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Original article

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SUMMARY

Background & aims: Several studies with diabetes-specific formulas (DSFs) for hyperglycaemic patients in need of nutritional support have been conducted in non-malnourished patients, mainly comparing products with varying macronutrient compositions. Here, the effect of a high energy, high protein DSF on postprandial responses was compared to a product with a similar macronutrient composition in malnourished or at risk of malnutrition patients with type 2 diabetes.

Methods: In this randomised, double-blind cross-over study, 20 patients were included. After overnight fasting, patients consumed 200 mL of a DSF or standard supplement (control) (19.6 g protein, 31.2 g carbohydrates and 10.6 g fat), while continuing their anti-diabetic medication. The formulas differed in type of carbohydrates and presence of fibre. The postprandial glucose, insulin and glucagon responses were monitored over 4 h. Data were analysed with a Linear Mixed Model, and results of the modified ITT population ($n = 19$) are shown.

Results: Postprandial glucose response as incremental area under the curve (iAUC), was lower after consumption of DSF compared with control (489.7 ± 268.5 (mean ± SD) vs 581.3 ± 273.9 mmol/L min, respectively; $p = 0.008$). Also, the incremental maximum concentration of glucose (iCmax) was lower for DSF vs control (3.5 ± 1.4 vs 4.0 ± 1.4 mmol/L; $p = 0.007$). Postprandial insulin and glucagon levels, expressed as iAUC or iCmax, were not significantly different between groups.

Conclusions: Consumption of a high energy, high protein DSF by older malnourished or at risk of malnutrition type 2 diabetes patients resulted in a significantly lower glucose response compared to control. These data suggest that the use of a DSF is preferred for patients with diabetes in need of nutritional support.

1. Introduction

Malnutrition is highly prevalent among older patients with type 2 diabetes in a hospital or geriatric care setting [1,2] and is an important predictor for longer hospital stays and poorer clinical outcomes [1,3]. Nutritional management is an integral part of diabetes care, but additional considerations apply for older adults with diabetes. Maintaining a proper nutritional status can be quite challenging due to acute disease, functional status or severe co-morbidities [4]. If an individual's nutritional needs cannot be reached with usual dietary intake or meal modifications, other interventions are encouraged such as the use of oral nutritional supplements between meals [4].

Oral nutritional supplements should provide sufficient macro and micro-nutrients including energy, protein, vitamins and minerals to reduce the risk of malnutrition [5]. However, many standard oral nutritional supplements may result in high postprandial glucose responses in patients with type 2 diabetes. On the short

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term, hyperglycemia can result in glucosuria, characterized by an increased urinary excretion of glucose and thus energy, as well as an increased risk of infections and urinary incontinence. In hospitalized patients, hyperglycemia is associated with increased morbidity, mortality and longer hospital stay [6]. Preventing high blood glucose excursions, thus, seems a valid target to improve the patients' quality of life and save health care resources associated with poor outcome.

Nutritional requirements of malnourished patients with diabetes could be met with specially designed diabetes formulas. In the past, diabetes specific formulas (DSFs) contained ingredients such as high levels of fructose and/-or a large amount of mono-unsaturated fatty acids, aimed to limit postprandial glucose excursions as much as possible. It was demonstrated that the DSFs compared with standard formulas improved blood glucose levels [7]. However, the levels of fructose and contribution of >35% energy of fat in these formulas were still of concern, due to potential detrimental effects on lipid metabolism and a low compliance with the nutritional guidelines [8,9]. Currently, there are commercially available DSFs that comply with a lower energy % of fat, and most of them contain a slow digestible form of carbohydrates [10].

However, no studies have been performed with these supplements in the target population of these products: diabetes patients with malnutrition or at risk of malnutrition. In addition, most of the comparisons between DSFs and standard nutritional supplements used different levels of macronutrients contributing to total energy content [11], these could differentially modulate postprandial control [12] and limits the conclusion on a clear mechanism of action. The aim of this study was, therefore, to examine in malnourished or at risk of malnutrition type 2 diabetes patients whether a DSF (high energy, high protein and part of the carbohydrate fraction including isomaltulose as a slow release sugar source) would result in an attenuated postprandial glucose response compared to a standard nutritional supplement with similar energy content and similar percentages of carbohydrate, fat and protein macronutrients contributing to the total energy. In addition, during an open label study extension, glycaemic responses were determined after oral intake of a full serving compared to two half servings of the diabetes specific formula.

2. Materials and methods

2.1. Patients

Patients were recruited in hospitals, rehabilitation centres and/or nursing homes. Inclusion criteria were; patients aged ≥18 years with the diagnosis of type 2 diabetes for at least six months prior to study entry and be on stable anti-hyperglycaemic therapy (oral medication and/or insulin) for at least 1 month prior to study entry. Patients should also be malnourished or at risk of malnutrition according to the presence of one or more of the following criteria that were partly derived from the French clinical practice guidelines on nutritional support strategy for protein-energy malnutrition in the elderly [13] and the use of the Mini Nutritional Assessment®-Short Form (MNA®-SF) [14]: 1) ≥5% involuntary weight loss in the last month, or 2) ≥10% involuntary weight loss in the last 6 months, or 3) Serum albumin <35 g/L, or 4) Age ≥ 70 yrs and body mass index (BMI) < 21.0 kg/m^2, or 5) Age < 70 yrs and BMI < 18.5 kg/m^2, or Age ≥ 65 yrs and MNA®-SF score ≤ 11. In addition, MNA®-SF score was recorded for all included patients.

