Research article

Efficacy and Safety of a Diabetes Specific Formula in Patients with Type 2 Diabetes Mellitus: A Randomized, Open-label, Crossover Study.

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ABSTRACT

Managing postprandial hyperglycemia is a frequent challenge for individuals with Type 2 diabetes (T2D). There is a paucity of data examining use of a diabetes-specific formula (DSF) versus a matched isocaloric diet and improved PPG. The present study aimed to evaluate the effects of a new DSF compared to a matched macronutrient isocaloric diet on postprandial glucose (PPG), insulin, and safety in patients with T2D. In this randomized, open-label, crossover study, 30 T2D subjects were randomized into one of two groups: group A received the new DSF and group B received the isocaloric diet. After one-week, participants crossed over to the alternative nutrition intervention. Blood samples measured glucose and insulin levels at baseline, 30, 60, and 120 min post-meal. PPG levels and incremental area under the curve (iAUC) for glucose were significantly lower for group A compared to group B (P=0.007). Postprandial insulin levels were lower at 60 and 120 min for group A compared to group B, though not statistically different. The DSF was well tolerated and no serious adverse events were reported. This study demonstrates that use of a DSF is superior to an isocaloric diet in reducing PPG and tend to improving insulin response in T2D patients. These data suggest use of a DSF offers glycemic benefits and should be included as a medical nutrition therapy for patients with Type 2 diabetes.

Key words: Diabetes; Diabetes specific formula; Postprandial glucose; Insulin; Glycemic index

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บทความวิจัย

ประสิทธิผลและความปลอดภัยของอาหารสูตรเบาหวาน ในผู้ป่วยเบาหวานชนิดที่ 2 การศึกษาแบบสองระยะไขว้กัน แบบสุ่ม

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[1]สาขาวิชาโภชนวิทยาและชีวเคมีทางการแพทย์ ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล กรุงเทพ, [2]กลุ่มสาขาวิชาโภชนศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล กรุงเทพ, [3]หน่วยโภชนาการ งานสนับสนุนทางการแพทย์เฉพาะทาง โรงพยาบาลรามาธิบดีจักรีนฤบดินทร์ มหาวิทยาลัยมหิดล สมุทรปราการ, [4] หน่วยบริการพยาบาลผู้ป่วยที่บ้าน งานการพยาบาลป้องกันโรคและส่งเสริมสุขภาพ ฝ่ายการพยาบาล คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล กรุงเทพ, [5] Nestlé Health Science, Metabolic Health, สหรัฐอเมริกา

บทคัดย่อ

ภาวะน้ำตาลในเลือดหลังอาหารสูงในผู้ป่วยเบาหวานชนิดที่ 2 เป็นปัญหาที่พบได้บ่อย แต่ข้อมูลเรื่องผลของการให้อาหารสูตรเบาหวานเทียบกับอาหารปกติที่ให้พลังงานเท่ากันต่อระดับน้ำตาลในเลือดหลังอาหารยังมีน้อย วัตถุประสงค์ของการศึกษานี้เพื่อศึกษาผลของอาหารทางการแพทย์สูตรเบาหวานเปรียบเทียบกับอาหารปกติที่ให้พลังงานเท่ากันต่อระดับน้ำตาลและอินซูลินในเลือดหลังอาหารรวมถึงศึกษาเรื่องความปลอดภัยในผู้ป่วยเบาหวานชนิดที่ 2 การศึกษานี้เป็นการศึกษาแบบสองระยะไขว้กัน มีผู้เข้าร่วมงานวิจัยจำนวน 30 คนซึ่งจะได้รับการสุ่มให้อยู่กลุ่ม A หรือ B โดยระยะแรก กลุ่ม A ได้รับอาหารทางการแพทย์ Nutren Diabetes และกลุ่ม B ได้รับอาหารที่ให้พลังงานเท่ากัน หลังจากนั้น 1 สัปดาห์ ผู้เข้าร่วมงานวิจัยทั้ง 2 กลุ่มจะได้รับอาหารสลับชนิดกัน โดยทั้งสองระยะผู้เข้าร่วมงานวิจัยจะได้รับการตรวจ เลือดเพื่อวัดระดับน้ำตาลและอินซูลินในเลือดภายหลังรับประทานอาหารแต่ละชนิดที่เวลา 0, 30, 60 และ 120 นาที ผลการศึกษาพบว่าระดับน้ำตาลในเลือดหลังอาหาร และการเพิ่มขึ้นของพื้นที่ใต้กราฟของน้ำตาลของกลุ่ม A ต่ำกว่ากลุ่ม B อย่างมีนัยสำคัญ (P=0.007) ระดับอินซูลินในเลือดหลังอาหารที่เวลา 60 และ120 นาทีในกลุ่ม A มีแนวโน้มต่ำกว่ากลุ่ม B การศึกษานี้ไม่พบผลข้างเคียงรุนแรงจากการใช้อาหารทางการแพทย์สูตรเบาหวาน การศึกษานี้แสดงให้เห็นว่าการให้อาหารทางการแพทย์สูตรเบาหวานช่วยลดระดับน้ำตาลในเลือดหลังอาหารและเพิ่มการตอบสนองการทำงานของอินซูลินเมื่อเปรียบเทียบกับอาหารปกติที่พลังงานเท่ากัน การให้อาหารทางการแพทย์สูตรเบาหวานควรเป็นส่วนหนึ่งในการให้โภชนบำบัดในผู้ป่วยเบาหวานชนิดที่ 2

