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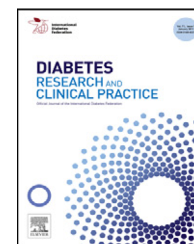

Lower postprandial glucose responses at baseline and after 4 weeks use of a diabetes-specific formula in diabetes type 2 patients

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ABSTRACT

Aims: To determine whether lower postprandial glucose (PPG) levels after intake of a diabetes-specific formula (DSF) compared with a standard formula were maintained after 4 weeks use.

Methods: Randomized, controlled, double-blind, parallel-group study. Forty-four type 2 diabetes patients on oral anti-diabetes medication consumed 2 × 200 mL/day of a DSF (Diasip®) or an isocaloric standard, fiber-containing formula for 4 weeks. PPG responses were assessed at baseline and after 4 weeks by iAUC and (delta) peak glucose concentrations.

Results: PPG response was significantly lower in the DSF group after first intake and remained significantly lower after 4 weeks use. Postprandial insulin, fasting glucose, insulin resistance, fructosamine and lipid levels did not differ between groups after 4 weeks. Within the standard group, fasting glucose and $HOMA_{IR}$ significantly increased over the intervention period. Changes in body weight between groups were significantly different, with an increase in the standard group. Both products were equally well tolerated.

Conclusions: Superior PPG control by DSF was maintained after 4 weeks use, showing that this formula has added value with respect to PPG control for type 2 diabetes patients compared to a standard, fiber-containing formula. The observed effects on body weight, fasting glucose and $HOMA_{IR}$ may further support the use of a DSF.

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1. Introduction

Postprandial hyperglycemia significantly contributes to overall glycemic control in type 2 diabetes patients [1,2]. Furthermore, epidemiological studies have shown a strong and independent relationship between postprandial blood glucose excursions and cardiovascular co-morbidities in type 2 diabetes patients [3–5]. Hyperglycemia and fluctuating blood glucose levels have been attributed directly to the development of cardiovascular disease [6–8]. The International Diabetes Federation has recently recognized, in specific guidelines, the significance and harmful effects of postprandial hyperglycemia and the need to measure and treat it [9]. Diets with a low glycemic load are recommended in controlling postprandial plasma glucose levels [10,11].

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Abbreviations: ANOVA, analysis of variance; BMI, body mass index; En%, energy percent; GI, glycemic index; HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; $HOMA_{IR}$, homeostasis model assessment for insulin resistance; iAUC, incremental area under the curve; ITT, intention-to-treat; LDL, low density lipoprotein; SD, standard deviation; SE, standard error.

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For diabetes patients in need of nutritional support, specific oral formulas have been developed, which aim to result in lower (postprandial) glucose levels than standard formulas. Traditionally, these formulas contained less carbohydrate (35–40 energy percent (En%)) and typically more fat (40–50 En%), with a large contribution from monounsaturated fatty acids, typically more than 60% of total fat content [12]. However, nutritional guidelines for diabetes patients published by the Diabetes Nutrition Study Group of the European Association for the Study of Diabetes recommend that the fat content of a diet should not exceed 35 En%, and carbohydrate intake should range between 45 and 60 En% [13].