Patients were excluded if: 1) they had any gastrointestinal disease that interferes with bowel function and nutritional intake, heart failure (New York Heart Association (NYHA) class IV), kidney disease (Chronic Kidney Disease (CKD) ≥ stage 4), hepatic disease (transaminases > 5 times upper limit of normal), severe anaemia (haemoglobin <8 g/dl or 5 mmol/L), 2) their current condition or treatment interferes with stable glucose metabolism, such as uncontrolled thyroid disease, post operation, pregnancy, or having major infections, 3) When the diet pattern includes: a fibre free diet, intolerance of any of the ingredients in the study products, alcohol intake of >21 units and >14 units for men and women, respectively, 4) they had difficulties swallowing the study products or are dependent on parenteral or tube feeding, 5) in case the investigators are uncertain about the willingness or ability of the subject to comply with the protocol requirements, or when the patients are already participating in another study. Throughout the study, the patients were requested to keep medication constant and to maintain their normal dietary habits whenever possible.

All patients gave written informed consent before screening and were aware that they could stop the study at any time they desired. The study protocol was approved by Comite de protection des personnes – Hôpital Hôtel-Dieu; 1, place du Parvis-de-Notre-Dame, 75181 Paris Cedex, France and the study was registered at http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3734 as NTR3734.

2.2. Study design

The study had a randomised, double blind, crossover design with an open label extension day. For investigation of the primary objective, patients had to complete two study days in randomised order, receiving either the diabetes-specific formula (DSF) on the first study day (visit 1) and the standard nutritional supplement (control) on the second study day (visit 2) or vice versa. The wash-out period between the study days was 3–14 days. After a second wash-out period, the patients could complete an open label third study day (visit 3) to investigate the effect of serving size. On the morning of each study day, the patients arrived at the research centre after an overnight fast and no changes were made in diabetes medicine prescription or treatment protocol. Fifteen minutes before the first blood samples were taken, an intravenous cannula was placed in a forearm vein to allow repeated blood sample collection for 4 h. Subjects received the study product at t = 0 min and had to consume it within 10 min. Venous blood samples were drawn at two time-points before (t −10 and t −5 min) and at 8 time-points after starting consumption of the study product (t 15, t 30, t 45, t 60, t 90, t 120, t 180, and t 240 min) to measure the 4-h postprandial blood glucose, insulin and glucagon responses. During these measurements, subjects were instructed to sit or lie down quietly, e.g. reading a book or watching television. Thereafter, the cannula was removed, and a lunch was provided. On visit days 1 and 2, fasting and postprandial (t = 30, 60, 120, 240 min) C-peptide was also determined. On the first study day, fasting blood samples were used for the analyses of HbA1c, serum albumin, triglycerides, total cholesterol, LDL-cholesterol and HDL-cholesterol. During the open-label extension study day, the patients consumed the DSF in serving sizes of 100 mL (2 × 100 mL), of which the first serving at breakfast (t 0) and the second serving 2 h later (during the postprandial measurements at t 120).

2.3. Study product(s)

The DSF used was Fortimel DiaCare (Nutricia N.V, Zoetermeer, the Netherlands), which is a 200 mL high-energy (1.51 kcal/mL), high-protein, ready to drink oral nutritional supplement (ONS), enriched with soluble fibre and containing specific carbohydrates (Table 1). As control, Fortimel Extra (Nutricia N.V., Zoetermeer, The Netherlands) was used, which is also a high-energy (1.50 kcal/mL), high-protein, ready to drink ONS with a similar macronutrient composition as the DSF except for the fibre content and the

Table 1
Energy content and macronutrient composition on the study products.

	DSF (100 mL)	Control (100 mL)
Energy (kcal)	151	150
Protein g (En%)	9.8 (26)	9.8 (26.2)
- Casein g	7.84	7.84
- Whey g	1.96	1.96
Carbohydrate g (En%)	15.6 (41.2)	15.6 (41.5)
- Glucose/Maltose g	0.7	0.6
- Lactose g	3.4	3.1
- Isomaltulose g	5.6	–
- Sucrose	–	1.3
- Polysaccharides	5.5	10.4
- Other	0.4	0.3
Fat g (En%)	5.3 (31.9)	5.3 (32.2)
- Saturated g	0.64	0.63
- MUFA g	3.17	3.17
- PUFA g	1.53	1.53
Fibre g (En%)	0.7 (0.9)	–

DSF; diabetes specific formula, Control; Standard Nutritional Supplement, MUFA; mono unsaturated fatty acid, PUFA; poly unsaturated fatty acid.

carbohydrate composition (Table 1). Both supplements contained vitamins, minerals and trace elements in accordance with the regulations for Food for Special Medical Purposes (FSMP) (1999/21/EC).

