

ORIGINAL ARTICLE

Metabolic effects of an enteral nutrition formula for diabetes: comparison with standard formulas in patients with type 1 diabetes

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Abstract—Aim: To evaluate the metabolic response (glucose, cholesterol, triglycerides and β -hydroxy-butyrate) in patients with type 1 diabetes after a trial breakfast with an enteral nutrition formula designed for patients with diabetes and compare it with standard formulas (with and without fibre).

Material and methods: Each of 11 patients with type 1 diabetes consumed three types of liquid breakfast with a 1 week interval between each. (1) A standard diet (SD) with 49% carbohydrates, 35% lipids, 16% proteins—casein—and without fibre; (2) A fibre-enriched diet (FD): with 49% carbohydrates, 35% lipids, 16% casein and 15 g/1000 ml fibre; (3) A diet designed for patients with diabetes (DD) with 45% carbohydrates, 38% lipids, 16% soy protein and 15 g/1000 ml fibre. Each subject consumed 250 ml of each preparation at 9.00 AM after having administered their usual insulin dose, which was the same for each diet. Blood samples were taken at baseline and each 30 min, up to 150 min.

Results: The increase in postprandial glycaemia was lower with DD than with the standard preparations, reaching statistical significance at 60 min. There were no significant variations in the levels of cholesterol, triglycerides or β -hydroxy-butyrate between the three preparations.

Conclusions: After a trial breakfast, a diet designed for patients with diabetes provoked lower increases in postprandial glycaemia (with no changes in lipid or β -hydroxy-butyrate levels) compared to the standard diets evaluated (with and without fibre).

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Key words: enteral nutrition; diabetes mellitus

Introduction

Diabetes mellitus is considered to be one of the main health problems worldwide. It is a chronic disease with a marked social and economic impact, which is likely to increase over the coming years (1). The prevalence of diabetes in hospitalised patients is very high, reaching almost 20% (2), and its presence is associated with an increased risk of dying whilst in hospital, as well as with a longer hospital stay and a 30–40% increase in costs (3,4). Patients with diabetes also tend to have an increased risk of hospitalisation due to diseases other than those derived from acute or chronic complications of diabetes (5). Consequently, patients with diabetes often have diseases requiring enteral nutrition support.

The long-term efficacy of strict metabolic control on the development and progression of complications, in particular microvascular complications, has been clearly demonstrated in patients with both type 1 (6) and type 2 (7) diabetes mellitus. Short-term hyperglycaemia in hospitalised patients has been related

with an increased susceptibility to infections, with the corresponding rise in associated morbidity and costs, as well as other pathophysiological changes, such as increased oxidative stress, increased coagulability, and dyslipaemia (8). Intensive insulin therapy to achieve optimum metabolic control has been shown to reduce the morbidity and mortality of patients receiving intensive care (9). Patients with diabetes receiving enteral nutrition support should, therefore, not only receive adequate nutrients but also maintain acceptable glycaemic and lipid metabolic control.

The nutritional recommendations for patients with diabetes have varied widely over recent years, with a tendency, depending on the dietary habits of the patient, to increase the percentage of calories coming from lipids, provided they are mainly monounsaturated (10). Several different formulas have therefore appeared on the market specially designed for diabetic patients, which increase the percentage content of monounsaturated fats and reduce the proportion of carbohydrates. We evaluated the metabolic response after a trial breakfast with a new formula designed for diabetic patients.

Material and methods

Subjects

Eleven patients with type 1 diabetes were selected from the outpatients clinic of the Endocrinology and Nutrition Service of our hospital. All fulfilled the criteria for type 1 diabetes, which had been present for more than 1 year prior to starting the study (mean: 40.5 ± 32 months, range 15–120 months). In the four patients with diabetes for less than 24 months the existence of a honeymoon period was ruled out by measurement of baseline levels of C peptide lower than 1 ng/ml. Their mean age was 30.4 ± 6 years (range: 23–41 years), and the BMI was 23.7 ± 3.9 kg/m². They were all receiving stable doses of insulin and their levels of glycosylated haemoglobin (HbA_{1c}) were between 5% and 7%. Eight patients injected NPH + lispro insulin, one NPH plus regular and two NPH alone. The insulin dose at breakfast was 15.3 ± 7 IU. None of them had any important gastrointestinal disease, such as diabetic gastroparesis, hepatic insufficiency, increased transaminases, peptic ulcer or gastritis, or renal insufficiency (creatinine < 1.2 mg/dl), nor were they receiving any other medication apart from insulin. The patients were informed of the nature of the study and gave their written consent.

