A randomized clinical trial with two enteral diabetes-specific supplements in patients with diabetes mellitus type 2: metabolic effects

D.A. DE LUIS, O. IZAOLA, R. ALLER*, L. CUELLAR, M.C. TERROBA, T. MARTIN, G. CABEZAS, S. ROJO, M. DOMINGO

Institute of Endocrinology and Nutrition, Medicine School and Unit of Investigation Hospital Rio Hortega, Hospital Clinico*, University of Valladolid, Valladolid (Spain)

Abstract. – The aim of this study was to investigate whether two specific diabetes enteral formulas could improve nutritional as well as metabolic parameters in elderly patients with diabetes mellitus type 2.

A population of 30 elderly patients with diabetes mellitus type 2 with recent weight loss was recruited. At basal time diabetic patients were asked to consume randomly two cans per day of two different specially designed high monounsaturated fatty acid diabetes-specific supplement: one with 49.95% of calories provided by fats (I), the second with a 34% of calories provided by fats (II), for a ten week period.

A significative decrease of glucose (119.8 ± 42 vs 95.1 ± 16.8 mg/dl: p < 0.05) and Hba1c (8.2 ± 2.8 vs 5.8 ± 0.7%: p < 0.05) levels was observed in group I with a significant increase in serum albumin levels (3.1 ± 0.8 vs 3.5 ± 0.5 g/dl: p < 0.05). A significant increase of serum albumin (3.1 ± 0.4 vs 3.7 ± 0.6 g/dl: p < 0.05) and total proteins (6.3 ± 0.5 vs 6.9 ± 0.3 g/dl: p < 0.05) was observed in group II. Patients of group II had a significant improvement in weight (56.5 ± 16 vs 58.3 ± 15 kg: p < 0.05), body mass index (21.8 ± 5.6 vs 22.5 ± 5.3 kg/m²: p < 0.05) and fat mass (15.7 ± 6.4 vs 16.9 ± 6.2 kg: p < 0.05).

In conclusion, high monounsaturated fatty acid diabetes-specific enteral supplement improved glucose, HbA1c and albumin levels. A diabetes-specific supplement with lower fat percentage than the first improved weight and protein levels without significative metabolic effects.

Key Words:
Diabetes mellitus, Malnutrition, Specific formulas.

Introduction

The effect of glycemic control on long-term clinical outcome is well known in patients with diabetes mellitus, where hyperglycemia may result in life-threatening complications and comorbidities. Patients with diabetes are known to be admitted to the hospital more often than other patient groups. Many of these hospitalized patients will require nutritional support, secondary to undernutrition. And, an increasing number of patients received home enteral tube feeding, including those with diabetes mellitus.

Standard enteral formulas are high in carbohydrate, low in fat and low in fiber. These formulas may compromise glycemic control in patients with diabetes mellitus, due to a rapid nutrient assimilation and rapid gastric emptying rate. However, diabetes-specific formulas contain a defined nutrient composition designed to control glycemic levels. Such nutrients include soy protein, monounsaturated fatty acids, fiber and fructose. 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. However, there are no specific guidelines for patients with diabetes who are at risk for malnutrition, requiring nutritional support.

Malnutrition is observed in several patients with diabetes mellitus in the elderly. In these patients, malnutrition is associated with increased susceptibility to infections, failure to heal and functional
In the other hand, age magnifies the hazard of hypoglycemia in the elderly. The normal physiologic response generated by the body in an attempt to correct hypoglycemia is diminished in the elderly due to the decrease of counter-regulatory hormonal response to hypoglycemia and hyperglycemia is more common and potentially more serious in the elderly\textsuperscript{12}. Perhaps, nutritional support using diabetes-specific formulas in these patient groups may prevent such complications.

The aim of our study was to investigate whether two specific diabetes enteral formulas could improve nutritional variables as well as metabolic parameters in elderly patients with diabetes mellitus type 2.

**Materials and Methods**

**Patients**

A population of 30 elderly (> 65 years) patients with diabetes mellitus type 2 with recent weight loss (> 5% during previous 3 months) were enrolled and randomized (sealed envelopes). Exclusion criteria included; severely impaired hepatic function (total bilirubin concentration >3.5 mg/dl) and/or renal function (serum creatinine concentration > 2.5 mg/dl), ongoing infections, major gastrointestinal disease, autoimmune disorders, steroids treatment and medication could modulate weight.

Patients participating in the study were not allowed to receive mineral or vitamin supplementation during the study period, and administration of hypolipidemic drugs or oral hypoglycemic agents was considered a reason to removal of the patients from the study. Patients received subcutaneous insulin doses with the goal of maintaining blood glucose levels between 80 and 160 mg/dl.