2.4. Blood analysis and calculations

All blood samples were analysed by a certified laboratory (Reinier de Graaf Hospital, Department of Clinical Chemistry, Delft, The Netherlands). Blood HbA1c was determined by HPLC (Tosoh Diagnostics, Tessenderlo, Belgium), plasma glucagon was determined using a radio immune assay (Siemens Healthcare Diagnostics, Breda, The Netherlands), serum insulin and C-peptide were studied via immunoluminometric assays (Siemens Healthcare Diagnostics, Breda, The Netherlands) and serum glucose, TAG, total-, LDL- and HDL-cholesterol were analysed using commercial kits (Abbott Diagnostics, Olst, The Netherlands).

Plasma glucose, insulin, glucagon and C-peptide responses were calculated for the individual time curves as positive iAUC above baseline levels (t = 0 min) according to the methodology described by Brouns et al. [15]. For plasma glucose, insulin and glucagon, also the Cmax and iCmax were calculated as the average of the individual Cmax and iCmax values. Cmax is the postprandial peak glucose concentration and iCmax the postprandial delta peak glucose concentration (postprandial peak glucose concentration minus the baseline glucose concentration).

2.5. Statistical analyses

Before initiation of the study, a sample size of 10 patients per group was calculated (Proc Power, SAS Enterprise Guide version 4.3) to be sufficient to detect a 30% reduction in iAUC between the test and the control product, with a power of 80% and a significance level (α) of 0.05, assuming an iAUC0-4h glucose of 666 mmol/L min in the control group and a standard deviation of 290 [16]. Comparisons between the DSF and control groups were analysed using a PROC MIXED model with a compound symmetry covariance structure; and with period and product as fixed factors and subject number as repeated factor. Underlying assumptions for the application of mixed models were checked and if assumptions were not met, data transformations and/or non-parametric test (paired-sample Wilcoxon signed rank test) were used to assess the statistical differences between the treatments. Comparisons between the full DSF serving and 2 halve servings of DSF were analysed using a paired t-test. SAS Enterprise Guide 4.3 for Windows (SAS Institute) software was used for all statistical analyses. In this paper, the results of the modified ITT population are shown, which consisted of all randomized subjects (n = 20) minus one subject who had violated one exclusion criterion. After unblinding, it became clear that this subject had violated the exclusion criterium: 'Concurrent condition/treatment that interferes with stable glucose metabolism (i.e. immediately post-operative)'. For the safety analysis, the all subjects randomized population (n = 20) was used. Statistical significance was defined as a 2-tailed $p < 0.05$ and data in text and tables are expressed as means ± SEMs, unless otherwise indicated.

3. Results

3.1. Patient enrolment

In total, 21 patients were screened, of which 20 patients were randomized at visit 1. These patients were staying in a rehabilitation centre (n = 6), a nursing home (n = 7) and a long term-care home (n = 7). The one patient not randomized died just before visit 1. Twenty subjects completed the study. The open-label study extension was started and finalized by 17 patients. Of the 3 patients in the main study that did not start the open-label study, one patient diet shortly after the last visit of the main study and 2 patients did not attend the experimental day of the open label study due to practical reasons.

3.2. Patient characteristics

The mean age of the patients (10 male/9 female) was 82.3 ± 6.5 y, weight 76.5 ± 18.5 kg, height 1.60 ± 0.08 m, BMI 29.8 ± 7.0 kg/m^2, waist circumference 107.8 ± 17.2 cm, diabetes duration 256 ± 203 months (means ± SD). Baseline laboratory parameters describing patient characteristics (HbA1c, HDL, LDL, Albumin, Chol, TAG) are shown in Table 2. Of the 19 patients, 17 were on insulin alone (9 basal insulin and 8 premix insulin), 2 were on oral medication (DPP IV inhibitor and sulfonylurea, DPP IV inhibitor and metformin). Seven patients were malnourished or at risk of malnutrition based on a serum albumin level below 35 g/L. Among these 7 patients older than 65 y, 2 had a concomitant C reactive protein concentration higher than 20 mg/L and according to MNA®-SF, 3 were malnourished and 4 were at risk of malnutrition. The other patients were included based on an MNA®-SF score of 11 or lower and older than 65 y and the last one was older than 70 with a BMI lower than 21 with an MNA®-SF lower than 11.

3.3. Glucose responses

Plasma glucose concentrations at each time point after the oral intake of the different supplements are shown in Fig. 1A. The iAUC was significantly lower after intake of the DSF compared with the control (p = 0.008) (Fig. 1B). Maximal incremental concentration of

Table 2
Laboratory blood parameters describing baseline patient characteristics (Mean ± SD, n = 19).

