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A randomized clinical trial with two doses of an enteral diabetes-specific suplements in elderly patients with diabetes mellitus type 2

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Abstract. – OBJECTIVES: The aim of our study was to investigate whether two different daily doses of a high monounsaturated fatty acid (MUFA) specific diabetes enteral formula could improve nutritional variables as well as metabolic parameters.

PATIENTS AND METHODS: We conducted a randomized, open-label, multicenter, parallel group study. 27 patients with diabetes mellitus type 2 with recent weight loss were randomized to one of two study groups: group 1 (two cans per day) and group 2 (three cans per day) for a ten week period.

RESULTS: A significative decrease of HbA1c was detected in both groups. The decrease 0.98% (confidence interval 95% 0.19-1.88) was higher in group 2 than group 1 0.60% (confidence interval 95% 0.14-1.04). A significant increase of weight, body mass index, fat mass, albumin, prealbumin and transferrin was observed in both groups without statistical differences in this improvement between both groups. The increase of weight 4.59kg (confidence interval 95% 1.71-9.49) was higher in group 2 than group 1 1.46% (confidence interval 95% 0.39-2.54). Gastrointestinal tolerance (diarrhea episodes) with both formulas was good, without statistical differences (7.60% vs 7.14%: ns).

CONCLUSIONS: A high monounsaturated fatty acid diabetes-specific supplement improved HbA1c and nutritional status. These improvements were higher with three supplements than with two per day.

Key Words:
Enteral nutrition, Diabetes mellitus, Specific formulas.

Introduction

A tight glycemic control has a positive impact on long-term clinical outcomes in subjects with diabetes by delaying and slowing the progression of diabetes-associated complications[1-2]. The primary goal of diet composition in diabetic patients is to achieve and near-normal fasting and postprandial glucose levels, thereby, preventing complications. Some diabetic patients will require nutritional support, secondary to undernutrition. And, an increasing number of patients received home enteral tube feeding, including those with Standard enteral formulas high in carbohydrate, low in fat and low in fiber. These formulas are derived from rapidly absorbed carbohydrate[5-6] and produce hyperglycaemia in subjects with diabetes mellitus, due to a rapid nutrient assimilation. These last years have appeared new formulas to diabetic patients; these formulas contain nutrients, monounsaturated fatty acids[7], fiber[8] and fructose[9]. A systematic review of studies using these diabetes-specific formulas compared with standard formulas has consistently demonstrated significantly lower postprandial blood glucose and glucose under the curve (AUC)[10]. However, there are no specific guidelines for patients with diabetes who are at risk for malnutrition, requiring nutritional support. Over the last decade, there has been increasing advice for the recommendation to optimize the nutrient profile for enteral nutrition in diabetic patients in order to moderate the amount of carbohydrate provided as well as the liberalization of the dose of monounsaturated fatty acid (MUFA) supplied[1]. In a previous study[12], a high monounsaturated fatty acid diabetes-specific enteral supplement improved glucose, HbA1c and albumin levels. However, a diabetes-specific supplement with lower fat percentage than the previous formula improved weight and protein levels wihout significative metabolic effects. As malnutrition is observed in several diabetic patients in the elderly[13], it is important evaluated if a high dose of MUFA diabetes specific formula could improve metabolic parameters, again, and weight.

The aim of our study was to investigate whether two different daily doses of a high MUFA specific diabetes enteral formula could improve nutritional variables as well as metabolic parameters in elderly patients with type 2 diabetes mellitus.

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Patients and Methods

Subjects and Research Design

We conducted a randomized, open-label, multicenter, parallel group study. 27 elderly (> 65 years) patients with type 2 diabetes mellitus with recent weight loss (> 5% during previous 3 months) were randomized (1:1) to one of two study groups: group 1 (two cans per day of a high MUFA diabetes specific supplement and group 2 (three cans per day of this specific formula). Exclusion criteria included; ongoing infections, major gastrointestinal diseases, severel impaired hepatic function (total bilirubin concentration > 3.5 mg/dl) and/or renal function (serum creatinine concentration > 3 mg/dl), steroids treatment, medication could modulate weight, mineral or vitamin supplementation during the study period, and administration of hypolipidemic drugs or oral hypoglycemic agents.