The study was a prospective randomized trial carried out from November 2005 to November 2007. Baseline studies on all patients consisted of complete history taking and physical examination. General assessment of nutritional status included measurements of height, body weight, body mass index (kg/m\textsuperscript{2}) and additional bioimpedance.

**Nutrition**

At basal time, diabetic patients were asked to consume two cans per day of either a specially designed high monounsaturated fatty acid diabetes-specific supplement with 49.95\% of calories provided by fats (I) or other diabetes-specific supplement with a 34\% of calories provided by fats (II) for a ten week period. Table I shows the composition of the two supplements. Three day dietaries completed at baseline (week 0), and weeks 10 were used to assess the patient’s dietary intakes. One weekend day and two weekdays were studied to account for potential day of the week effects on dietary intake. A dietitian instructed patients on how to record food and beverage intake. Mean total energy and macronutrient intakes were calculated using country-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.

**Patient Monitoring**

At the initial assessment body weight was measured to an accuracy of 0.1 kg and body mass index computed as body weight/height\textsuperscript{2}. Bipolar body electrical bioimpedance was used to determine body composition\textsuperscript{13}. An electric current of 0.8 mA and 50 kHz was produced by a calibrated signal generator (Biodynamics Model 310e, Seattle, WA, USA) and applied to the skin using adhesive electrodes placed on right-side limbs. Resistance and reactance were used to calculate total body water, fat and fat-free mass. BIA measures the geometrical components of electrical impedance $Z_c$, i.e., resistance $R$ (the sum of in-phase vectors) and the capacitive component, reactance $X$ (the sum of out-phase vectors) derived from $Z_c = R^2 + X_c^2$. The phase angle

<table>
<thead>
<tr>
<th>Group</th>
<th>Total energy (Kcal)</th>
<th>Protein (g)</th>
<th>Total lipid (g)</th>
<th>MUFA (g)</th>
<th>PUFA (g)</th>
<th>SFA (g)</th>
<th>Carbohydrate (g)</th>
<th>Dietary fiber (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>245</td>
<td>10.5</td>
<td>13.6</td>
<td>10.3 (37%)</td>
<td>1.67 (6%)</td>
<td>1.62 (4%)</td>
<td>20.3</td>
<td>3.6</td>
</tr>
<tr>
<td>II</td>
<td>205</td>
<td>10.7</td>
<td>7.8</td>
<td>5.82 (24%)</td>
<td>0.94 (4%)</td>
<td>0.69 (3%)</td>
<td>26</td>
<td>1</td>
</tr>
</tbody>
</table>

Group I (Glucerna\textsuperscript{®}); carbohydrates (60.8\% maltodextrine, 18.9\% fructose, 20.3 soy polysaccharide). Dietary fiber source: soy polysaccharide.

Group II (Glucerna SR\textsuperscript{®}); carbohydrates (49\% Maltodextrine, 22\% Maltitol, 26\% fructose). Dietary fiber source: oligofructose. MUFA: monounsaturated fatty acids. PUFA: polyunsaturated fatty acids. SFA: saturated fatty acids.
\[ \alpha \text{ is determined by the equation } [PA^o = (X_c/R) \times (180^\circ/\pi)]. \] 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.

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

**Assays**

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) ([H]itachi, ATM, Mannheim, Germany), and lymphocytes (1.2-3.5.10^10/uL) (Beckman Coulter, Inc, LA, CA, USA).

Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay ([H]itachi 917, Roche Diagnostics, Mannheim, Germany). Glycated haemoglobin was measured as HbA1c by HPLC (Menarini, Florence, Italy). Plasma glucose levels were determined by using an automated glucose oxidase method ([H]itachi 917, Roche Diagnostics, Mannheim, Germany).

**Statistical Analysis**

The results were expressed as mean ± SD. The distribution of variables was analyzed with Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with two tailed paired or unpaired Student’s t-test and analysis of variance (ANOVA) as needed. Nonparametric variables were analyzed with the Friedman and Wilcoxon tests. 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). A p-value under 0.05 was considered statistically significant.

A power calculation based on weight improvement was performed. Twelve patients in each group were necessary to detect an improvement of 2 kg, with an error type I < 0.05 and a statistical power of 80%.

**Results**

Thirty patients with diabetes mellitus were enrolled in the study. The mean age was 76.1 ± 9.95 years (17 females/13 males). There were 16 patients in the group I and 14 patients group II. Characteristics of the patients on enrollment were similar for the two groups, reflecting the homogeneity of the patients. There were no significant differences with regard to gender, mean age, body weight and basal glycemic control (Table II). Twelve patients died during the study, 37.5% in group I and 42.85% in group II.