	Total (n = 19)
Triglycerides (mmol/L)	2.12 ± 1.27
Cholesterol (mmol/L)	5.16 ± 1.69
LDL Cholesterol (mmol/L)	2.95 ± 1.15
HDL Cholesterol (mmol/L)	0.96 ± 0.24
Albumin (g/L)	35.58 ± 2.63
Haemoglobin A1C (mmol/mol)[a]	54.55 ± 9.26

[a] n = 16.

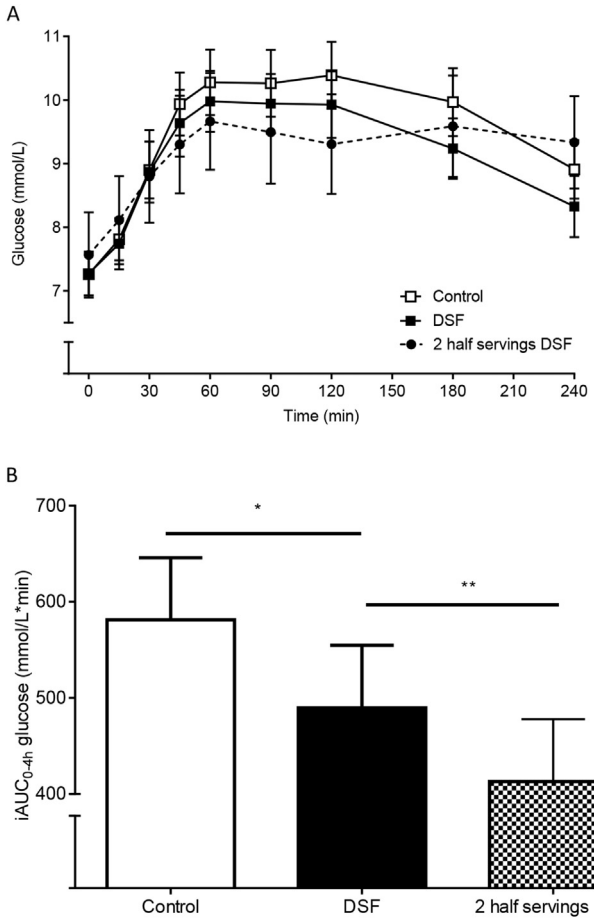

Fig. 1. Postprandial response of glucose (A) and postprandial incremental area under the curve of glucose (B) after consumption of a high energy, high protein diabetes specific formula (DSF), an isocaloric control supplement or two half servings of the diabetes specific formula (means ± SEM), *p < 0.01 comparing control vs DSF, **p < 0.05 comparing DSF vs 2 half servings of DSF.

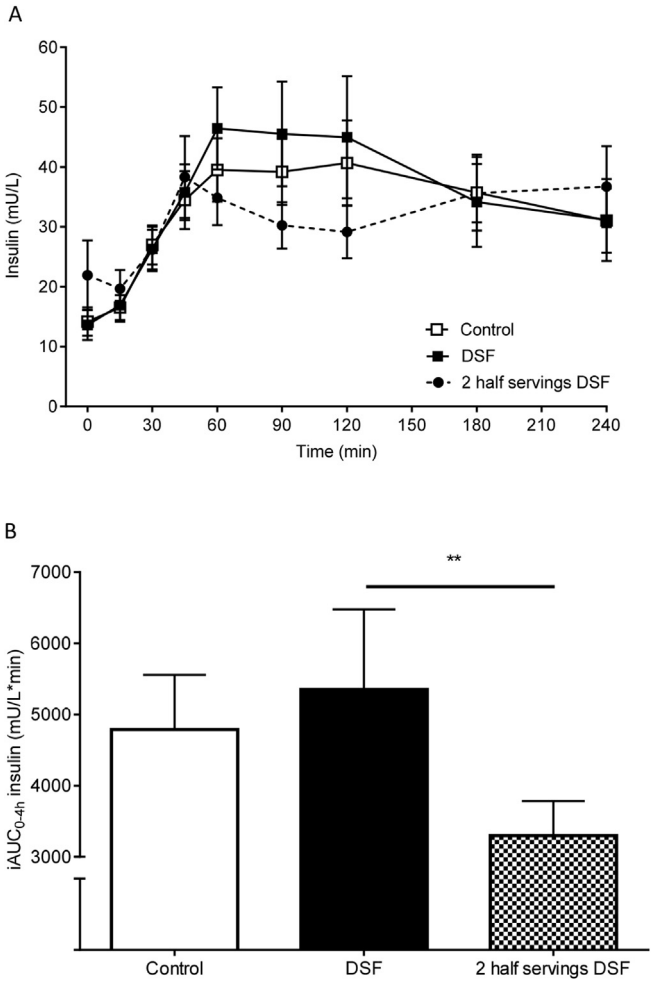

Fig. 2. Postprandial response of insulin (A) and postprandial incremental area under the curve of insulin (B) after consumption of a high energy, high protein diabetes specific formula (DSF), an isocaloric control supplement or two half servings of the diabetes specific formula (means ± SEM), **p < 0.05 comparing DSF vs 2 half servings of DSF.

glucose was significantly lower after consumption of the DSF compared to control (p = 0.007), but the difference in Cmax of glucose between the formulas did not reach statistical significance (p = 0.107) (Table 3). Comparison of the oral intake of two half servings of DSF within 240 min with one full serving in a similar time span showed a significantly lower iAUC in the two half serving condition (p < 0.05) (Fig. 1B). No differences between both treatments were shown on glucose Cmax (p = 0.9) or glucose iCmax (p = 0.16) (Table 3).