The study was a prospective randomized trial carried out from November 2008 to January 2010. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and approved by the HURH Ethics Committee. Written informed consent was obtained from all patients and signed. Baseline studies on all patients consisted of complete history taking and physical examination. General assessment of nutritional status included measurements of body weight, height, body mass index (BMI) (kg/m^2) and bioimpedance. Patients received subcutaneous insulin doses with the goal of maintaning blood glucose levels between 80 and 160 mg/dl.

Nutritional Intervention

At basal time, diabetic patients were randomized to consume two cans or three cans per day of a specially designed high monounsaturated fatty acid (MUFA) diabetes-specific supplement with 31% of calories provided by fats for a ten week period. Table I shows the composition of this specific supplement (Abbott, Abbott Park, North Chicago, IL, USA). A dietitian instructed patients on how to record food and beverage intake. Three day diet diaries completed at baseline (week 0), and weeks 10 were used to assess the patient's dietary intakes. Two weekdays and one weekend day were studied to account for potential day of the week effects on dietary intake. Mean total energy and macronutrient intakes were calculated using a specific computerized dietary analysis packages. Total dietary intake was calculated by adding oral supplement consumption to spontaneous food intake, asking to record the number of cans of supplements or parts therefore.

Table I. Composition of supplement.

	(1 unit 220 ml)
Total energy (Kcal)	197
Protein (g)	10.2
Total lipid (g)	7.4
MUFA	5.6 (24%)
PUFA	0.9 (4%)
SFA	0.6 (3%)
Carbohydrate (g)	24
Dietary fiber (g)	1.7

(Glucerna SR®): carbohydrates (49% Maltrine, 22% Maltitol, 26% fructose). Dietary fiber source: oligofructose. MUFA: monounsaturated fatty acid. PUFA: polyunsaturated fatty acid. SFA: saturated fatty acid.

Procedures

At the initial and after ten weeks of nutritional intervention, assessment body weight was measured to an accuracy of 0.1 kg and BMI computed as body weight/(height^2). Bipolar body electrical bioimpedance was used to determine body composition[14] (EFG Akern, Florence, Italy). Precautions taken to insure valid BIA measurements were; no alcohol within 24 hours of taking the test, no exercise or food for four hours before taking the test.

At the initial and after ten weeks of nutritional intervention, fasting blood samples were drawn for measurement of albumin (3.5-4.5 g/dl), prealbumin (18-28 mg/dl), transferrin (250-350 mg/dl) (Hitachi, ATM, Mannheim, Germany), and limphocytes ($1.2\text{-}3.5.10^3$/uL) (Beckman Coulter, Inc, Los Angeles, CA, USA). Glycated haemoglobin was measured as HbA_{1c} by HPLC (Menarini, Florence, Italy). Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Hitachi 917, Roche Diagnostics, Mannheim, Germany). Plasma glucose levels were determined by using an automated glucose oxidase method (Hitachi 917, Roche Diagnostics, Mannheim, Germany).

Gastrointestinal problems related to enteral feeding were recorded (diarrhea). Hypoglycemic events (glucose levels < 50 mg/dl and clinical symptoms) were recorded, too.

Statistical Analysis

A power calculation based on weight improvement was performed. Thirteen patients in each group were necessary to detect an improvement of 1,5 kg, with a error type I < 0.05 and a statistical

power of 80%. Statistical tests were two-tailed and conducted at the 0.05 significance level, and *p*-values were rounded to four decimal places. Quantitative variables with normal distribution were analyzed with two tailed paired or unpaired Student's *t*-test. Non-parametric variables were analyzed with Wilcoxon test. To minimize the potential for introducing bias, all randomized patients were included in the comparisons, irrespective of whether or not and for how long they complied with their allocated regimen (intention-to-treat analysis) (SPSS Inc. 15.0, Chicago, IL, USA).