Recently, a diabetes-specific formula containing less than 35% of fat (34 En%) and more than 45 En% carbohydrate (47 En%) was developed. The diabetes-specific formula contains several low (GI) and/or slowly digestible carbohydrates, like isomaltulose lactose and slowly digestible starch [14–17] (starch which is slowly digested and therefore, intake of this type of starch leads to a smaller rise in postmeal glucose levels compared to "normal" starch, which is quickly digested [17]), whereas the major carbohydrate in the standard formula is the high-GI maltodextrin. These specific carbohydrates were combined with specific proteins (soy and whey) and fibers in order to keep the postprandial glucose response as low as possible. Single bolus or day-long consumption of this formula resulted in lower postprandial glucose levels than a standard, fiber-enriched nutritional formula in type 2 diabetic patients [18,19]. However, no data are available on the effects of this formula on postprandial glucose levels after longer term use and whether adaptation by the body occurs after longer term use. There are for instance no experimental data available on the effect of longer term use of isomaltulose on the enzyme kinetics or expression levels of the responsible isomaltulose degrading enzymes. Isomaltulose is one of the major components in the formula providing the lower postmeal glucose levels. In theory, the enzyme kinetics of isomaltulose may be adapted after longer term exposure of the body to isomaltulose, resulting in a more rapid digestion and thereby higher postmeal glucose response. Therefore, in the present study, the effect of the diabetes-specific formula on postprandial glucose levels was studied after 4 weeks consumption by type 2 diabetes patients. Furthermore, the effects of 4 weeks consumption on other glycemic and lipid parameters, weight and tolerance were studied. The formula was used as a breakfast and afternoon or evening snack replacer in type 2 diabetes patients. Since it is sometimes thought that diabetes patients can use standard formulas as long as these contain fibers, an isocaloric, liquid, fiber-containing standard formula was used for comparison.

2. Materials and methods

The study was a randomized, controlled, double-blind, parallel-group study, performed at one study center in the Netherlands (Julius Center, Utrecht, The Netherlands).

2.1. Subjects

In total, 44 ambulatory type 2 diabetes patients (25 male, 19 female) were included in this study.

Inclusion criteria were diagnosis of type 2 diabetes according to WHO criteria for more than 6 months, male with an age >18 years or postmenopausal female, HbA1c between 6.5% and 8.0%, body mass index (BMI) between 18 and 35 kg/m^2, and stable treatment with metformin and/or sulfonylureas for at least 2 months and expected to remain stable throughout the duration of the study. If lipid-lowering drugs were used, their use was to be stable and controlled for at least 2 months and expected to remain stable throughout the duration of the study.

Exclusion criteria were a weight-loss diet, any gastrointestinal disease that interferes with bowel function and nutritional intake, significant heart (NYHA class IV), hepatic (transaminase greater than 3 times upper limit of normal), or renal disease (requiring dialysis or creatinine > 160 μmol/L), infection requiring antibiotics within 3 weeks prior to study entry, concomitant therapy with insulin or anti-diabetic medication other than metformin and sulfonylureas, therapy with systemic glucocorticoids at or within 2 weeks prior to study entry, alcohol abuse, fever and participation in other intervention studies within 4 weeks of screening. Subjects with galactosemia or lactose intolerance, and subjects requiring a fiber-free diet, were also excluded.

The Independent Review Board Nijmegen (The Netherlands) approved the study protocol. All subjects were informed about the nature of the study and gave written informed consent prior to study screening. The study was performed in accordance with the principles relating to the Declaration of Helsinki and GCP.

2.2. Treatments

Subjects were randomly allocated to receive either the diabetes-specific formula or an isocaloric standard formula according to a computer-generated randomization list using two different randomization codes per treatment.

The subjects in the diabetes-specific formula group consumed Diasip® (Nutricia N.V., Zoetermeer, The Netherlands), a flavored, 1 kcal/mL, diabetes-specific nutritional supplement (47 En% carbohydrates, 19 En% protein, 34 En% fat (20 En% monounsaturated fatty acids) and 2 g fibers/100 mL). The control group received a flavored isocaloric, fiber-containing standard formula (50 En% carbohydrates, 16 En% protein, 34 En% fat (20 En% monounsaturated fatty acids) and 1.5 g fibers/100 mL). Both formulas contained the same amount and quality of fat. Both formulas contained vitamins, minerals, and trace elements in accordance with the regulations for Food for Special Medical Purposes (1999/21/EC). Subjects consumed two 200 mL portions per day of either of the products for 4 weeks, one as a replacement for breakfast and one as an in-between snack in the afternoon or evening. Table 1 shows the characteristics of the formula compositions.

