurine and L-carnitine [23]. Another study, followed a sample of patients for 8 weeks, where breakfast, lunch and dinner were replaced by a specific liquid formula composed of equal parts of proteins and carbohydrates; and 5% fat, the final data showed a marked decrease in weight (-9.6 Kg) and percentage of body fat (-7.6%) in the participants [24].

The standard Soy-Yoghurt-Honey (SYH) formula known as almased for commercial purposes; is composed mainly by soy and milk protein, in addition to antioxidants, enzymes and oligofructose from honey. In order to quantify its efficacy this formula was implemented during a controlled trial conducted in 88 diabetic and overweight subjects, randomized in two groups; meal replacements formulas and conservative therapy (lifestyle modifications). The high protein formula was administrated for 6 weeks, obtaining better results in terms of weight reduction (180% more) and fat mass (p<0.01) in comparison to lifestyle group. With that in mind experts have approved the meal replacement diet approach as an effective strategy to lose weight in diabetic patients, especially if it is part of the initial phase in the therapeutic program [25]. Another soy-based formula showed similar results in a longer intervention, where weight loss in female patients was greater (-7.6 ± 7.9 kg) (p<0.001) than the control group [26].

Effect of meal replacements on fasting insulin

Commonly used nutritional formulas are composed of high percentages of carbohydrates and/or proteins. Additionally, specific features of DSF include their low glycemic index, normoproteic and normocaloric balance, as well as 100% PHGG (partially hydrolyzed guar gum) soluble fiber, target population are diabetics who need to maintain this type of diet for long amounts of time. An experimental therapy was carried out in a clinical trial on 15 patients, achieving a lower average in the concentration of serum insulin (p=0.039) compared to the subgroup that took the standard polymeric nutritional formula. Specifically, insulin levels in the 60 and 90 minutes of the curve showed lower insulin requirements [27].

The Soy-Yoghurt-Honey (SYH) formula, was a standard weight-loss formula used to replace breakfast in a group of patients during a randomize trial, obtaining post-prandial glycemic and insulinemic responses lower than the traditional breakfast group [25]. Other meal replacement therapies also showed significant decreases in serum insulin levels (14.1 ± 1.3 IU/ml, p<0.05) compare to 29.3 ± 10.9 IU/ml in groups that had other diet programs [24]. Another specific formula with similar effects is Glucerna SR, which was incorporated into a randomized, crossover clinical trial, within 14 obese patients. Upon completion of the intervention, participants showed an increase in insulin sensitivity coupled with a decrease in insulin secretion [28].

When it comes to comparing standard formulas *vs.* Oral Nutritional Supplements for Diabetic patients (ONS-D), the latter demonstrate lower glycemic response and greater control in postprandial appetite. These outcomes are presumably because ONS-D such as Glucerna and Diasip are composed of sucrose analogs; sucromalt and isomaltulose respectively. Both components are low digesting carbohydrates that provoke increase GLP-1 secretion, which consequently might lower GIP and insulin concentration. On the other hand, blood glucose levels after ingesting ONS-D returned to baseline in approximately 150 minutes in contrast to standard nutritional supplements (180 minutes), which proves that ONS-D promotes a healthier metabolic profile in diabetic patients [29].

Effect of meal replacements on lipid profile

When using nutritional formulas under a properly structured plan, reductions in the biochemical values of cholesterol, triglycerides, LDL

and HDL are also observed [30]. An example of this was evidenced in a multicenter, controlled trial, where the experimental group of patients received once a day the formula of meal replacement 'Once Pro' composed of 40% carbohydrate, 20% protein and 40% fat added to a controlled diet, and the other subgroup only followed a dietary regimen. At the end of 3 months both groups obtained lower HDL cholesterol values, but only the MR group had lower LDL and total cholesterol values [31]. In another intervention, using the Glucerna formula similar results were obtained, post analysis data showed decreased values in C-HDL-C, VLDL-C and triglycerides [32] [Tables 1 and 2].