Results

Overall, 27 subjects were enrolled and completed the study. The mean age was 77.2±10.9 years (16 females/11 males). Patients in both treatment groups were comparable with regards to demographic and baseline characteristics. There were 13 patients in the group 1 and 14 patients group 2. There were no significant differences with regard to gender, mean age, body weight and basal glycaemic control (Table II).

To assure adherence to study supplementation program, we dispensed enough formula to our patients to provide 2 units per day in group 1 and 3 units per day in group 2. The volumetric consumption rates of the formula were higher in group 2 than group 1 (group 1: 1.8±0.72 units/day vs. group 1: 2.7±0.92 units/day). Final total calorie, carbohydrate, fat and protein consumption, based on both formula and dietary intake with 3 days food records, were higher in group 2 than group 1, (calories: group 1 1600.1±323.7 cal/day vs. group 2 1879.3±163.1 cal/day: $p < 0.05$), (proteins: group 1 83.3±11.5 g/day vs. group 2 93.1±15.1 g/day: $p < 0.05$),(fat: group 1 68.7±15.5 g/day vs. group 2 73.3±6.8 g/day: $p < 0.05$) and (carbohydrates: group 1 162.6.7±46.5 g/day vs. group 2 188.9±35.9 g/day: $p < 0.05$). Dietary fiber consumption was higher in group 2 than 1 proteins: group 1 12.3±5.3 g/day vs. group 2 14.7±2.6 g/day: $p < 0.05$). Formula consumption represented a 22.4% of caloric intake in group 1 and 29.5% of caloric intake in group 2.

Table II. Patients characteristics.

	Group 1 N = 13	Group 2 N = 14
Age (years)	75.6 ± 7.27	8.1 ± 8.7
Women/men	8/5	8/6
Body weight (kg)	57.1 ± 14.9	55.9 ± 7.3
BMI	21.8 ± 5.5	20.7 ± 4.3
Diabetes course (years)	15.1 ± 3.2	14.9 ± 4.7

No statistical differences.

A significative decrease of HbA1c levels was observed in group 1 and 2. The decrease 0.98% (confidence interval 95% 0.19-1.88) was higher in group 2 than group 1 0.60% (confidence interval 95% 0.14-1.04) (Table III). A significant increase of albumin, prealbumin and transferrin was observed in both groups without statistical differences in this improvement beteewn both groups (Table III).

Patients of both groups (Table IV) had a significant improvement in weight, BMI and fat mass. The increase of weight 4.59 kg (confidence interval 95% 1.71-9.49) was higher in group 2 than group 1 1.46% (confidence interval 95% 0.39-2.54) (Table III). Gastrointestinal tolerance (diarrhea episodes) with both formulas was good, without statistical differences (7.60% vs

Table III. Metabolic control and biochemical nutritional parameters.

Parameters	Group 1		Group 2	
	Baseline	10 weeks	Baseline	10 weeks
Glucose (mg/dl)	117.6 ± 39.1	115.6 ± 42.8	125.9 ± 38.6	121.8 ± 33.4
Total ch. (mg/dl)	163.7 ± 43.4	174.3 ± 37.1	182.5 ± 38.9	173.8 ± 49.8
TG (mg/dl)	135.0 ± 59.2	136.6 ± 55.3	122.7 ± 46.5	107.9 ± 39.1
HbA1c (%)	7.9 ± 1.7	7.3 ± 1.4*	8.5 ± 1.9	7.5 ± 1.6*
T. protein (g/dL)	6.3 ± 1.1	6.7 ± 0.7	6.5 ± 0.9	6.6 ± 0.9
Albumin (g/dL)	3.0 ± 0.7	3.8 ± 1.2*	2.6 ± 0.6	3.3 ± 0.6*
Prealbumin (mg/dl)	14.5 ± 7.7	18.6 ± 9.0*	14.3 ± 3.9	19.7 ± 7.1*
Transferrin (mg/dl)	189.4 ± 63.5	218.8 ± 68*	161.1± 32.2	191.5 ± 55.7*
Limphocytes (10^3 uL/mm^3)	1510 ± 910	1536 ± 818*	1553 ± 482	1543 ± 516

Chol: Cholesterol. TG: Triglycerides. T. Protein: total protein. T Student test and Wilcoxon test were used as statistical methods. *$p < 0.05$, in each group with basal values.