2.3. Study design

After screening, the subjects visited the research center at the beginning (visit 1, day 1) and at the end (visit 2, day 29) of the 4-week period. Subjects had to refrain from alcohol consumption and intense physical activities for, respectively, 24 and 48 h before both visits and had to eat a standard meal (450 g, 125 kcal/100 g, 57 En% carbohydrates, 13 En% protein, and

Table 1 – Macronutrient composition of the formulas per 100 mL product (=100 kcal).

Ingredient	Unit	Diabetes-specific formula	Standard formula
Energy	kcal	100	100
Protein	g/En%	4.86/19	4.02/16
Whey protein		2.41	–
Soy protein		2.44	–
Casein		–	3.95
Other (from raw materials)		0.01	0.07
Carbohydrate	g/En%	11.63/47	12.55/50
Lactose		3.6	–
Isomaltulose		4.4	–
Glucose		0.3	–
Polysaccharides		3.1	12.2
Other (from raw materials)		0.3	0.35
Fat	g/En%	3.78/34	3.78/34
Fiber		2.0	1.5

–: product does not contain the ingredient.

30 En% fat) the evening before. Subjects came to the study center in the morning after an overnight fast (10 h) and body temperature and weight were measured. Venous blood was collected via a canula which was placed at least 30 min before the first blood sample was taken. Subjects took their anti-diabetes medication with 150 mL water 20 min before intake of the study product. Subjects consumed either the diabetes-specific formula or the standard formula (200 mL) and had to finish it within 5 min. To determine the postprandial glucose and insulin responses, venous blood samples were drawn 5 min prior to product intake (basal sample) and 15, 30, 45, 60, 75, 90, 120, 150, 180, 210 and 240 min after intake. The sample taken 5 min prior to product intake was used to determine fasting glucose levels. Besides postprandial measurements, also fasting blood samples were collected at visits 1 and 2 for the measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, and for alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, and creatinine and serum fructosamine levels. During the assessment period subjects had to sit quietly.

During the 4-week study period, subjects filled out a diary daily on actual formula consumption. Subjects had to record volume and time of study product intake. On the 4 days immediately preceding visit 1, on days 1–4, on days 15–18 and on days 25–28, a gastrointestinal tolerance questionnaire was completed by the subjects, reporting the intensity for the symptoms 'dry mouth', 'thirst', 'belching', 'heartburn', 'bloating', 'stomach pain', 'stomach cramps', 'abdominal pain', 'flatulence', and 'nausea' on a 4-point scale ranging from 'not at all' to 'very much'. Furthermore, subjects recorded defecation frequency and consistency on a 5-point scale. Any clinical study event that was judged as an adverse event, either spontaneously reported by the subject or observed by the investigator, was recorded in the study database and the investigator documented the relationship with the study product.

2.4. *Laboratory methods*

All blood samples were centrifuged immediately (1000 × *g*, 10 min, 4 °C), except for serum, which was allowed to clot at room temperature (30 min) first. After centrifugation, plasma and serum aliquots were stored at -20 °C until analysis. For the analysis of HbA1c, EDTA whole blood was collected and stored at 4 °C until analysis on the same day.

Plasma glucose and triglycerides were analyzed enzymatically on a DxC (Beckman Coulter, Brea, CA, USA). Serum insulin was measured using a chemiluminescence immunoassay (E170, Roche Diagnostics, Basel, Switzerland) and serum fructosamine was measured using a colorimetric assay (Pentra 400, Horiba ABX Inc., Irvine, CA, USA). Plasma total cholesterol and HDL cholesterol were determined on a DxC (Beckman Coulter) using enzymatic colorimetric kits. LDL cholesterol was estimated using the Friedewald equation [20].

Biochemical parameters and HbA1c were measured using standardized HPLC methods (HA-8160, Menarini, Valkenswaard, The Netherlands).