3.4. Insulin responses

Postprandial plasma insulin concentrations are shown in Fig. 2A. The iAUC was not significantly different after consumption of the DSF compared with the control (p = 0.185) (Fig. 2B). Maximal incremental concentration of insulin trended to be higher in the DSF vs the control (p = 0.07), but was not significantly different for insulin Cmax (0.124) (Table 3).

Consumption of twice half a serving of DSF compared with one full serving showed a significantly lower insulin iAUC (p < 0.05) (Fig. 2B). Maximal incremental insulin concentration was also lower after consumption of 2 half servings compared to a full serving of the DSF (p < 0.05) (Table 3). Absolute postprandial insulin Cmax was not significantly different between both conditions (Table 3).

3.5. Glucagon and C-peptide responses

Plasma glucagon concentrations after oral intake of the different supplements are shown in Fig. 3A. Overall postprandial glucagon iAUC was not significantly different between the DSF and the

Table 3
Maximal (CMax) and incremental maximal (iCMax) glucose, insulin and glucagon responses after consumption of the test products (mean ± SEM).

	Glucose		Insulin		Glucagon	
	Cmax (mmol/L)	iCmax (mmol/L)	Cmax (mU/L)	iCmax (mU/L)	Cmax (pmol/L)	iCmax (pmol/L)
Control	11.3 ± 0.5	4 ± 0.3	48 ± 7.2	33.8 ± 5.0	31.5 ± 3.6	15.3 ± 3.5
DSF	10.8 ± 0.5	3.5 ± 0.3*	56.8 ± 10.6	43.2 ± 8.5	31.8 ± 4.2	15.9 ± 3.8
2* half DSF	10.6 ± 0.8	3 ± 0.4	49 ± 7.9	27.1 ± 3.7**	25.8 ± 2.1	10.1 ± 1.9

Control and DSF n = 19, 2* half DSF n = 17, *p < 0.01 comparing control vs DSF, **p < 0.05 comparing DSF vs 2* half DSF (DSF: diabetes specific formula).

control (Fig. 3B). Also, no significant differences were observed between the DSF and the control for Cmax of glucagon ($p = 0.96$) or iCmax of glucagon ($p = 0.73$) (Table 3). Oral intake of two half servings of DSF showed a trend for a lower glucagon iAUC compared to a full serving of DSF ($p = 0.076$, Fig. 3B). No significant changes were observed between the full and 2 half servings for Cmax of glucagon ($p = 0.21$) and iCmax of glucagon ($p = 0.15$) (Table 3).

There was no statistically significant difference in iAUC of C-peptide after the DSF compared with the control (206.60 ± 31.3 nmol/L*min vs. 197.06 ± 29.4 nmol/L*min, resp., $p = 0.416$).

3.6. Compliance and safety

All patients consumed the DSF or control within 10 min and were reported to be 100% compliant for each dosing during intake. In total, 5 persons reported 10 adverse events during the course of the study. One patient had 2 serious adverse events (peripheral ischaemia). This patient was excluded from the ITT due to violation of an exclusion criterion. Of the remaining 4 patients, 3 reported AEs in the period the test product was studied and 1 patient when the control product was studied. None of the events were considered related to the intake of the study products. These reported events had the body system classification: nervous system disorder ($n = 2$), infections and infestations ($n = 1$), gastrointestinal disorders ($n = 2$) and injury ($n = 3$), which are consistent with the polypathologic nature of older adult malnourished or at risk of malnutrition patients with diabetes type II in a long term care unit, and, therefore, did not qualify as a safety signal.