Table IV. Evolution of anthropometric parameters.

Parameters	Group 1		Group 2	
	Baseline	10 weeks	Baseline	10 weeks
Weight (kg)	57.1 ± 14.9	58.5 ± 14.6*	55.9 ± 7.3	59.5 ± 7.2*
BMI (kg/m^2)	21.8 ± 5.5	22.4 ± 5.4*	20.7 ± 4.3	21.9 ± 4.3*
Fat free mass (kg)	41.1 ± 12	41.8 ± 11.3	45.7 ± 10.4	44.8 ± 10.9
Fat mass (kg)	15.8 ± 9.0	16.8 ± 8.1*	13.5 ± 7.7	16.9 ± 8.2*

BMI: body mass index. *$p < 0.05$, differences between time 0 and at 10 weeks in each group.

7.14%: ns). No subjects experienced nausea, cramps, abdominal distension, or vomiting. There were no drop-out due to intolerance.

Hypoglycaemic events were similar in both groups, two episodes in both groups (15.3% vs 14.3%: $p < 0.05$).

Insulin dose at the end of the study did not show statistical differences (group 1:48.1±10.1 vs group 2:52.1±2.8 UI/day:ns). The requirements per g carbohydrate ingested was similar in both groups (group 1:0.41±0.03 vs group 2:0.43±0.09 UI/day: ns).

Discussion

The results of the present trial have confirmed the beneficial effects on glycemic control and nutritional status of a high MUFA diabetes-specific formula. Secondly, weight gain and improvement of HbA1c are higher with three supplements per day than with two per day.

Other previous clinical trials[15-19] reported favorables effects of diabetes-specific formulas on HbA1c, as our high monounsaturated-enhanced formula. The role of carbohydrates in glucose response and insulin resistance has been studied in recent years. Research in this area suggests that replacing simple carbohydrates with a fat source rich in MUFA results in a favorable insulin response and an in improved glycemic response. This type of fat, as an energy source, could improve cardiovascular risk profile, too. In conclusion, the beneficial effect on glycemic control seen with this formula might be ascribed to the lower carbohydrate and higher MUFA content of the supplement.

In previous studies[16-17], no significant effect on total cholesterol or LDL/HDL cholesterol[20] was found of those fed diabetes-specific formulas, as our data. In the majority of the studies, the specific formulas showed lower triglyceride concentrations than the standard formulas[15-16,20]. In a meta-analysis, there were insufficient data to address the effects of diabetes-specific vs standard enteral formulas on HDL and LDL cholesterol[10].

The effect of these specific formulas on weight is not a main evaluated outcome in randomized trials. In one study[21], oral supplements provided 85% of total energy intake, and no significant differences in BMI or weight between those fed diabetes-specific versus standard formulas were found. Our design showed a significative increase in weight in both groups. The increase was higher in group with 3 cans secondary to a high caloric intake.

Some studies[15,17,22] reported reduced insulin requirements in those receiving diabetes-specific formulas versus standard formulas. In our study, although the use of the high MUFA diabetes-specific supplement showed an improvement in dietary intake, requirements per g carbohydrate ingested was similar than the used previous dose to the trial in both groups.

Tolerance of this type of formulas is excellent. Constipation, diarrhea, and nausea have a low rate in our study, without differences between both doses. Furthermore, one study[23] showed that patients in standard formula group arm showed a significantly higher occurrence of diarrhea than patients in specific diabetes formula.

The good tolerance of these formulas, as well as its benefits for weight and metabolic parameters, makes these formulas should be preferred to supplement malnourished diabetic patients. A recent study has demonstrated significantly better 24 hours glucose profiles than fibre-containing formula[24]. Alish et al[25] have reported that the diabetes-specific formula reduced glycemic variability and short-acting insulin requirements.

Conclusions

A high MUFA diabetes-specific supplement improved HbA1c and nutritional status. These improvements were higher with three supplements per day than with two per day. However, a limitation of

our study us the lack of a control group, furtehr studies are needed to evaluate the role of this specific formulas.

Conflict of Interest

None.

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