Recommendations and Conclusion

In overweight patients, DSF should be taken 2-3 times per day together with a reduced calorie meal plan, either as a calorie replacement for a meal, as a partial meal or as a snack. The calorie goal for this group of patients is as follows: patients <250 lb=1,200 to 1,500 calories, while patients >250 lb=1500 to 1800. The approach in normal weight patients varies if the diabetes is controlled (HbA1c ≤ 7%) or uncontrolled (HbA1c>7%). For patients with controlled diabetes, the use of DSF depends on the physician criteria an the patients' characteristics. However, for patients with uncontrolled diabetes, DSF should be incorporated 1-2 times per day into a meal plan, either as a calorie replacement for a meal, as a partial meal or as a snack. In underweight patients, is recommended to use 1-3 units of DSF per day, depending on management goals [33].

Standard formulas have been associated with adverse effects such as hyperglycemia, osmotic diuresis and loss of electrolytes, so they are not ideal for diabetic patients. To cover this sector of the population,

Table 1: Shows distinct diabetes-specific formulas and their composition.

Formula	Protein	CHO	Fat	Fiber
Extended-release carbohydrates (Glucerna) [7]	Total: 21%	Total: 56%	Total: 15%	3.6 g / 100mL
	-Calcium caseinate (98%)	Maltodextrin, fructose and maltitol	Oleic acid and soy oil.	
	-Soy protein (2%)			
High protein content (Diasip) [8]	Total: 16%	Total: 35%	Total: 49%	2.5 g / 100mL
	Protein blend	Fructose (2.3 g)	-MUFA (3.6 g / 100mL)	
High energy and high protein (DiaCare) [11]	Total: 26%	Total: 41%	Total: 32%	0.7 g / 100mL
	-Whey (1.96 g)	-Glucose (0.7g)	-Saturated (0.64 g)	
	-Casein (7.84 g)	-Lactose (3.4 g)	-MUFA (3.17 g)	
		-Isomaltulose (5.6g)	-PUFA (1.53 g)	
		-Polysaccharides (5.5g)		
High protein and low fat (Almased) [16]	Total: 53%	Total: 31%	Total: 2%	0.4 g / 100mL
	-Soy protein 50%	-Glucose 30%	-Saturated (50%)	
	-Raw enzyme-rich bee honey 25%			
	-Skim milk yogurt powder 23%			
Composed of lactose, isomaltulose, and resistant starch [29]	Total: 19%	Total: 47%	Total: 32%	2 g/ 100mL
	-Whey: 2.4 g	-Sugars: 11.3 g	(/100mL)	
	-Soy: 2.4 g	-Lactose: 3.6 g	-Saturated: 0.5 g	
			-MUFA: 2.2 g	
			-PUFA: 1.1 g	
Novasource® Diabet [27] (/100mL)	Total: 4.6 g	Total: 12 g	Total: 3.8 g	1.7g / 100mL
			-Saturated: 1.3 g	
			-MUFA: 1.4 g	
			-PUFA: 0.8 g	
Nutren Diabetes [9]	Total: 15%	Total: 45%	Total: 40%	15.3/ 1000 kcal
			-Saturated 4%	
			-MUFA: 26%	
			-PUFA: 8% (TEI)	
Ultra-Glucose Control [10]	Total: 15 g	Total: 27 g	Total: 7g	3g / 56g
			-MUFA:4.5 g	
			-Saturated: 1g	
Standard Formula** [27]	Total: 4 g	Total: 13.6 g	Total: 3.3 g	N/A
		-Sugars: 0.4 g	-Saturated fat: 1.3 g	
		-Lactose:<0.01	-MUFA: 1.4 g	
			-PUFA: 0.8	

MUFA: monounsaturated fatty acid, PUFA: polyunsaturated fatty acid, N/A: not available
*There are no diabetes 1/2 specific formulas
**Brand name not specified

Table 2: Summary of studies evaluating DSF as meal replacement.