Study design

Each patient consumed three different breakfasts on 3 days, with a 1-week interval between each. They consisted of 250 ml of three enteral formulas: Nutrison diabetes[®] (DD), Nutrison standard[®] without flavour (SD), and Nutrison multifibre[®] (FD). The differences in the composition of the three formulas are shown in Tables 1 and 2. The order in which the formulas were taken was randomised for each patient. The patient

Table 1 Composition of the three study diets per 100 ml (showing only those components which varied between diets)

	SD	FD	DD
Energy	100 kcal	100 kcal	100 kcal
Protein	4.0 g	4.0 g	4.3 g
Nitrogen	0.6 g	0.6 g	0.7 g
Casein	4.0 g	4.0 g	—
Soy protein	—	—	4.3 g
Carbohydrates	12.3 g	12.3 g	11.3 g
Lactose	<0.020 g	<0.020 g	<0.01 g
Dextrin maltose	12.1 g	12.1 g	—
Starch	—	—	8.8 g
Fructose	—	—	2.3 g
Other organics	0.2 g	0.2 g	0.1 g
Lipids (vegetal oil)	3.9 g	3.9 g	4.2 g
Saturated fatty acids	10.2%	10.2%	10.7%
Monounsaturated fatty acids	59.4%	59.4%	67%
Polyunsaturated fatty acids	30.4%	30.4%	22.3%
Fibre	—	1.5 g	1.5 g
Soluble	—	0.74 g	0.74 g
Insoluble	—	0.76 g	0.76 g
Molybdenum	10 µg	10 µg	16 µg

SD: standard diet; FD: fibre-enriched diet; DD: diet designed for patients with diabetes.

Table 2 Composition of the three study breakfasts in fats and amino acids

	SD	FD	DD
Capric acid	0.03	0.03	—
Lauric acid	0.05	0.05	—
Myristic acid	0.13	0.13	—
Palmitic acid	5.65	5.65	5.53
Palmitoleic acid	0.22	0.22	0.14
Stearic acid	2.78	2.78	3.46
Oleic acid	57.8	57.8	65.6
Linoleic acid	25.0	25.0	20.1
a-Linolenic acid	5.19	5.19	2.53
g-Linolenic acid	0.27	0.27	0.11
Arachidic acid	0.43	0.43	0.43
Eicosenoic acid	1.06	1.06	0.45
Behenic acid	0.43	0.43	0.67
Erucic acid	0.16	0.16	0.07
Tetracosanoic acid	0.09	0.09	0.04
Others	0.64	0.64	0.92
I-Isoleucine	5.7	5.7	5.1
I-Lysine	10.2	10.2	5.6
I-Cystine	0.3	0.3	1.2
I-Tyrosine	6.1	6.1	3.9
I-Tryptophan	1.4	1.4	1.3
I-Arginine	4.0	4.0	7.8
I-Alanine	3.4	3.4	4.5
I-Glutamic acid	25.0	25.0	20.5
I-Proline	10.0	10.0	4.9
I-Leucine	10.5	10.5	8.4
I-Methionine	3.3	3.3	1.4
I-Phenylalanine	5.6	5.6	5.5
I-Threonine	4.9	4.9	3.9
I-Valine	7.2	7.2	5.1
I-Histidine	3.2	3.2	2.5
I-Aspartic acid	7.8	7.8	11.8
Glycine	2.0	2.0	4.4
I-Serine	6.6	6.6	5.2

SD: standard diet; FD: fibre-enriched diet; DD: diet designed for patients with diabetes. Composition in grams of amino acids or fatty acids per 100 g of proteins and 100 g of total fatty acids, respectively.