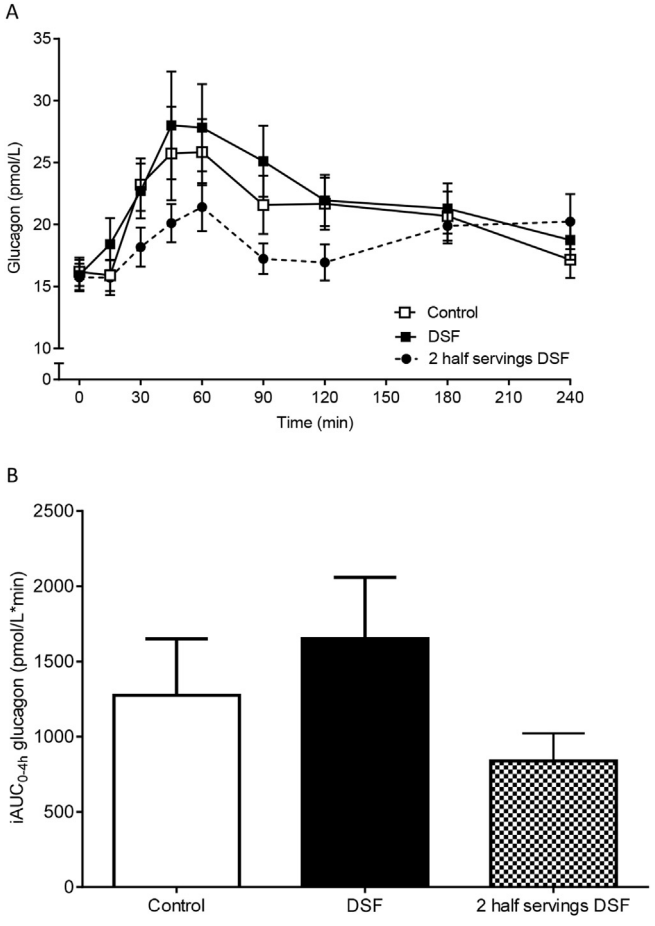

Fig. 3. Postprandial response of glucagon (A) and postprandial incremental area under the curve of glucagon (B) after consumption of a high energy, high protein diabetes specific formula (DSF), an isocaloric control supplement or two half servings of the diabetes specific formula (means ± SEM).

4. Discussion

This study showed that consumption of a high energy, high protein, diabetes specific formula (DSF) resulted in a lower postprandial glucose response compared to a standard nutritional supplement (control) with the same macronutrient energy composition in older malnourished or at risk of malnutrition type 2 diabetes patients.

Other recent studies have described the beneficial effects of a diabetes specific oral supplement on postprandial glucose or longer term glucose control compared to other formulas or meals [10,11,17–21]. For instance, Garcia-Rodriguez et al. [11] showed an improved postprandial glucose response comparing a novel DSF against two other commercially available DSFs due to the addition of slowly digestible carbohydrate resistant starch type IV as part of the carbohydrates and 2% fibres from inulin and cellulose. Although differences in caloric content, amount and type of protein and amount and type of fat between the different DSFs were not taken into account separately, it is likely that the entire combination contributed to the observed effects. In contrast, Buranapin et al. [19] demonstrated a significantly lower postprandial glucose response after DSF intake compared to standard ONS with matched energy content and macronutrient percentages. This DSF was a modified standard formula with multiple substitutions in all the macronutrients. Since the individual adjustments of the composition were not studied in isolation probably all adjustments together contributed to the beneficial effect on postprandial glucose level. Unfortunately, no insulin or glucagon responses were measured, which may have provided additional insights in the macronutrient induced changes in postprandial metabolism. A modified protein composition could, for example, impact pancreas insulin output or glucagon secretion increasing liver glycolysis.

In this study, we specifically aimed to match for caloric content, type and energy % of protein and type and energy % of fat comparing control and a DSF. We substituted part of the carbohydrates (maltodextrin) for isomaltulose, which resulted in an attenuated postprandial glucose response and without an excessive insulin or glucagon response. Isomaltulose (palatinose) is a disaccharide produced by enzymatic conversion of the 1,2-glycosidic linkage between glucose and fructose of sucrose to a α-1,6-linked glucose and fructose [22]. Therefore, isomaltulose is slowly digested, and the resulting glucose and fructose are released at a slow pace creating an excellent source to manage postprandial glucose responses. Isomaltulose consumed in a drink with a meal has indeed been shown to attenuate the postprandial rise in glucose levels compared to sucrose in impaired glucose-tolerant subjects [23]. Furthermore, head to head comparison between sucrose and isomaltulose on postprandial glucose responses during a euglycaemic–hyperinsulinemic clamp in type 2 diabetes patients showed a slower absorption of isomaltulose, which resulted in lower levels of glucose, insulin, glucagon and c-peptide [24].

The DSF also provided galacto-oligosaccharides (GOS) as non-digestible soluble fibres, which contributed less than 1% to total energy intake and thus not likely to be effective on glucose control. Consumption of 2.5 g per day has been shown to convey a prebiotic effect stimulating growth of the intestinal Bifidobacteria [25]. Furthermore, several other proposed benefits of GOS include: protection against infections, increased mineral absorption and a reduction in toxigenic microbial metabolism [26]. In this acute study, no side effects or gastrointestinal complaints were observed after consumption of both formulas. Whether increased and longer

term consumption of the formula would indeed deliver prebiotic effects and additional health benefits remains subject of future study.