Title	Objective	Population	Study Designs	Formula Composition	Measured Variables	Outcomes
Randomised controlled trial of four commercial weight loss programmes in the UK: initial findings from the BBC "diet trials" (2006)	To compare the effectiveness of four commercial weight loss diets available to adults in the United Kingdom	210 individuals who were aged between 18 and 65 and had a self-reported body mass index between 27 and 40.	A multi-center, open-label, randomized controlled study. Interventions Dr Atkins' new diet revolution, Slim-Fast plan, Weight Watchers pure points programme, and Rosemary Conley's eat yourself slim diet and fitness plan. TIME FRAME: 6 months	N/S	Weight reduction, fat loss, age, BMI, waist circumference, blood pressure, glucose, total cholesterol, compliance and withdrawal.	-After six months all diets resulted in a clinically useful mean -Body weight reduction: Rosemary Conley 9.9% (SD 5.6%), Weight Watchers 9.0% (5.6%), Atkins 8.9% (5.6%), and Slim-Fast 6.8% (5.3%); -Regression analysis showed that total Weight loss over time had the greatest influence on systolic and diastolic pressure (adjusted R2 0.61 for change in systolic pressure and 0.79 for change in diastolic pressure). -Weight Watchers group was fasting glucose significantly lower than in the control group.
Effect of a nutritional liquid supplement designed for the patient with diabetes mellitus (Glucerna SR) on the postprandial glucose state, insulin secretion and insulin sensitivity in healthy subjects (2006)	Identify the effect of a nutritional liquid supplement designed for the patient with diabetes mellitus (Glucerna SR) in single administration on the postprandial glucose state, insulin secretion and insulin sensitivity in healthy subjects.	14 non-obese volunteers. Subjects received a single administration of 300 kcal, gauged with water at 350 ml, of each of the following (at least 3 days apart) Glucerna; Ensure.	A randomized, single-blind, cross-over, clinical trial. TIME FRAME: 1 day	Ensure high calcium provides 0.95 kcal, 54.7% carbohydrates, 21.3% proteins and 24.0% fat. On the other hand, each milliliter of Glucerna SR supplies 0.93 kcal, 47.2% carbohydrates, 20.0% proteins and 32.8% fat.	Glucose level, insulin, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, creatinine, and uric acid, was measured.	-Glucose level at 120 min was significantly lower after receiving Ensure high calcium or Glucerna SR compared to glucose 75 g -Total insulin secretion was significantly reduced after Glucerna SR, with a statistic tendency to be lower in its first phase (p=0.07). -Insulin sensitivity was increased with Glucerna SR
Nutrient adequacy during weight loss interventions: a randomized study in women comparing the dietary intake in a meal replacement group with a traditional food group. (2007)	To determine and analyze the nutritional adequacy of a traditional food-group diet intervention compared to a traditional food-group diet intervention that also incorporated meal replacements as a strategy for weight loss.	96 healthy overweight / obese women aged between 25-50.	A randomized, cross over, controlled trial. Traditional Food Group or a Meal Replacement group, the latter incorporated 1-2 meal replacement bars o drinks each day. TIME FRAME: 1 year	Protein 7-10g CHO 40-46 g Fat 1.5-3g Fibre 5g Energy 220 kcal	Weight loss, body fat, weight, waist circumference, resting energy expenditure.	-Mean weight loss was not significantly different between the two groups. -Mean intake of meal replacements was lower than recommended.
Administration of a new diabetes-specific enteral formula results in an improved 24 h glucose profile in type2 diabetic patients (2009)	To study the effect of several boluses of a new diabetes-specific formula (DSF) during the day on 24 h glucose profile.	12 diabetic type subjects with a mean age of 67 years.	A randomized, controlled, double-blind, cross-over study in Netherlands. Group I first received the diabetes-specific formula followed by the standard formula and group II received the formulas in opposite order. TIME FRAME: 24h	Energy Kcal (ml)393 ± 47 Protein(g)19.3 ±2.3 CHO (g) 45.6 ± 5.5 Fat (g)14.9 ±1.8 Fibres (g) 7.9 ± 0.9	Glycemia, insulin, glucagon	-Fasting glucose levels were not significantly different among the two groups. -Mean glucose level was significantly lower in the diabetes-specific formula group during the total 24h. -Diabetes specific formula administration provided a 26% reduction of total hyperglycemic time (>10 mmol/L) over 24 h compared with the standard formula (7.5 2.3 h versus 10.2 2.0 h, $p < 0.05$).