To assure adherence to study supplementation program, we dispensed enough formula to our patients to provide 2 units per day. The volumetric consumption rates of the formula were identical for the two groups, with an average of taken units (1.6 ± 0.62 units/day). Final total calorie and protein consumption, based on both formula and dietary intake with 3 days food records, were similar in both groups, (calories: group I 1667 ± 300 vs group II 1610 ± 119 cal/day; p: ns) and (proteins: group I 79.8 ± 25 vs group II 82.4 ± 17.8 g/day; p: ns). Formula consumption represented a 23.9% of calorics intakes in group I and 22.85% of calorics intake in group II.

A significative decrease of glucose and Hba1c levels was observed in group I with a significant increase in albumin levels (Table III). A significant increase of albumin and total proteins was observed in group II without changes in metabolic parameters (Table III).

Patients of group II (Table IV) had a significant improvement in weight, body mass index and fat mass. Parameters in group I remained unchanged.

Gastrointestinal tolerance (diarrhea episodes) with both formulas was good, without statistical differences (6.25% vs 7.14%; p: ns). No subjects experienced nausea, cramps, abdominal distension, or vomiting. There were no dropouts due to intolerance.

Hypoglycaemic events were similar in both groups, two episodes in the same patient in both groups (12.5% vs 14.28%; p < 0.05).

**Table II. Patients characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Group I N = 16</th>
<th>Group II N = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74.6 ± 7.1</td>
<td>77.1 ± 8.7</td>
</tr>
<tr>
<td>Women/men</td>
<td>9/7</td>
<td>8/6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>56.9 ± 15</td>
<td>56.4 ± 16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.4 ± 4.7</td>
<td>21.8 ± 5.6</td>
</tr>
<tr>
<td>Diabetes course (years)</td>
<td>14.7 ± 4.2</td>
<td>14.3 ± 5.7</td>
</tr>
</tbody>
</table>

No statistical differences.
Insulin dose at the end of the study did not show statistical differences (group I: 35.3 ± 5 vs group II: 36.5 ± 6 UI/day; p: ns). The requirements per gram carbohydrate ingested was lower in group I than II (group I: 0.21 ± 0.05 vs group II: 0.39 ± 0.06 UI/day: \( p < 0.05 \)).

Discussion

Our data show that a high monounsaturated fatty acid diabetes-specific supplement with 49.95% of calories provided by fats improved metabolic control and albumin levels. Secondly, diabetes-specific supplement with a 34% of calories provided by fats improved weight and protein levels without metabolic effects.

Three long-term clinical trials involving enteral tube feeding\(^{15,16}\) and oral supplements\(^{17}\) reported favorables effects of diabetes-specific formulas on HbA1c and fructosamine concentrations, as our high monounsaturated-enhanced formula.

In previous studies\(^{16,17}\), no significant effect on total cholesterol was found of those fed diabetes-specific formulas, as our data. Other studies\(^{18}\) did not report significant differences in LDL or HDL concentrations. In the majority of the studies, the diabetes-specific formulas showed lower triglyceride concentrations than the standard formulas\(^{14-16,18}\).

Only two studies\(^{14,17}\) have been reported complications as an outcome, and neither showed a significant difference in overall complication rates between standard formulas and diabetes-specific formulas on enteral tube feeding. However, the study of Graig et al.\(^{14}\) post-hoc analysis demonstrated a tendency for a lower incidence of pneumonia, urinary tract infections and episodes of fever in the diabetes-specific formula. Only one study\(^{17}\) of enteral tube feeding in critically ill