คำสำคัญ: โรคเบาหวาน; อาหารสูตรเบาหวาน; ภาวะน้ำตาลในเลือดหลังอาหาร; Insulin; ดัชนีน้ำตาล

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Introduction

The diabetes epidemic is a significant public health burden. The International Diabetes Federation (IDF) estimated in 2017 that there were 425 million adults worldwide living with diabetes and this number would rise to 629 million by 2045. Globally, the prevalence of diabetes is significantly higher in middle-to-low-income countries[1]. The Thai National Health Examination Surveys showed that the prevalence of diabetes in individuals aged 20 years and older has increased substantially over the past decade from 7.0% in 2004 to 9.7% in 2014[2]. Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputation. Moreover, diabetes is the sixth leading cause of death and in Thailand accounted for approximately 14,000 deaths in 2017[3]. Appropriate glycemic control has been associated with a reduction in micro- and microvascular complications. A lifestyle intervention that includes a well-balanced and nutrient-dense diet, daily physical activity, and a healthy weight are the cornerstones of diabetes management.

Managing postprandial hyperglycemia is a frequent challenge for individuals with Type 2 diabetes (T2D). Postprandial plasma glucose (PPG) levels are influenced by both the amount and quality of dietary carbohydrate (CHO), which, in turn, significantly contributes to overall HbA1c levels; when HbA1c levels are greater than 7.3% the contribution decreases progressively with increasing HbA1c levels[4] . The glycemic index (GI) is one approach used to assess carbohydrate quality based on the blood glucose response after food consumption as compared to a reference food (usually glucose or white bread)[5]. Carbohydrate-rich foods, such as rice, have a high GI and are rapidly digested, thereby significantly increasing the PPG response. On the other hand, consumption of low GI foods results in slower digestion and a blunted PPG response. Specifically, foods that contain carbohydrate sources derived from high fiber, resistant starches typically have a low-GI. For example, Isomaltulose, a disaccharide composed of alpha-1,6–linked glucose and fructose, is slowly yet completely hydrolyzed by isomaltase and absorbed in the small intestine[6]. This results in a blunted PPG response and a low GI of 32[7]. Recent meta-analyses support that diets rich in resistant starch and a low GI index improve fasting glucose and insulin levels, HbA1c, reduce insulin resistance, and increase insulin sensitivity[8]. These outcomes are in line with other meta-analyses that demonstrate the benefit of a low GI diet on overall glycemic control in patients with T2D[9]. Although there is no ideal diet for individuals with diabetes, several organizations recommend a high fiber (14 g of fiber/1,000 kcal), low GI nutrient-dense, and low carbohydrate diet that limits the intake of added sugars and sugar-sweetened beverages[10].

Diabetes-Specific Formulas (DSFs) are designed to provide complete nutrition and optimize glycemic control in individuals with hyperglycemia. The common features of DSFs are low carbohydrate content, modified carbohydrate composition (i.e., a sugar substitute and slowly digested-carbohydrate), high fiber content, a low GI, high mono-unsaturated fatty acid (MUFA), low cholesterol, saturated and trans-fat with moderate high-quality protein content. A systematic review and meta-analysis have revealed that the use of DSFs, given as an oral nutrition supplement or by tube feeding, is associated with improved glycemic

control and decreased insulin requirements compared to a standard formula[11]. Additionally, the review findings highlighted the benefits of using a DSF for glycemic control in diabetic individuals[12, 13]. A nutritional intervention, which includes incorporating a DSF as an oral nutrition supplement or meal replacement, may facilitate glycemic control and improve co-morbidities in diabetic individuals[14, 15]. There is a paucity of data examining use of a diabetes-specific formula (DSF) versus a matched isocaloric diet and improved postprandial glycemic control. Consequently, this study's aim was to compare the effects a DSF versus an isocaloric diet on postprandial glucose and fasting plasma insulin levels, satiety, as well as safety and tolerability in patient with T2D.