Effects of short-term low- and high-carbohydrate diets on postprandial metabolism in non diabetic and diabetic subjects (2009)	To clarify whether the apparently adverse metabolic effects of high-carbohydrate diets, at least in the short-term, are dependent upon the nature of the carbohydrate that replaces the fat.	Eight healthy non-diabetic subjects. Ages ranging from 40-61 years.	A randomized cross-over study consisting of a short-term, intensive dietary modification. TIME FRAME: Short-term	High-fat: -50% fat-15% protein-35% CHO High-starch: -15%fat-15% protein -70% CHO. High-sugar: -15% fat -15% protein-70% CHO.	Plasma glucose, insulin, plasma triacylglycerol, non-esterified fatty acids	-Fasting tryacilglycerol concentrations were greatest following the high-sugar diet (mean SEM for all subjects 1900420 mmol/l) and lowest following high-fat (1010130 mmol/l) (P = 0.001); high-starch (mean 1500310) and high-fat did not differ significantly (P = 0.06). -Fasting glucose concentrations were not affected by prior diet, but postprandial glucose concentrations were (P = 0.018), with significantly higher values after the high-fat than the high-sugar diet (P = 0.03).
Effect of a low-calorie high nutritional value formula on weight loss in type 2 diabetes mellitus (2010)	Demonstrate that substitution of one of the main meals with a low-calorie diabetes-specific meal replacement could improve the weight loss without interfering negatively with the nutritional status of the obese type 2diabetic subjects.	96 obese diabetic subjects (BMI 33-44 kg/m^2)	An open label, non randomized, cross-over intervention. TIME FRAME: 24 weeks	Protein (g) 9.0 (20% kcal). Fat (g) 6.0 (33% kcal). CHO (g) 25.0 (47% kcal)	Body weight, HbA1c, plasma glucose, insulin, iron, iron-binding capacity, hemogram, protein electrophoresis and lipids	-The standard deviation of blood glucose mean was reduced by 50% in the intervention group but did not change in the control group. -The diastolic blood pressure difference did not reach statistical significance in the intervention group
Effects of a diabetes-specific enteral nutrition on nutritional and immune status of diabetic, obese, and endotoxemic rats: Interest of a graded arginine supply (2012)	To investigate the effects of a diabetes-specific diet enriched or not with arginine in a model of infectious stress in a diabetes and obesity situation. As a large intake of arginine may be deleterious, this amino acid was given in graded fashion.	22 eleven-week-old male ZDF (fa/fa) rats, obtained from Charles River Laboratories (Saint-Germain sur l' Abresle, France).	A randomized controlled experimental study where diabetic rats were administered intraperitoneal lipopolysaccharide and fed with either a diabetes-specific formula (two variations 1,2) or with graded arginine supply, or a standard nutrition. TIME FRAME: 7 days	Formula HP G -Energy (kcal) 500500 -Proteins (g)25 19 -Fat (g)19.322 -Saturated fatty acids (g) 9.33 MUFAs (g)3.7 16 PUFAs (g) 4 3 -CHO (g) 56.7 55 Saccharose (g) 6.7 <0.5 Starch (g) 50 55 -Fibers (g) 0.1 7.5 Soluble (%)N/A 75 Insoluble (%)N/A 25	Plasma glucose, tal cholesterol, tryglicerides, insulin, individual free amino acids, plasma proteins.	-Survival rate was higher in the G group. -All animals lost weight, but the HP group weight loss was more pronounced, although not statiscally significant. (GA: 4.2 ± 1.4 g, G: 4.5 ± 0.8 g, HP: 8.0 ± 1.2 g).
Meal Replacements for Weight Loss in Type 2 Diabetes in a Community Setting (2012)	Evaluate the use of MR compared with a diet book for 6 months	120 overweight and obese subjects with type 2 diabetes mellitus were recruited. Inclusion criteria were type 2 diabetes (HbA1c 6.5–12%), age 20–65 years, not greater than 140 kg	A open label, randomized, controlled intervention. Subjects in the intervention were advised to consume 2 MR/day for 3months and 1 MR/day for 3 months and follow the manufacturers' instructions from printed material and the website. Subjects in the control arm were given a commercially available diet book. TIME FRAME: 6 months	N/S	Weight loss, HbA1c, serum lipids, plasma glucose and insulin.	-Consumption of 2 MR for 3 months and 1 MR for the subsequent 3 months led to weight loss of 5.5 kg (5%) while the diet book group had a weight loss of 3 kg (3%) (P = 0.027). -Decreases in HbA1c were 0.22% and 0.12%, for intervention and control group respectively. -Weight loss at 6 months was 3.4 kg in MR and 1.8 kg in control (P = 0.07).
Respuesta glucémica e insulinémica a dos fórmulas enterales isocalóricas en pacientes con diabetes mellitus tipo 2 (2013)	To compare glycemic and insulinemic response on type 2 diabetes patients after administration of either a diabtes-specific formula or a standard formula.	15 diabetes type 2 patients whose HbA1C < 9,0%.	A cross-over randomized study where patients received either a diabetes-specific formula or a standar isocaloric formula. TIME FRAME: 2 weeks	Protein Total: 4.6 g CHO Total: 12 g Fat Total: 3.8 g -Saturated: 1.3 g -MUFA: 1.4 g -PUFA: 0.8 g Fibre Total:1.7g / 100mL	Glycemia, insulin	-Insulinemia was lower in the disbetes-specific formula during the length of the study. 4,39 µU/ml (IC 95%:0,927 a 7,87) -Glycemia levels were lower in the diabetes-specific formula at 60, 90, 120, 150, 180 minutes than the standard formula group.