2.5. *Outcome measures*

The primary outcome measure was the 4 h postprandial plasma glucose response, as assessed by the incremental area under the curve (iAUC). As secondary outcome measures, fasting glucose and insulin, postprandial peak glucose and insulin, maximum postprandial glucose and insulin increase from baseline (delta peak), postprandial glucose and insulin levels per protocol time, 4 h postprandial insulin response (iAUC), and gastrointestinal tolerance were defined. Other parameters included product compliance, body weight, fasting fructosamine, fasting plasma lipid profile and insulin resistance assessed by $HOMA_{IR}$.

2.6. *Sample size*

Calculation was performed for the parameter postprandial glucose response, as assessed with iAUC0-4 h. Based on results of a previously performed study [18] with a comparable diabetes-specific product and a standard product containing 5 En% more carbohydrates, it was assumed that the mean difference between groups was 40% (210 units). Based on this and another previously performed study [21] it is assumed that the common within-group standard deviation is 226. Applying

a significance level (alpha) of 0.050, a 2-tailed test, and a power of 80% to detect a difference of 210, a sample size of 20 for each of the two groups was assumed to detect a statistically significant difference between the groups. Assuming a dropout rate of 10%, 22 subjects were needed per group to detect a statistically significant difference.

2.7. *Statistical analyses*

All the data presented are from the intention-to-treat (ITT) population.

Subject characteristics at screening and baseline were evaluated using means (and SD) or median (and minimum and maximum) for continuous parameters, and using percentages and absolute numbers for dichotomous and categorical parameters. BMI, duration of diabetes, HbA1c, fasting glucose and the outcome measures were compared between the study groups using ANOVA or the non-parametric Mann–Whitney test, depending on the distribution of the data. Differences in distribution of categorical data between study groups were assessed by Fisher's exact test.

The outcome measures were compared at visit 1, visit 2 and for the change during the supplementation period (Δvisit 2 − visit 1) between groups.

Within-group changes were analyzed using paired samples *t*-test or the non-parametric paired Wilcoxon test, depending on the distribution of the data. Possible confounding effects of baseline BMI and fasting glucose concentrations at visit 1 were tested for 4 h postprandial glucose response, postprandial (delta) peak glucose concentration and $HOMA_{IR}$ at visit 1, visit 2 and the change during the supplementation period (Δvisit 2 − visit 1).

All statistical analyses were performed using a two-sided significance level of 5%, using SPSS version 15.0 for Windows, Rel. 6 Sep. 2006, Chicago: SPSS Inc.

3. Results

Forty-four subjects were enrolled, 22 per treatment group, and included in the ITT analyses. Forty-two subjects completed the study. In the standard formula group, one subject dropped out since he indicated that he would most likely forget to take the study product twice a day. In the diabetes-specific formula group, one subject dropped out due to difficulties in placing a canula.

3.1. *Subject characteristics and demographics*

Baseline demographic data and subject characteristics are shown in Table 2. Table 3 shows the metabolic characteristics for all subjects at visit 1. Groups were comparable with regard to all baseline characteristics.

3.2. *Compliance*

Subjects in the diabetes-specific formula and standard formula group consumed on average 95.7 ± 2.33 and 92.2 ± 4.66% ($p = 0.79$) of total daily intake (400 mL), respectively.

3.3. *Primary efficacy parameter*

The 4 h postprandial glucose response (iAUC) was significantly lower after consumption of the diabetes-specific formula as compared with the standard formula group at visit 1 (129.8 ± 26.0 and 264.8 ± 26.6 mmol/L min, respectively; $p = 0.001$) and remained significantly lower after the 4-week intervention period (visit 2; 128.1 ± 27.3 and 266.3 ± 26.7; $p = 0.001$). The *change* in iAUC over time was not different between groups.

Table 2 – Baseline characteristics of study population.