Materials and Methods

Participants

Eligible participants had T2D and were between the ages of 18 to 70 years. All had a baseline HbA1c of <8.5% or FBG <200 mg/dL, were being treated with diet and/or a steady dose of oral hypoglycemic agents or lipid lowering medications, and maintained a stable body weight within past six months (changes less than 3%). Major exclusion criteria included currently on insulin or GLP-1 agonist therapy, renal failure with an eGFR <30 ml/min/1.73 m^2, malabsorption, decompensated liver cirrhosis, alcoholism, drug abuse, pregnancy, lactation, and a history of allergy to any ingredients in DSFs, soybean milk, and bologna sandwiches.

Study Design

A randomized, open-label, cross-over study was conducted at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, from August 2018 to May 2019. The primary outcomes included fasting plasma glucose, postprandial plasma glucose, and incremental area under the curve (iAUC) for blood glucose. Secondary outcomes included fasting plasma insulin, changes in hunger and satiety, and safety. All participants received and signed written consent forms before enrollment. The study was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University.

Study Procedures

After completing the screening process, eligible participants entered a run-in period (visit 1, D0) during which baseline demographics were measured and dietary and exercise counselling for weight maintenance was performed. At the end of the run-in period, patients were randomized into one of two groups according to a four block randomization schedule.

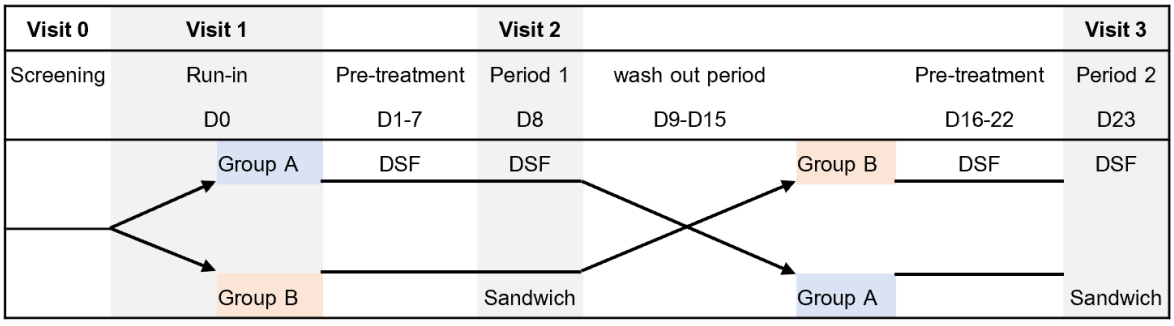


Figure 1. Study design

Group A received a DSF and group B received a matched isocaloric diet with equivalent macronutrient distribution (Figure 1).

The Diabetes specific formula (DSF; Nutren Diabetes®, Nestlé Health Science, Switzerland) used in this study provides 360 kcal with a balanced amount of nutrients: 18% (16 g) protein from a blend of whey protein (50%) and potassium caseinate (50%); 39% (15.7 g) from a fat blend of high oleic sunflower oil, sunflower oil, and low erucic rapeseed oil; 43% (35 g) carbohydrate blend from tapioca and potato starch and isomaltulose; and 6.8 g fiber blend from acacia gum, pea fiber and inulin The matched isocaloric meal provides as a carton of soy milk (250 ml) and bologna sandwiches (two slices of bread) with mayonnaise approximately 360 kcal; 39 g (45%) of carbohydrate (%); 3 g fiber (g): 3; Fiber (g); 15 g (17%) protein; 15 g (38%) fat; GI was not calculated (**Table 1**).