Meal replacement reduces insulin requirement, HbA1c and weight long-term in type 2 diabetes patients with >100 U insulin per day (2013)	Examine whether an energy-restricted protein-rich meal replacement (PRMR) can help to reduce the insulin requirement in patients with type 2 diabetes using >100U insulin per day and simultaneously improve HbA1c, weight and other cardiometabolic risk factors.	22 patients with type 2 diabetes, body mass index (BMI) >27, age 35-75 years, insulin therapy with >100 U insulin per day.	An open label, clinical trial, non-randomized. TIME FRAME: 12 weeks	Energy 360 kcal Protein (%)53.4 Fat (%)2.0 CHO (%)30.6 Fibres (g)0.4	Insulin requirement, HbA1C, weight loss, body mass index, blood lipid levels.	-Mean insulin dose was reduced from 147 (75) U to 65 (32) U (P < 0.0001) after 12 weeks of study. -HbA1c decreased from 8.8% (1.4%) to 8.1% (1.6%) (P = 0.048) -Weight decreased from 118.0 (19.7) kg to 107.4 (19.2) kg (P < 0.0001).
Blood Glucose and Insulin Responses to Two Hypocaloric Enteral Formulasin Patients with Diabetes Mellitus Type 2 (2013)	Compare the glycaemic and insulinemic response of type 2 diabetic patients after oral administration of 250 ml of two enteral formulas: a specific formula (Nova source ® Diabet Smartflex ®) against a standard isocaloric formula.	15 patientes with controlled type 2 diabetes mellitus(dietary advice or oral antidiabetics), and aglycosylated hemoglobin less than 9.0%	A cross-over, randomized, controlled trial. TIME FRAME: 1 week	Energy103 kcal Protein (g)4,6 Fat (g)3,8 CHO (g) 12,0 Fibres (g) 1,7	Blood glucose, insulin, weight, BMI	-Patients receiving DSF showed a lower mean AUC0-t of glucose, mean difference -4,753.26 mg/min/dl (95% CI: -7,256.7 to -2,249.82), Intervention group showed mean insulinemia significantly lower AUC0-t, mean difference: 930.27 uU/min/ml (95% CI -1,696.34 to -164.2). -Analysis of glucose concentrations in the total study shows that the group with the specific formula has a lower mean glucose 25.77 mg / dl (95% CI 18.29 to 33.25), the same fact was detected with insulinemia 4.39 mU/ml (95% CI: 0.927 to 7.87).
Taking a Low Glycemic Index Multi-Nutrient Supplement as Breakfast Improves Glycemic Control in Patients with Type 2 Diabetes Mellitus: A Randomized Controlled Trial (2014)	Examine the effect of a low glycemic index (GI) multi-nutrient supplement, consumed in place of breakfast, on glycemic control in patients with type 2 diabetes mellitus (T2DM).	A total of 71 participants were randomized at a 2:1 ratio into either a breakfast replacement group or a normal breakfast group for a 12-week interventional study.	A randomized, open label, interventional study on patients with T2DM. TIME FRAME: 12 weeks	Energy Kcal 404.9 ± 180.0 Protein (g)12.9 ± 5.5 Fat (g)10.3 ± 7.9 CHO (g) 67.2 ± 33.2 Fibres (g)3.0 ± 2.7	Age, Body Mass Index, waist circumference, blood pressure, physical activity, fasting glucose level, liver function, renal function, blood lipid levels, blood glucose levels and HbA1c	-The breakfast replacement group had no significant increase in fasting blood glucose (FBG) at week 12, while the FBG in control group increased by 1.4 mmol/L (95% CI for change, 0.8 to 1.9 mmol/L, p < 0.001). -There was a statistically significant difference in BMI between the treatment and control groups (p = 0.032) due to the weight gain in the control group (mean change was 0.5; 95% CI was 0.2 to 0.9, p = 0.007).
The impact of a weight reduction program with and without meal-replacement on health-related quality of life in middle-aged obese females (2014)	Assess the impact of two 12-month weight reduction interventions (one arm including a meal replacement) on changes in HRQOL among obese females.	31 obese adults (between 30-41 kg/m^2) were recruited. One group received the weight-reduction lifestyle program without a meal replacement (LS) and the other group received the same lifestyle program with the addition of a soy-based meal replacement product (LSMR).	An open label, non-randomized, controlled trial. TIME FRAME: 12 months	Protein (%)53.3 Fat (%)2 CHO (%) 31 Fibres (g) 0.4	Health-Related Quality of Life (SF-36), BMI, total activity and weight loss.	-Females taking the meal replacement product (LSMR) reported lower baseline HRQOL scores than the control subgroup. This difference was significant in six of eight HRQOL dimensions and was most pronounced in the scores for vitality and health perception -After 12 months of the intervention, body weight was reduced in both groups (LS: -6.6 ± 6 .6 p < 0.001 vs. LSMR-7.6 ± 7.9 kg; p < 0.001). Weight reduction was more pronounced (p = 0.1) in the females taking the soy-based meal replacement product. -Lifestyle behavior expressed by physical fitness (Watt/kg body weight) and leisure time physical activity (hours of physical activity per week) increased similarly in both groups