	Diabetes-specific ($n = 22$)	Standard ($n = 22$)	*p*-value
Age (years)	65.2 ± 7.4	64.2 ± 5.9	–
Sex			
Male (*n* (%))	9 (41)	16 (73)	–
Female (*n* (%))	13 (59)	6 (27)	–
Height (m)	1.69 ± 0.09	1.73 ± 0.08	–
Weight (kg)	85.6 ± 10.2	84.8 ± 12.3	–
BMI (kg/m^2)	30.1 ± 2.9	28.3 ± 3.3	0.06[a]
Duration of diabetes (months)	84 (18–216)	66 (10–504)	0.55[b]
HbA1c (%)	6.9 (6.5–7.6)	6.9 (6.5–8.0)	0.56[b]
Class of anti-diabetic medication			
Metformin (*n* (%))	8 (36)	5 (23)	–
Sulfonylureas (*n* (%))	3 (14)	4 (18)	
Combination (*n* (%))	11 (50)	13 (59)	
Statin use			
No (*n* (%))	6 (27)	2 (9)	–
Yes (*n* (%))	16 (73)	20 (91)	

Data are mean ± SD or median (range) for continuous parameters, and *n* (%) for categorical parameters.
–: not determined.
[a] *p*-value for differences between groups, ANOVA.
[b] *p*-value for differences between groups, Mann–Whitney.

Table 3 – Metabolic characteristics for all subjects randomized at visit 1.

	Diabetes-specific ($n = 21$)	Standard ($n = 22$)	p-value[a]
Glucose (mmol/L)	8.32 ± 1.49	7.61 ± 1.13	0.085
Triglycerides (mmol/L)	1.2 (0.6–2.9)	1.6 (0.5–3.2)	0.429
Total cholesterol (mmol/L)	4.2 (2.4–5.3)	3.9 (2.0–5.6)	0.503
HDL cholesterol (mmol/L)	1.08 (0.74–2.07)	1.04 (0.70–1.96)	0.444
LDL cholesterol (mmol/L)	2.3 (0.4–3.9)	2.0 (1.0–3.4)	0.318
Fructosamine (μmol/L)	252 (214–497)	278 (228–506)	0.259
Fasting insulin (mU/L)	9.0 (4.0–24.0)	8.0 (3.0–20.0)	0.407

Data are mean ± SD or median (range).
[a] p-value for differences between groups was tested with Mann–Whitney for all parameters, except for fasting glucose, which was tested using ANOVA.

3.4. Secondary efficacy parameters

As shown in Fig. 1, from 60 until 90 min after consumption at visit 1 and from 45 until 90 min at visit 2, the diabetes-specific formula resulted in significantly lower plasma glucose concentrations compared with the standard formula. The maximum increase in postprandial plasma glucose levels above baseline plasma glucose levels (delta peak) was also significantly lower in the diabetes-specific formula group compared with the standard formula group at both visits (1.8 ± 0.2 vs. 3.6 ± 0.3 mmol/L at visit 1 and 1.7 ± 0.3 vs. 3.7 ± 0.2 mmol/L at visit 2, both $p < 0.001$). At visit 1 and visit 2, fasting plasma glucose concentrations were not significantly different between groups ($p = 0.085$ and $p = 0.823$, respectively). The *change* in fasting glucose levels during the 4-week study period did not differ significantly between groups ($p = 0.068$), but fasting glucose levels were significantly increased after 4 weeks in the group consuming the standard formula (from 7.73 ± 0.22 to 8.22 ± 0.26 mmol/L; $p = 0.011$) and were not altered in the diabetes-specific group (from 8.32 ± 0.33 to 8.13 ± 0.33 mmol/L; $p = 0.555$).

The 4 h postprandial insulin response (iAUC) did not differ significantly between the two groups after first intake (visit 1, $p = 0.058$) nor after the 4-week intervention period (visit 2, $p = 0.181$). No significant differences were observed between the two groups in insulin levels over time in the 4 h postprandial period (Fig. 2). Also no significant differences were observed between the groups at either of the visits in the (delta) postprandial peak insulin concentrations (data not shown). Fasting serum insulin levels were comparable between groups at the start of the study and also the change during the 4-week study period was not different between groups ($p = 0.206$).