injected the usual insulin dose on the evening prior to consuming the formula, with the last food being consumed at 11 PM. After an overnight fast, the patient injected the usual insulin dose at 8.40 AM if it was NPH or NPH plus regular or at 8.55 AM if it was insulin lispro plus NPH. The same insulin doses were injected at the same time on each of the three study days. At 9.00 AM a baseline blood sample was taken, after which the patients consumed the liquid formula (250 ml) over a maximum period of 5 min. Five more blood samples were then taken 30, 60, 90, 120 and 150 min later. The samples were centrifuged immediately after extraction to separate the plasma, which was stored at -70°C until analysis. Measurements were made of levels of glucose, 3-β-hydroxy-butyrate, plasma cholesterol and triglycerides (by automatised enzymatic methods).

All the patients started the test with capillary glycaemia lower than 250 mg/dl and with negative baseline ketonuria (measured by reagent strips).

Statistical analysis

The effect of the trial breakfast on the response curve of each variable (glucose, cholesterol, triglycerides and

β -hydroxy-butyrate) was analysed using repeated measures multiple analysis of variance according to time and diet. Age, sex, BMI and insulin dose were covariables. Posthoc comparisons were made by Dunnett's test.

Results

Figure 1 shows the mean glycaemia values according to type of breakfast and time. Table 3 summarises the results, expressed as an increase over baseline values, of glycaemia, cholesterol, triglycerides and β -hydroxy-butyrate, after the intake of the trial breakfast. There were significant differences between the various times at which the glycaemia was measured for the diets as a whole ($P < 0.01$) and for the individual diets, but not for the other variables: cholesterol ($P = 0.278$); triglycerides ($P = 0.077$) and β -hydroxy-butyrate ($P = 0.74$).

Comparison of the type of diet showed clinically relevant differences in the increased glycaemia between the three diets at all time points, which were statistically

significant at minute 60. This statistical significance remained after adjusting the contrast hypothesis for the other covariables (insulin dose, age, sex and BMI). Comparison of the DD vs SD showed differences which were significant at minutes 60 ($P = 0.005$) and 90 ($P = 0.03$), and almost significant at 120 ($P = 0.053$). Comparison of the DD vs FD showed significant differences at minute 60 ($P = 0.049$). No significant differences were detected for any of the other variables studied.

For glucose, there were obvious differences in the area under the curve (expressed in mg/dl per minute), though they were not statistically significant ($P = 0.08$): SD 26.547 ± 10.831 ; FD 24.281 ± 7.215 , and DD 19.269 ± 4.300 . The differences for the other parameters were also small and not statistically significant.

Discussion

This study demonstrated a lower increase in glucose levels after intake of a trial breakfast with a new enteral

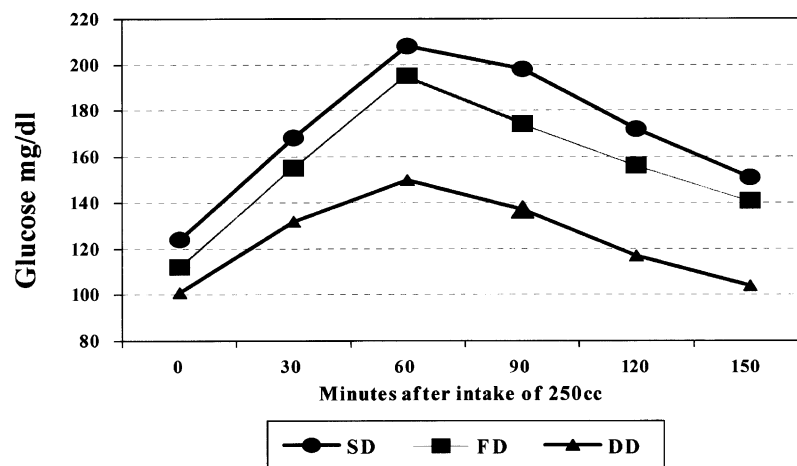


Fig. 1 Mean glycaemia values after the intake of 250 ml of the three study breakfasts. SD: standard diet; FD: fibre-enriched diet; DD: diet designed for patients with diabetes.