Effect of consuming a formula with carbohydrates. prolonged release on the glycemic response and insulin post-prandial in healthy individuals. (2016)	To determine the glycemic response and post-prandial response of healthy individuals when they consumed an extended-release carbohydrate formula.	21 healthy subjects, 11 men and 10 women. Ages between 17-25 years.	A crossover study where subjects went through 4 different tests, 1-weekinterval between each test and type of nutrition. 2 weeks for the reference meal and 2 weeks for the enteral formula. TIME FRAME: 4 weeks	Protein Total: 21% -Calcium casein ate (98%) -Soy protein (2%) CHO Total: 56% Maltodextrin, fructose and maltitol Fat Total: 15% Oleic acid and soy oil. Fibre 3.6 g / 100mL	BMI, abdominal circumference, basal and post pandrial insulin, basal and post pandrial glycemia, cholesterol, triglycerides.	-Post prandial glycemia was significantly lower when taking the diabetes-specific formula. -There was no significant difference between the two groups at 120min insulin measurement. -Area under the curve was significantly smaller when compared to the reference meal.
Structured lifestyle intervention based on a trans-cultural diabetes-specific nutrition algorithm (tDNA) in individuals with type 2 diabetes: a randomized controlled trial (2017)	To evaluate the effectiveness of the trans-cultural diabetes nutrition algorithm (tDNA) versus usual Diabetes care in primary care settings.	230 subjects with type 2 diabetes with HbA1c levels 7%-11%, not treated with insulin.	A randomized, open-label, clinical trial in Malaysia. TIME FRAME: 1 year	N/S	HbA1c, weight, fasting plasma glucose, systolic blood pressure, lipid profile, C reactive protein.	-The median values for FPG was significantly ($p<0.001$) lower in the tDNA-MI patients (6.9 ± 1.8mmol/L) compared with tDNA-CC (7.6 ± 2.9mmol/L) and UC (7.8 ± 2.7mmol/L). -The body weight and BMI reduced significantly in both the tDNA intervention groups, where tDNA-MI group achieved a greater (mean ± SE) weight loss of 6.9 ± 1.3kg ($p<0.001$). -At 6 months, A1c decreased significantly in tDNA-MI (-1.1 ± 0.1%, $p<0.001$) and tDNA-CC (-0.5 ± 0.1%, $p=0.001$) but not in UC (-0.2 ± 0.1%, p=NS).
Effects of meal replacement therapy on metabolic outcomes in Thai patients with type 2 diabetes: A randomized controlled trial (2018)	To compare metabolic outcomes between T2DM patients receiving the new MR formula (ONCE PRO) and normal controlled diets.	110 diabetes 2 patients mean age 53 years.	A multi-center open label randomized controlled study in Thailand .Subjects were assigned to either a meal replacement group or a normal controlled diet. TIME FRAME: 10 months	Protein Total: 20% -Soy protein isolate (50%) -Whey protein isolate (50%) CHO Total:40% -Maltodextrin (46.5%) -Isomaltulose (18.5%) -Maltitol (18.5%) -Fibersol (9.26%) -Fructooligosaccharide (4.62%) Other (2.53%) Fat (MUFAs 23% of total calories) -Canola oil (48.8%) -High-oleic safflower oil (24.4%) -Rice bran oil (22.0%) -Fish oil (4.87%)	HbA1c, fasting plasma glucose, lipid profile, waist circumference, body mass index, systolic and diastolic blood pressure.	-HbA1c reduction was only statically significant on the control group at the third month from 7.82 + / 0.61 to 7.55 +/ 0.79, p= 0.001. -LDL- C level increased in the control group (+6.01 mg/dL) and decreased in the meal replacement group (-2.72 mg/dL). Difference between groups was significant, (p = 0.049). -BMI decreased significantly in both groups at the third month however; there was no statistical difference between groups at the end of the intervention.
Individualized Meal Replacement Therapy Improves Clinically Relevant Long-Term Glycemic Control in Poorly Controlled Type 2 Diabetes Patients (2018)	Validate whether individualized intense meal replacement by a low-carbohydrate formula diet with accompanied self-monitoring of blood glucose (SMBG) contributes to long-term improvements in HbA1c, weight, and cardiometabolic risk factors in poorly controlled type 2 diabetes.	409 patients with type 2 diabetes, aged 25–79 years with poorly controlled glucose levels (HbA1c 7.5%), and body mass index (BMI) 27 kg/m2 were included in the study.	A randomized, open label, clinical trial, parallel groups. Study consisted of one observational control group and either a moderate group (M-group) with two meal replacements/day or a stringent group (S-group) with three meal replacements/day. TIME FRAME: 12 weeks of meal replacement intervention and 52 weeks of follow-up	Energy360 kcal Protein (%)53.4 Fat (%)2.0 CHO (%)30.6 Fibres (g)0.4	Sex, age weight, BMI, HbA1c, fasting blood glucose, blood pressure, blood lipids, current treatment.	-Both intervention groups achieved improvements in HbA1c, fasting blood glucose, blood pressure, and weight (all $p < 0.001$) within 12 weeks. -S-group showed a clinically relevant improvement in HbA1c of -0.81% [-1.06; -0.55] ($p < 0.001$) after 52 weeks of follow-up, whereas HbA1c was not statistically different between the M- and control group