3.5. Other efficacy parameters

No differences between the groups at either visit were found in the $HOMA_{IR}$. The *change* in $HOMA_{IR}$ during the 4-week study period was not significantly different between groups ($p = 0.078$) but this change was significant after correction for baseline BMI ($p = 0.037$). Within the standard group $HOMA_{IR}$ significantly increased from 2.84 (median) (range 0.91–7.91) to 3.38 (1.11–9.71) ($p = 0.013$), whereas no significant changes were observed within the diabetes-specific group: 3.52 (1.39–11.31) to 2.89 (1.32–11.33) ($p = 1.000$).

Fasting levels of fructosamine, triglycerides and total, HDL and LDL cholesterol were not significantly different between groups at the start of the study, nor after 4 weeks. Also the changes over time in any of these parameters were not different between groups (data not shown).

Interestingly, the *change* in body weight was significantly different between groups (−0.3 ± 0.2 kg in diabetes-specific group and 0.6 ± 0.2 kg in standard group; $p = 0.006$). The body weight was not significantly different between groups at either of the visits.

3.6. Tolerance and safety

Overall, both products were equally well tolerated, with a low incidence and mild intensity of reported symptoms. For instance, in the diabetes-specific group, for 'abdominal pain' 15 study participants reported 'not at all', 4 reported 'a little', 2

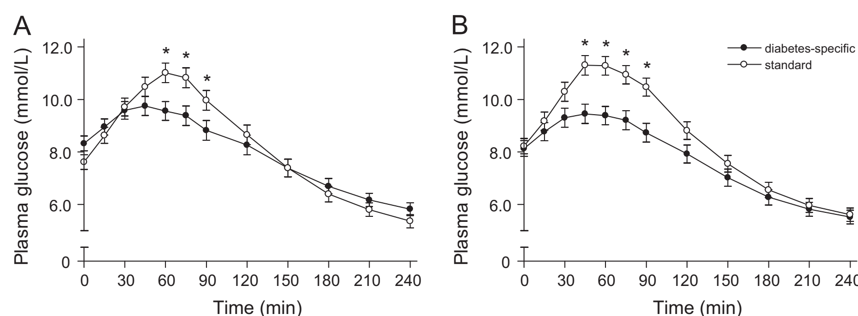

Fig. 1 – Plasma glucose concentrations over time (mmol/L) at visit 1 (A) and after 4 weeks (B). Data are means. Error bars are SEs. *$p < 0.05$.

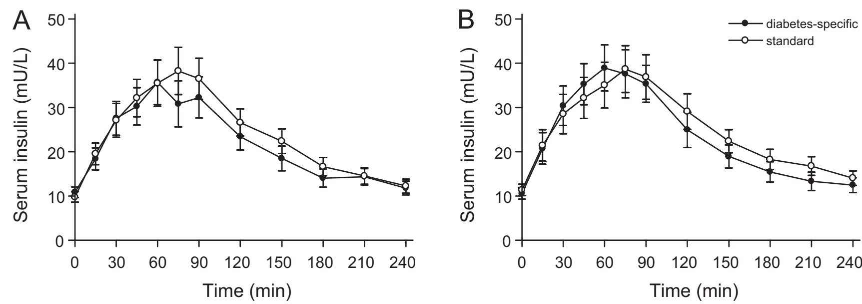

Fig. 2 – Serum insulin concentrations over time (mU/L) at visit 1 (A) and after 4 weeks (B). Data are means. Error bars are SEs.

reported ‘somewhat’; and no person reported ‘very much’. In the standard group these numbers were 14, 6, 1, and 0, respectively. Biochemical parameters of liver and kidney function were comparable between groups at baseline and week 4 and did not change over time, except for a clinically non-relevant increase in median plasma gamma glutamyl-transferase concentrations in the standard group ($p = 0.048$).