Table 3 Metabolic effects after intake of each of the three trial breakfasts (250 cm³), expressed as an increase over the baseline in mg/dl

		30'	60'	90'	120'	150'	Means
SD	Glucose	43.4 ± 7.4	83.7 ± 11.2*	65.6 ± 13.6*	37 ± 13.4	18.4 ± 13.3	49.6 ± 8.4
	Cholesterol	-11.7 ± 2.4	-14.1 ± 5.3	-10.1 ± 2.1	-5 ± 7.9	-3.1 ± 6.1	-8.8 ± 3
	Triglycerides	8.9 ± 6	22.5 ± 6.8	18.6 ± 5.2	7.9 ± 3.2	2.6 ± 4.2	12.1 ± 3.2
	β -hydroxy-butyrate	2.17 ± 1.59	0.67 ± 1.23	-0.07 ± 0.42	-0.68 ± 0.55	0.15 ± 0.76	0.45 ± 0.65
FD	Glucose	41.3 ± 6.1	80 ± 11.8**	54.4 ± 19.6	33.7 ± 21.8	19.7 ± 16.7	45.8 ± 14
	Cholesterol	0 ± 5.6	-7.4 ± 2.5	-8 ± 5.6	-4.3 ± 3.4	-10.9 ± 5.8	-6.1 ± 3
	Triglycerides	10.4 ± 5.9	29 ± 8.9	9.5 ± 8.4	5.1 ± 5.4	0.1 ± 4.7	10.8 ± 4.6
	β -hydroxy-butyrate	-2.13 ± 1.81	-1.12 ± 1.68	-1.62 ± 1.66	-1.65 ± 1.53	-0.13 ± 1.18	-1.33 ± 1.49
DD	Glucose	29 ± 8.6	46 ± 10.6***	31.3 ± 10.6	11.3 ± 10.4	-0.8 ± 9.9	23.5 ± 8.2
	Cholesterol	-11.3 ± 5	-12 ± 1.4	-7.3 ± 2.4	-5.3 ± 2.8	-1.6 ± 5.6	-7.5 ± 2.2
	Triglycerides	-7.4 ± 7	20 ± 5.7	19.3 ± 12.3	14.1 ± 9.7	0.9 ± 8.8	9.4 ± 4.4
	β -hydroxy-butyrate	-0.18 ± 1.13	-0.15 ± 1.01	1.45 ± 1.27	0.17 ± 1.04	0.55 ± 1.28	0.37 ± 0.96

SD: standard diet; FD: fibre-enriched diet; DD: diet designed for patients with diabetes.

* $P < 0.05$ between DD and SD.

** $P < 0.05$ between DD and FD.

*** $P = 0.04$ between the three breakfasts.

formula specially designed for patients with diabetes, with no changes in levels of lipids or β -hydroxybutyrate, when compared with standard formulas, with and without fibre.

The nutritional recommendations for patients with diabetes have varied greatly over recent years. Until 1994, emphasis was placed on providing a diet high in carbohydrates and low in lipids. However, this was then changed to an individualised diet, varying according to the person's lifestyle and social customs, with 10–20% of the total caloric content in the form of proteins, less than 10% from saturated fats and up to 10% from polyunsaturated fats, with the remaining 65% being divided between carbohydrates and monounsaturated fats (10). This change was the result of data showing that diets with a moderate increase in monounsaturated fats result in improved control of glycaemia and lipids, and even of blood pressure and hypercoagulability (11).

Typical standard commercial formulas used for enteral nutrition have a high carbohydrate content, about 50%, and are low in fibre and lipids, around 30–35%. However, since these formulas increase the glycaemic response in patients with diabetes mellitus (12), different commercial formulas have recently been marketed, designed specifically for patients with diabetes, in order to reduce the metabolic response to their intake. Initially there were two types of these special formulas; one with a calorie distribution consisting of standard macronutrients with added fibre and, as a source of carbohydrate, 20% fructose and the rest complex sugars (starch, maltodextrin); and the other type, with a high content of monounsaturated fats (50% lipids) to which fructose and soy fibre were also added in similar proportions as above.