Change in Cardiometabolic Risk Factors Associated With Magnitude of Weight Regain 3 Years After a 1-Year Intensive Lifestyle Intervention in Type 2 Diabetes Mellitus: The Look AHEAD Trial (2019)	Induce a mean loss ≥ 7% of initial weight and to increase participants' moderately intense physical activity to ≥ 175 minutes a week.	1561 individuals with a body mass index>25 kg/m2 (or>27 kg/m2 if taking insulin) and a type 2 diabetes mellitus diagnosis	A cross-over randomized trial. Lifestyle Intervention; Group treatment sessions during the first year; liquid meal replacements; and optional weight loss medication, after the first 6 months, with selected individuals. TIME FRAME: 1-year intensive lifestyle intervention and with year 4 follow-up data	Four meal replacements, including: Slim Fast (Slim Fast Foods), Glucerna (Ross Laboratories), OPTIFAST (Novartis Nutrition) and HMR (HMR, Inc.).	Weight loss, weekly physical activity, serum lipids, blood glucose, hormones, cardiovascular morbidity, medication and mortality.	-Participants with ≥ 10% initial weight loss had a significantly lower proportion of participants starting on diabetes mellitus medication (3.1% versus 7.5%) -In men only, losing ≥ 10% initial weight was associated with a significantly lower proportion starting antihypertensive medication (15.5% versus 7.4%) -Among men, at baseline, those with <10%initial weight loss had significantly higher HbA1cconcentrations and diastolic blood pressure than those with ≥ 10% initial weight loss
Effect of Oral Nutritional Supplements with Sucromalt and Isomaltulose versus Standard Formula on Glycaemic Index, Entero-Insular Axis Peptides and Subjective Appetite in Patients with Type 2 Diabetes: A Randomised Cross-Over Study (2019)	Assess sucromalt/ isomaltulose ONS-D effects on the glycaemic response (GI/GL), EIAP release and postprandial SA in type 2 diabetic individuals	23 DM2 subjects over 50 years old; Body mass index (BMI) between18.5 kg/m2–35 kg/m	A randomized, double-blind, cross-over study. In this study, three oral nutritional supplements were examined: non-diabetes-specific standard oral nutritional supplements (ET; Ensure); oral supplements with a blend of slow-digesting carbohydrates including resistant maltodextrin and sucromalt (GS; Glucerna) and oral supplements composed of lactose, isomaltulose, and resistant starch (DI; Dia sip) TIME FRAME: 1 day	Composition* ET, DI GS Calories (kcal) 10510493 Protein (g) 3.84.94.3 Fat (g) 2.53.83.5 Carbohydrate (g) 17.311.710.9 Dietary Fibre (g)1.02.0 1.8 *ET(Ensure); GS (Glucerna); DI (Diasip)	Plasma insuline, BMI, weight, blood glucose, HbA1c, Plasma total GIP, GLP-1, total cholesterol, triacylglycerides, LDL-C and HDL-Clevels.	-At 150 min, ET presented a higher glucose concentration than DSF ($p < 0.001$), but no significant differences were found in insulin concentration between DI and GS ($p = 0.976$). At 150 min, value of this incretin was significantly higher for GS when compared with both, ET ($p < 0.001$) and DI ($p < 0.001$). -The AUC0–180 min in insulin response was significantly lower in GS when compared with the other supplements ($p < 0.001$) -The maximum peak of this incretin was observed at 90 min with ET and DI, which was higher when compared to GS levels ($p < 0.05$).