There were no differences between the diabetes-specific and standard formulas in the total number of product-related (9 and 12, respectively) and non-related adverse events (9 and 17, respectively). There were equal numbers of subjects with product-related adverse events (6 and 6, respectively). There was no statistically significant difference between the groups in the number of subjects with (12 in the diabetes-specific group and 15 in the control) or without (10 and 7, respectively) one or more adverse events. There were numerically fewer reports of adverse events in the diabetes-specific group compared to the standard group for diarrhea (2 and 8, respectively) and flatulence (1 and 6, respectively). No serious adverse event occurred during the study and no subjects dropped out for product-related reasons.

4. Discussion

This study shows that ingestion of 200 mL of a diabetes-specific formula resulted in significantly lower postprandial glucose levels compared to a standard, fiber-containing formula, both after a single bolus and after continuous twice-daily use for 4 weeks. Postprandial insulin levels were not different. Furthermore, consumption of the standard formula increased fasting glucose levels and increased insulin resistance, in contrast to the diabetes-specific formula, which did not affect these parameters. The change in body weight was also significantly different between groups, with an increase in the standard and a decrease in the diabetes-specific formula group. No differences in fructosamine, insulin, or lipid levels were observed between groups after 4 weeks consumption. Both products were equally well tolerated, with a low incidence and mild intensity of reported symptoms, and no clinically relevant differences were observed in liver and kidney function.

The lower postprandial glucose response to the diabetes-specific formula after 4 weeks indicates that no adaptation to the diabetes-specific formula occurs after several weeks of use. Although the study period of 4 weeks is relatively short, there are no reasons to assume that after longer term use adaptation would occur. The lower postprandial glucose response may be due to several properties and/or ingredients of this formula, which are described in more detail elsewhere [18,19]. In short, the major carbohydrate in the diabetes-specific formula is isomaltulose a naturally occurring, low glycemic index, slowly digestible carbohydrate. In vitro studies using human small intestinal mucosa homogenate as enzyme source, show that human intestinal enzymes are able to hydrolyze isomaltulose, but the rates are slow compared with sugars as maltose or sucrose [14,22]. This slower hydrolyzation during gastrointestinal passages may be responsible for the (s)lower rises in blood glucose and insulin levels observed after isomaltulose intake as compared with sucrose in both healthy and diabetic subjects [15,23]. In a recent study using an ileostomy model, isomaltulose was found to be essentially absorbed. Apparent digestibility of 50 g of isomaltulose from two different meals was 95.5 and 98.8%. Apparent absorption was 93.6 and 96.1%, respectively [24]. The protein source is also different between the two formulas: casein in the standard formula and a combination of whey and soy protein in the diabetes-specific formula [25–28]. The different types of fibers may have contributed to the difference in postprandial glucose response as well. Finally, the slightly different amount of carbohydrates, proteins and fibers may also have played a role in the observed effect.

Surprisingly, it was found that replacement of breakfast and one snack with a liquid, fiber-containing standard formula, but not with a diabetes-specific formula, increased fasting glucose levels and insulin resistance ($HOMA_{IR}$). There are a few other studies in which standard liquid meal replacements were used by type 2 diabetes patients, i.e. full meal replacement for 8 weeks providing 850 kcal/day [29] or partial meal replacements achieving a daily caloric deficit of 500 kcal [30]. However, in these trials, the objective was to lose weight and concomitantly with the observed weight loss (11% [29] and 6% [30]), decreases in fasting glucose, HbA1c, and lipids were found. The current trial was not designed to actively lead to weight loss. The formulas were isocaloric. However, the glycemic index of the diabetes-specific formula was low, whereas the standard product had a medium GI. Low-GI foods have consistently shown beneficial effects on blood glucose control in both the short-term and the long-term [31]. Since most low-GI foods are also rich in fiber, it is however