Table 1 Composition of test meal and diabetes-specific formula

Per portion	**Control diet**	**Diabetes-specific formula (Nutren Diabetes®) 360 ml**
	Soy milk 250 ml and Bologna sandwich with mayonnaise spreading	
Calories	360	360
Carbohydrate, g (%)	39 (45)	35 (43)
Fiber (g)	3	6.8
Protein, g (%)	15 (17)	16 (18)
Fat, g (%)	15 (38)	15.7 (39)
Glycemic index	NA	28

The DSF was prepared by adding 79g of powder (10 scoops) into 300 ml of water. Group A participants were instructed to consume 360 kcal of DSF at breakfast for 7 days (D1-D7) before the second visit to assess acceptance, tolerability, and safety of the DSF. On the second visit (visit 2, D8), all participants who came to the clinic fasted for a minimum of 12 hours overnight. All participants were instructed to withhold their medications the evening and morning before the test day. The breakfast test diet consumed was either the DSF or isocaloric diet (soymilk and sandwich).

Outcome Measurements

Baseline blood samples were collected to measure postprandial glucose levels and fasting plasma glucose and insulin levels at 30, 60, and 120 min after the meal. At the same time of blood collection, subjective sensations of hunger, satiety, and appetite were assessed using a visual analogue scale (VAS) questionnaire. The 100-mm VAS was scored by measuring the distance from

the left end of the scale to the mark placed by the participants. After group B participants completed period 1, they crossed over to the DSF regimen for one week. Similarly, after group A completed period 1, they crossed over to the isocaloric diet for one week. In addition, the safety and tolerability of the DSF was assessed for participants that had completed the pre-treatment period and received the DSF. The side effects recorded entailed changes in gastrointestinal symptoms including abdominal distention, nausea, vomiting, and stool frequency.

Blood chemistry measurement

All blood samples were fractionated using standard procedures and stored at -70 ºC until analysis. Glucose measurements were analyzed based on hexokinase methods by using Clinical Chemistry Glucose (R1) (Abbott Diagnostics, Abbott park, IL, USA) performed on Architect c16000 (Abbott Laboratories, Abbott park, IL, USA). Insulin values were analyzed based on a chemiluminescent microparticle immunoassay (CMIA) using the ARCHITECT Insulin assay reagent (Abbott Diagnostics, Abbott park, IL, USA) performed on Architect i2000 (Abbott Laboratories, Abbott park, IL, USA).

Sample Size

The sample size for each group was 13 participants based on a power analysis with 80% power and at a significance level of 5% to detect differences in 2-h PPG between groups.

Statistical Analyses

The statistical analysis was performed by using STATA 15.1 (StataCorp LP, College Station, TX) and *P*-values <0.05 were considered statistically significant. Continuous data were expressed as mean ± standard deviation and categorical data expressed as number and percentage. The area under the curve (AUC) was calculated using the trapezoidal model. The incremental area under the curve (iAUC) was calculated by subtracting the baseline level of glucose and insulin. Continuous variables were compared by using Paired T-Test and or Wilcoxon Matched pairs Signed Rank test as appropriate. Categorical variables were analyzed using chi-square tests.