Protein energy malnutrition can result in many detrimental health conditions, such as: muscle wasting, poor wound healing, impaired immune response and inactivity [27]. Therefore, this DSF was designed to provide high energy and a high protein content, in line with the nutritional support strategy for protein-energy malnourished older adults from the French Nutrition and Health Program (HAS: Haute Autorité de Santé) [13]. Protein content could be considered relatively high with 26 energy % per serving for patients with diabetes; nutritional guidelines generally recommend 20% of energy be contributed by protein on a daily basis [28,29]. Nevertheless, it should be taken into account that most malnourished or at risk of malnutrition (older adult) patients have an under consumption of not only energy but also protein, which is the underlying motivation to prescribe these patients the use of medical nutritional supplements and fill this gap in daily protein intake. Recently, the American Diabetes Association (ADA) communicated that the evidence for a general protein intake recommendation for diabetes patients was inconclusive [9]. Therefore, current protein intake recommendations for diabetes patients are prescribed on the basis of the individual's nutritional status and co-morbid condition. For example, it has been shown that diabetes is associated with a faster loss of muscle strength and a lower leg muscle quality compared to subjects with normal glycaemic control [30]. This may indicate that increased high quality dietary protein intake may be beneficial [27,31]. On the other hand, caution is necessary when prescribing the DSF for malnourished diabetes patients with an impaired kidney function, due to the presumed link between high protein intake and the increased risk for kidney failure [32].

An alternative strategy to lower the burden of a medical nutrition supplement on postprandial glucose and reduce glycaemic variability, while still supplying adequate calories and protein, might be the consumption of smaller dosages of the diabetes specific formula. Consecutive consumption of 2 half servings compared to the full serving resulted in a lower total postprandial glucose response (iAUC). Total insulin response was also significantly lower after the 2 half servings of the DSF compared with the full serving, while in total the same amount of nutrients were consumed. These results provide a solution for the individual nutritional needs of the malnourished patient with diabetes regarding energy and protein in the context of a low or high insulin and glucagon response.

A limitation of the study explaining the variation in the reported outcomes could be the patients' diverse treatment strategies. However, in general, this does reflect the heterogeneity of the patients in real life. Furthermore, the sample size of the current study is small, but due to its cross-over design and the measurement of 4 h instead of the standard 2 h postprandial response, a good representation of the effects of the consumption in daily life is obtained. Whether the beneficial effects on glycaemic control persist after longer term use could be the subject of future studies. Although, a previous study with a DSF already demonstrated that an acute attenuation of the postprandial glucose control in a T2D patient population was maintained after 4 weeks use of two servings a day [20].

5. Conclusion

Consumption of a high-energy, high-protein, fibre and low glycaemic index carbohydrate enriched diabetes specific formula resulted in a lower postprandial blood glucose response compared with an iso-caloric standard high-energy high-protein oral nutritional supplement in older malnourished or at risk of malnutrition type 2 diabetes patients. These data suggest that this DSF in full or 2 half servings is preferred for patients with diabetes in need of personalized nutritional support.

Author contributions

Isabelle Bourdel-Marchasson, Mirian Lansink and Andreas Pfeiffer contributed to conception/design of the research; Isabelle Bourdel-Marchasson, Hamid Laksir, Mirian Lansink, Andreas Pfeiffer, Sophie Regueme and Johan de Vogel contributed to acquisition, analysis, or interpretation of the data; Johan de Vogel drafted the manuscript; Isabelle Bourdel-Marchasson, Hamid Laksir, Mirian Lansink, Andreas Pfeiffer and Sophie Regueme critically revised the manuscript; and all authors agreed to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript. ML and JdVvdB are employees of Nutricia Research.

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Conflict of interest

None declared.

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References

[1] Sanz Paris A, Garcia JM, Gomez-Candela C, Burgos R, Martin A, Matia P, et al. Malnutrition prevalence in hospitalized elderly diabetic patients. Nutr Hosp 2013;28(3):592–9.
[2] Vischer UM, Perrenoud L, Genet C, Ardigo S, Registe-Rameau Y, Herrmann FR. The high prevalence of malnutrition in elderly diabetic patients: implications for anti-diabetic drug treatments. Diabet Med 2010;27(8):918–24.
[3] Ordonez AM, Madalozzo Schieferdecker ME, Cestonaro T, Cardoso Neto J, Ligocki Campos AC. Nutritional status influences the length of stay and clinical outcomes in patients hospitalized in internal medicine wards. Nutr Hosp 2013;28(4):1313–20.
[4] Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults: a consensus report. J Am Geriatr Soc 2012;60(12):2342–56.
[5] Gosmanov AR, Umpierrez GE. Medical nutrition therapy in hospitalized patients with diabetes. Curr Diab Rep 2012;12(1):93–100.
[6] Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003;78(12):1471–8.
[7] Elia M, Ceriello A, Laube H, Sinclair AJ, Engfer M, Stratton RJ. Enteral nutritional support and use of diabetes-specific formulas for patients with diabetes: a systematic review and meta-analysis. Diabetes Care 2005;28(9):2267–79.
[8] Mann JI, De Leeuw I, Hermansen K, Karamanos B, Karlstrom B, Katsilambros N, et al. Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. Nutr Metab Cardiovasc Dis 2004;14(6):373–94.
[9] Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care 2014;37(Suppl. 1):S120–43.
[10] Vanschoonbeek K, Lansink M, van Laere KM, Senden JM, Verdijk LB, van Loon LJ. Slowly digestible carbohydrate sources can be used to attenuate the postprandial glycemic response to the ingestion of diabetes-specific enteral formulas. Diabetes Educ 2009;35(4):631–40.
[11] Garcia-Rodriguez CE, Mesa MD, Olza J, Buccianti G, Perez M, Moreno-Torres R, et al. Postprandial glucose, insulin and gastrointestinal hormones in healthy and diabetic subjects fed a fructose-free and resistant starch type IV-enriched enteral formula. Eur J Nutr 2013;52(6):1569–78.
[12] Moghaddam E, Vogt JA, Wolever TM. The effects of fat and protein on glycemic responses in nondiabetic humans vary with waist circumference, fasting plasma insulin, and dietary fiber intake. J Nutr 2006;136(10):2506–11.
[13] Raynaud-Simon A, Revel-Delhom C, Hebuterne X, French N, Health Program FHHA. Clinical practice guidelines from the French Health High Authority:

nutritional support strategy in protein-energy malnutrition in the elderly. Clin Nutr 2011;30(3):312–9.
[14] Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: the Mini Nutritional Assessment as part of the geriatric evaluation. Nutr Rev 1996;54(1 Pt 2):S59–65.
[15] Brouns F, Bjorck I, Frayn KN, Gibbs AL, Lang V, Slama G, et al. Glycaemic index methodology. Nutr Res Rev 2005;18(1):145–71.
[16] Vaisman N, Lansink M, Rouws CH, van Laere KM, Segal R, Niv E, et al. Tube feeding with a diabetes-specific feed for 12 weeks improves glycaemic control in type 2 diabetes patients. Clin Nutr 2009;28(5):549–55.
[17] Devitt AA, Williams JA, Choe YS, Hustead DS, Mustad VA. Glycemic responses to glycemia-targeted specialized-nutrition beverages with varying carbohydrates compared to a standard nutritional beverage in adults with type 2 diabetes. Adv Biosci Biotechnol 2013;4:1–10.
[18] Gulati S, Misra A, Nanda K, Pandey RM, Garg V, Ganguly S, et al. Efficacy and tolerance of a diabetes specific formula in patients with type 2 diabetes mellitus: an open label, randomized, crossover study. Diabetes Metab Syndr 2015;9(4):252–7.
[19] Buranapin S, Siangruangsang S, Chantapanich V, Hengjeerajarus N. The comparative study of diabetic specific formula and standard formula on postprandial plasma glucose control in type 2 DM patients. J Med Assoc Thai 2014;97(6):582–8.
[20] Lansink M, van Laere KM, Vendrig L, Rutten GE. Lower postprandial glucose responses at baseline and after 4 weeks use of a diabetes-specific formula in diabetes type 2 patients. Diabetes Res Clin Pract 2011;93(3):421–9.
[21] Mayr P, Kuhn KS, Klein P, Stover JF, Pestana EA. A diabetes-specific oral nutritional supplement improves glycaemic control in type 2 diabetes patients. Exp Clin Endocrinol Diabetes 2016;124(7):401–9.
[22] Lina BA, Jonker D, Kozianowski G. Isomaltulose (Palatinose): a review of biological and toxicological studies. Food Chem Toxicol 2002;40(10):1375–81.
[23] van Can JG, van Loon LJ, Brouns F, Blaak EE. Reduced glycaemic and insulinaemic responses following trehalose and isomaltulose ingestion: implications for postprandial substrate use in impaired glucose-tolerant subjects. Br J Nutr 2012;108(7):1210–7.
[24] Ang M, Linn T. Comparison of the effects of slowly and rapidly absorbed carbohydrates on postprandial glucose metabolism in type 2 diabetes mellitus patients: a randomized trial. Am J Clin Nutr 2014;100(4):1059–68.
[25] Ito M, Deguchi Y, Matsumoto K, Kimura M, Onodera N, Yajima T. Influence of galactooligosaccharides on the human fecal microflora. J Nutr Sci Vitaminol (Tokyo) 1993;39(6):635–40.
[26] Torres DPM, Gonçalves MF, Teixeira JA, Rodrigues LR. Galacto-oligosaccharides: production, properties, applications, and significance as prebiotics. Compr Rev Food Sci Food Saf 2010;9(5):438–54.
[27] Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr 2014;33(6):929–36.
[28] Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, et al. Nutrition recommendations and interventions for diabetes–2006: a position statement of the American Diabetes Association. Diabetes Care 2006;29(9):2140–57.
[29] American Diabetes A, Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, et al. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care 2008;31(Suppl. 1):S61–78.
[30] Park SW, Goodpaster BH, Strotmeyer ES, Kuller LH, Broudeau R, Kammerer C, et al. Accelerated loss of skeletal muscle strength in older adults with type 2 diabetes: the health, aging, and body composition study. Diabetes Care 2007;30(6):1507–12.
[31] Cawood AL, Elia M, Stratton RJ. Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. Ageing Res Rev 2012;11(2):278–96.
[32] Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc 2013;14(8):542–59.