difficult to separate the contribution of low-GI and/or high fiber content to these health benefits. Only one study determined the effect of two diets differing solely in their GI, while containing the same amount of nutrients and dietary fiber, on glycemic control in type 2 diabetes patients [32]. After 24 days on the low GI diet, insulin sensitivity was improved and fasting glucose levels were decreased. These results suggest that the difference in GI between the two formulas tested in the current study may have contributed to the effects on insulin resistance and fasting glucose, although only one meal and one snack/day were replaced by a low-GI formula. Also the intake of isomaltulose may have lowered the glycemic response to the lunch, although this was not studied. In a study in healthy men consuming an isomaltulose-containing liquid formula during breakfast, lower levels of glucose and insulin were found after a standard lunch as compared with consumption of a high-GI formula during breakfast [33]. The different types of proteins may also have contributed to the effect on fasting glucose and insulin resistance. In a diabetes rat model (Goto Kakazaki), it was found that feeding for 2 weeks with a combination of whey and soy protein significantly improved insulin sensitivity, fasting glucose concentrations and fructosamine levels as compared with feeding with casein [28]. These effects may be explained by the higher aspartate content of the soy/whey protein combination as compared with casein and thereby an improvement in mitochondrial energy metabolism via better functioning of the aspartate/malate shuttle [34].

Some other studies also determined the effect of a diabetes-specific liquid formula as (part of) breakfast in patients with impaired glucose tolerance and/or diabetes [35,36]. In overweight Chinese type 2 diabetes patients, a liquid diabetes-specific formula was used to replace breakfast food items such as milk, soymilk, rice soup or congee at the morning meal [36]. Postprandial glucose levels were not determined, but fasting glucose, insulin and HbA1c levels were improved in the intervention group after 24 weeks. However, the intervention not only consisted of a diabetes-specific formula, but also diabetes education with frequent blood glucose monitoring, nutritional counseling, and weekly progress updates with study staff compared to diabetes education only in the reference group. Therefore, it is not possible to determine the contribution of the diabetes-specific formula to the observed effects. In another study, an isomaltulose-based liquid formula was used as part of breakfast during 5 months in subjects with impaired glucose tolerance or type 2 diabetes [35]. At the end of the study, HbA1c and serum 8-hydroxydeoxyguanosine levels were significantly decreased compared to those at baseline. Unfortunately, no control group was used, which makes it difficult to interpret the results. In the current study of 4 weeks, fructosamine levels were not significantly different between groups. It would be interesting to study the effects of longer-term use of the diabetes-specific formula on HbA1c. Not only fasting glucose levels, but also the postprandial glucose concentrations play a major role in overall glycemic control (HbA1c) [9,37].

Both formulas used in the present study had the same amount of calories. Nevertheless, after 4 weeks, the change in body weight was significantly different between the groups, being increased in the control group and slightly decreased in the diabetes-specific group. The isomaltulose in the diabetes formula may have contributed to this effect. In a study in 10 overweight persons, ingestion of isomaltulose as compared to sucrose was of benefit in stimulating postprandial fat oxidation [38], which implies a supportive effect on body weight control in obesity. A shift towards a greater postprandial fat use may also attenuate fat accumulation in non-adipose tissues leading to reduced insulin resistance. This is line with the observed effects in the current study on insulin resistance. In a rat study with an isomaltulose-based formula improved insulin sensitivity and reduced visceral fat accumulation were found as well [39]. Caloric intake was not recorded in this study, so it is not known whether a different caloric intake accounted for the differences in body weight.

In conclusion, the results of this study show that the superior postprandial glucose control after intake of a diabetes-specific formula was maintained after 4 weeks use by type 2 diabetes patients, compared to a standard formula. Furthermore, 4 weeks use of a standard liquid formula had negative effects on body weight, fasting glucose and $HOMA_{IR}$, although the latter two effects may be confounded by the observed effect on body weight. These results show that the use of a diabetes-specific formula as meal replacement has a clear added value with respect to postprandial glucose control compared to a standard, fiber-containing formula in people with type 2 diabetes and may contribute to improved glycemic control (HbA1c) in the longer term. A longer term study of at least 12 weeks would be necessary to show this.

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Conflict of interest

The authors have a competing interest to declare. ML and KvL are employees of Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition. GR has been member of one scientific advisory meeting by Nutricia Advanced Medical Nutrition. LV has no competing interest to declare

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