Comparison in patients with diabetes between enteral meals with formulas high in carbohydrates and specific diets for diabetic patients, high in lipids, showed a lower glycaemic response for the latter (12–14). However, comparison of formulas for diabetes with a high carbohydrate content vs standard diets with fibre have not shown the same benefits regarding the increase in postprandial glycaemia, which rose similarly in both diets (15, 16). Thus, with regard to the acute glycaemic response, the overall carbohydrate content would appear more important than the content of fructose, complex sugars or fibre.

The new enteral formula evaluated in this study had intermediate characteristics, with regard to the distribution of macronutrients, between the two models mentioned above, as the total caloric content was provided by 45% carbohydrates, 38% lipids (67% monounsaturated) and 17% proteins. It also provided a mixture of soluble (47%) and insoluble (53%) fibre. The results of this study corroborate data from others showing that diets with a greater proportion of fats improve the short-term glycaemic response, with no change in the lipid profile or induction of ketosis (13, 14, 16).

Compared with the other two diets, the DD diet produced lower increases in glucose levels, which were clinically relevant at all the time points studied, being statistically significant at minute 60. This is of note, as, quantitatively, the differences in grams provided were not important. In 250 ml, the standard formulas provided 30.6 g of carbohydrates and 9.75 g of lipids compared with 28.25 and 10.55 g in the DD diet, respectively. Although the presence of fructose and starch in the DD may have led to a lower glycaemic response, other factors are very likely to have been involved, including the type of fat. Thus, the dietary content of monounsaturated fatty acids seems to be related with improved glycaemic control and lower insulin requirements in patients with diabetes (17). In our study the proportion of monounsaturated fats was greater in the DD (67% of the total lipids), compared to 59% in the standard diets, although the total amount provided was moderate (5.7 g in the standard formulas and 7.06 g in the DD). The content in omega 3 fatty acids, which was lower in the DD, is another factor to be taken into account, although the differences were small.

The content and type of dietary fibre may also influence the results. As can be seen in Figure 1, the postprandial glycaemic increase was greater in the standard diet, followed closely by the standard fibre diet, and finally by the special diabetic diet. The differences between the two standard diets (with and without fibre) were less than those seen when they were compared with the special diet. This was so despite the fact that the DD and the FD had the same amount and type of fibre. Thus, if this factor were to influence the glycaemic response, the magnitude of its importance is probably very small.

Another difference between the diets was the type of proteins used. In the formula designed for diabetic patients the source of proteins was wholly from soy. The continuous intake of soy derivatives has been related with improvement in the lipid profile in healthy people (18) and in patients with diabetes mellitus (19). Soy-protein-based mixed diets in experimental animals appear to improve peripheral insulin sensitivity and reduce baseline glucose concentrations (20, 21). It is possible that soy proteins have a short-term effect on carbohydrate metabolism, modifying absorption of the carbohydrates and/or improving their metabolism.

The effect of the three diets on lipid metabolism was of little clinical importance. There were almost no changes in cholesterol levels and just a slight tendency, within the limits of normality and of no statistical significance between diets, for the levels of triglycerides to fall slowly in the patients receiving the DD, probably due to the greater content of lipids. The effect on the lipids would probably be more evident at higher doses and, above all, after long-term use.

The modification of the levels of β -hydroxy-butyrate was also slight, with no significant differences between diets. There was a small drop up to minute 90, followed by a rise to baseline levels at minute 150 in all three diets. This could be explained by the pharmacodynamics of injected insulin, with its influence on the endogenous production of β -hydroxy-butyrate from the metabolism of the fatty acids (22). The colonic production of β -hydroxy-butyrate from the fermentation of fibre and non-absorbed carbohydrates seems to be a much less important factor.

In summary, the formula designed for patients with diabetes resulted in a lower glycaemic response than the standard diet, with or without fibre, after a trial breakfast. These initial data may be useful as a basis for designing long-term studies to evaluate the metabolic effect of nutritional support and the possible consequences regarding morbidity and mortality in patients with diabetes.

Acknowledgements

This study was supported in part by a research grant from Nutricia SA, Spain. The authors wish to thank Ian Johnstone for his help with the English language version of the manuscript and David Prieto for help with the statistical analysis.

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Submission date: 22 August 2002 Accepted: 17 March 2003