Results

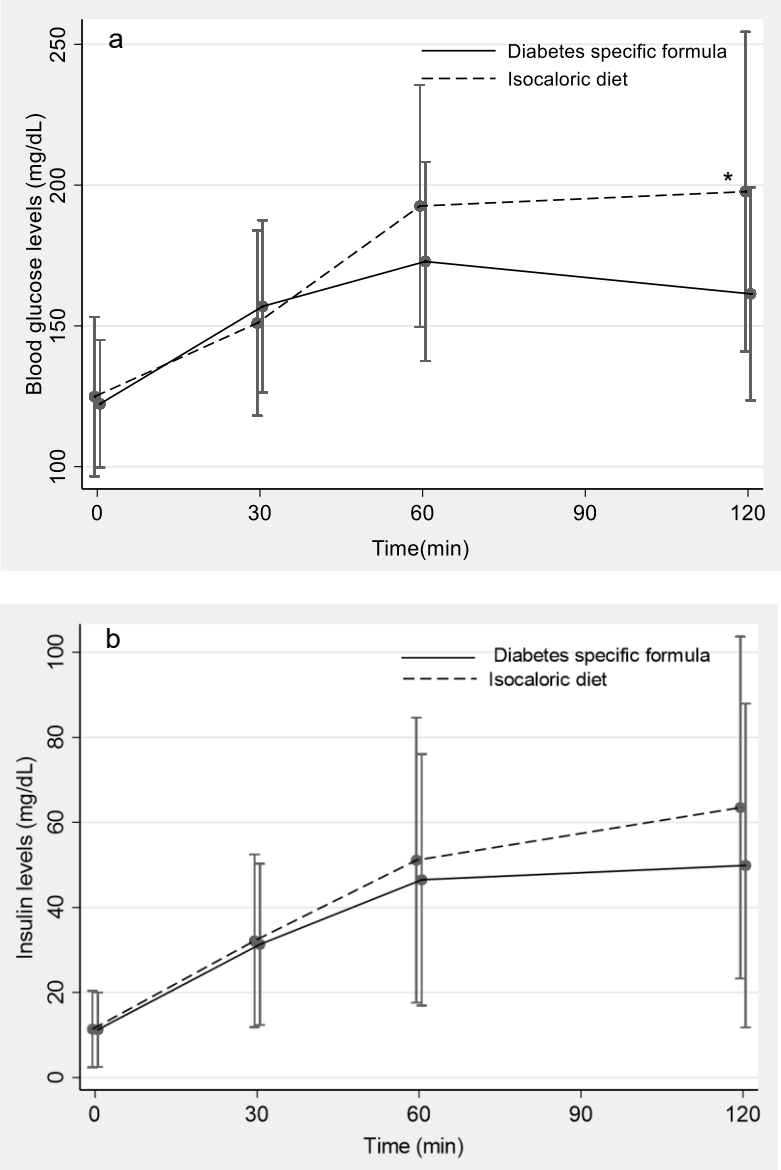
Baseline Characteristics

Thirty T2D patients (25 women, 5 men) were enrolled and completed all study visits. The mean age was 58.3 ± 8.3 years and BMI 30 ± 7 kg/m^2. Body weight of all participants was stable during the study period. The mean HbA1c at baseline was 6.8 ±0.7%. Mean fasting plasma glucose levels for the DSF and isocaloric diet groups were similar at baseline (130.3 ± 30.8 mg/dL vs. 129.5 ±24.8 mg/dL, *P*= 0.938). The PPG levels for the DSF group tended to be significantly lower compared to the isocaloric diet group at 60 min (172.9 ± 35.3 mg/dL vs. 192.6 ± 43 mg/dL, *P*=0.057) and were significantly lower at 120 min (161.4 ± 37.9 mg/dL vs. 197.7 ± 56.8 mg/dL, *P*=0.005), respectively (**Fig. 2a**). Moreover, the overall incremental area under the curve (iAUC) for blood glucose was significantly lower for the DSF compared to the isocaloric diet group (4,859.5 vs 6,551.7, *P*=0.007).

Clinical outcomes

Mean baseline fasting insulin levels were comparable between the two groups (18.4 ± 23.3 µIU/ml, 16.7 ± 12.7 µIU/ml, *P*=0.743, respectively). Postprandial insulin levels were lower at 60 min and 120 min for the DSF group, though the

difference did not reach statistical significance. Insulin AUCmin 0-120 and incremental insulin AUC showed no significant differences between meals. (**Fig. 2b**).



*$P \leq 0.05$

Figure 2 The 2-hr postprandial glucose (a) and insulin (b) level in diabetes specific formula and isocaloric diet

Hunger, Satiety and Appetite Evaluation

All patients were given a VAS questionnaire to assess changes in hunger and satiety. Results showed no significant differences in mean scores between a DSF and isocaloric diet (Table 2). The DSF was well-tolerated among most patients, and there were no reported serious adverse events during the study period. Only one patient reported mild nausea and two patients experienced (6.7%) mild diarrhea during the run-in period. All symptoms resolved spontaneously and did not require any medication or other treatment.

Table 2 Effect of study treatments on hunger and satiety by VAS questionnaire

	DSF (n=30)	Isocaloric diet (n=30)	*P* value
How hungry do you feel? Mean (SD):			
Before breakfast	42.0 (28.7)	39.4 (25.0)	0.717
30 min after breakfast	26.1 (24.2)	27.0 (25.4)	0.897
60 min after breakfast	28.8 (24.1)	34.8 (22.3)	0.324
120 min after breakfast	30.0 (23.3)	42.1 (25.4)	0.059
How satisfied do you feel? Mean (SD):			
Before breakfast	26.6 (19.6)	37.2 (26.2)	0.081
30 min after breakfast	58.1 (31.5)	66.0 (22.6)	0.269
60 min after breakfast	52.7 (30.8)	59.5 (19.3)	0.310
120 min after breakfast	39.6 (28.2)	47.2 (24.5)	0.270
How full do you feel? Mean (SD):			
Before breakfast	17.5 (14.0)	19.3 (16.0)	0.638
30 min after breakfast	30.9 (28.2)	31.8 (27.9)	0.902
60 min after breakfast	23.3 (22.6)	29.1 (20.8)	0.311
120 min after breakfast	21.7 (19.4)	28.4 (23.0)	0.225
How much do you think you can eat? Mean (SD):			
Before breakfast	60.9 (31.1)	52.3 (30.9)	0.289
30 min after breakfast	41.6 (34.4)	42.6 (29.0)	0.910
60 min after breakfast	52.3 (34.2)	42.9 (25.6)	0.233
120 min after breakfast	52.8 (34.2)	55.7 (29.0)	0.718