specific formulas for diabetics have been developed in the last decade. With the aim of being used with multidisciplinary weight management programs as meal replacements [28]. DSF provide a controlled caloric intake, minimizing postprandial glucose response; even in cases where patients are resistant to traditional weight loss therapy, adding the approach of meal replacements with these formulas has proven to be effective, improving weight loss to -5.4 kg in some studies [18,23].

Meanwhile standard formulas are well known and have been used over the past few decades, the used of DSFs is still controversial. Diverse studies have shown the important role of DSF for type-2 diabetic patients management in fields such as glycemic control (both capillary and plasma glucose), lowering insulin requirements, effective weight loss as well as reducing the risk of acquired infections in hospitalized patients [32]. Compared to standard formulas, DSF have lower glycemic index and its components are targeting a population who needs normoprotein-caloric diet [34]. An ideal nutritional formula for all types of diabetic patients has not yet been developed. For this reason, integrated therapy remains the best option [30]. One of the elements, exercise, is an irreplaceable component to achieve long-term maintenance of lost weight and reduce the risk of deaths from cardiovascular diseases in diabetics. The goal of achieving up to 10% of weight loss in obese diabetic patients brings long-term benefits such as reducing the need for hypoglycemic agents and better glycemic control [21].

On the other hand, there are still many aspects of topic pending for investigation, including comparison of the effects of protein-rich and fat-rich DSF on short-term and long-term. In addition, the scientific community still lacks enough clinical trials to investigate the impact of different therapies on morbidity and mortality among diabetic adults [20].

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