Discussion

This study demonstrates that consumption of a DSF by participants with T2D results in a significantly lower postprandial glucose response at 60 min and 120 min, compared to an isocaloric diet similar in macronutrient composition.

The DSF used in this study provided 43% of total calories as complex carbohydrate, which is comparable to a typical Asian breakfast meal. Furthermore, the DSF used in this study had a low GI (GI =28) and glycemic load (GL=6.9) by way of the slowly digestible carbohydrate and high fiber content. The protein content, comprised of casein (50%) and whey (50%), provided 18% of the total calories. Whey protein is a fast-acting protein and is rapidly absorbed into circulation whereas, in contrast, casein is a slow-acting protein and helps to delay gastric emptying time and aid in satiety. Moreover, the combination of the whey and casein protein may increase amino acid availability and contribute to a high amount of MUFA fiber that is consistent with the dietary recommendation of the American Diabetes Association. These findings demonstrate the benefits of using a high fiber, slowly digestible and low GI carbohydrate (isomaltulose) DSF in individuals with T2D. Furthermore, although the DSF and isocaloric diet were of comparable carbohydrate content, the lower GI of the DSF resulted in a lower postprandial glucose response. Soluble fibers in the studied DSF (inulin, FOS, and guar gum) also helped to delay digestion and absorption of carbohydrate, thus reducing postprandial hyperglycemia. Furthermore, the studied DSF was high in MUFA, which has been shown to be beneficial for glycemic control. Previous studies have indicated that replacing a simple carbohydrate with MUFA results in improved glycemic control and insulin response, as well as an improvement of lipid profiles when compared to high carbohydrate diet[16-19].

Postprandial hyperglycemia contributes to overall glycemic control[20,21] and has been associated with an increased risk for diabetes complications[22] and cardiovascular mortality[23]. Consequently, treatments that significantly reduce postprandial glucose excursions should be recommended to improve overall glycemic control and clinical outcomes. Using DSFs as part of medical nutrition therapy has been associated with improvement in postprandial glucose control[11]. In the current American Diabetes Association Standards of Medical Care, DSFs are recommended as an ideal option for patients requiring enteral feeding due to its superior ability in controlling postprandial glucose, A1C, and insulin response compared to a standard enteral formula[10]. Moreover, DSFs can serve as a meal replacement along with intensive behavioral lifestyle interventions to induce weight loss in obese diabetic individuals.

The postprandial insulin levels in the DSF group were lower at both 60 min and 120 min, but differences did not reach statistical significance. Consistent with the previous study, the DSF revealed a significantly lower PPG levels but not for postprandial insulin levels.[24.]

A possible explanation for this finding may be the small sample size and the different action of diabetic medications in T2D patients

like sulfonylureas or nonsulfonylurea insulin secretagogue that stimulate insulin secretion by pancreas[25].

There were no significant differences in hunger and satiety scores between the DSF and isocaloric groups. However, due to this study's small sample size, these findings may have been underpowered and thus were unable to detect differences. Moreover, we did not measure hunger and satiety hormones, which involves a complex hormonal and neuronal pathway.

Despite these limitations, the study findings are relevant and underscore the importance of medical nutrition therapy in the management of diabetes. However, to determine adequately the role of using a DSF in the management of diabetes across a broader population, additional long-term randomized control trials are warranted.

Conclusions

The present study revealed use of a DSF is superior in reducing PPG and improving insulin response in individuals with Type 2 diabetes. Moreover, the DSF was safe and well tolerated, suggesting use of a DSF offers many glycemic benefits and should be included as medical nutrition therapy for patients with Type 2 diabetes.

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Conflict of interest

The authors have no financial interests to declare.

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