### Table III. Metabolic control, blood protein concentrations and lymphocyte count.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I Baseline</th>
<th>Group I 10 weeks</th>
<th>Group II Baseline</th>
<th>Group II 10 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>119.8 ± 42</td>
<td>95.1 ± 16.8*</td>
<td>122.4 ± 22.8</td>
<td>130.6 ± 41.4</td>
</tr>
<tr>
<td>Total chol (mg/dl)</td>
<td>143 ± 38</td>
<td>155 ± 37</td>
<td>157.5 ± 52</td>
<td>176.1 ± 49.8</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>136 ± 56</td>
<td>142 ± 48</td>
<td>130.7 ± 61.8</td>
<td>134.6 ± 43.7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.2 ± 2.8</td>
<td>5.8 ± 0.7</td>
<td>7.58 ± 1.7</td>
<td>7.38 ± 1.5</td>
</tr>
<tr>
<td>T. protein (g/dL)</td>
<td>6.8 ± 0.8</td>
<td>6.3 ± 0.5</td>
<td>6.9 ± 0.3*</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.1 ± 0.8</td>
<td>3.5 ± 0.5*</td>
<td>3.7 ± 0.6*</td>
<td></td>
</tr>
<tr>
<td>Prealbumin (mg/dl)</td>
<td>13.8 ± 4.2</td>
<td>16.1 ± 4.9</td>
<td>14.9 ± 5.3</td>
<td>20.2 ± 9.1</td>
</tr>
<tr>
<td>Transferrin (mg/dl)</td>
<td>215 ± 49</td>
<td>233 ± 49</td>
<td>188.2 ± 63</td>
<td>223.6 ± 71</td>
</tr>
<tr>
<td>Lymphocytes (10(^3) microL/mm(^3))</td>
<td>1511 ± 980</td>
<td>1566 ± 908</td>
<td>1650 ± 475</td>
<td>1575 ± 506</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I Baseline</th>
<th>Group I 3 months</th>
<th>Group II Baseline</th>
<th>Group II 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>56.9 ± 15</td>
<td>57.4 ± 14.8</td>
<td>56.5 ± 16</td>
<td>58.3 ± 15*</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>22.4 ± 4.7</td>
<td>22.9 ± 4.1</td>
<td>21.8 ± 5.6</td>
<td>22.5 ± 5.3*</td>
</tr>
<tr>
<td>Fat free mass (kg)</td>
<td>45 ± 15</td>
<td>45.2 ± 14</td>
<td>40.2 ± 12</td>
<td>41.5 ± 10</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>3.9 ± 5.6</td>
<td>14.5 ± 5.1</td>
<td>15.7 ± 6.4</td>
<td>16.9 ± 6.2*</td>
</tr>
<tr>
<td>PA(*)</td>
<td>6.1 ± 2.4</td>
<td>5.9 ± 1.5</td>
<td>5.4 ± 1.8</td>
<td>5.5 ± 1.1</td>
</tr>
</tbody>
</table>

BMI: body mass index. PA(*) : phase angle. \( (*) p < 0.05 \), differences between time 0 and at 3 months in each group.
patients reported data on mortality, without significant differences in the 2-week study period, as our data.

Only one study has been evaluated anthropometric data\(^1\) in this study, oral supplements provided 85% of total energy intake, and no significant differences in body mass index, weight, total body fat, or waist-to-hip ratio between those fed diabetes-specific versus standard formulas were found. Our study showed a significant increase in anthropometric parameters in group II. Perhaps different composition of both formulas plays an unknown role in anthropometric improvement without a clear explanation.

The requirements for medication have been evaluated by 4 studies\(^{14-15,17,20}\) in patients with diabetes mellitus type 2. These studies reported reduced insulin requirements in those receiving diabetes-specific formulas versus standard formulas. The insulin requirements differences were 26%\(^{15}\) and 71%\(^{17}\) lower in the specific formula groups than standard formula groups. The requirements per g carbohydrate ingested were low, too. In our study, high monounsaturated fatty acid diabetes-specific supplement showed lower requirements per g carbohydrate ingested than the other specific formula. Different authors\(^{21-22}\) have suggested that control of metabolic parameters in hospitalized patients is more closely related to the carbohydrate supply than to the source of carbohydrates or to the overall composition of the feed. One hypothesis in our study is that the overall composition of the formula (fructose, starch, soluble fiber and MUFA) contributes to a better glycemic control in group I than II rather than the total amount of carbohydrates alone. It has been demonstrated that moderate amount of fructose improves sensitivity to insulin in diabetic patients (123) and that MUFA, as saturated fatty acids (SFA) substitute, reduce insulin response to glucose levels\(^{21}\). However, Hofman et al\(^{24}\) have demonstrated that special feeds with a low carbohydrate, high MUFA and high fibre content improve glycemic balance (peak glucose concentration and area under the curve) in healthy volunteers and patients with diabetes mellitus type 2 as our data showed.

All previous studies have been performed in patients with diabetes mellitus type 2. Only one study\(^ {25}\) has been designed in diabetes mellitus type 1 population. In this work a enteral nutrition formula for diabetes (45% carbohydrates, 38% lipids, 16% soy protein and 15 g/1000 ml fibre) provoked lower increases in postprandial glycemia, with no changes in lipid levels compared to a standard diet with and without fibre.

Gastrointestinal side effects of these formulas are not usual to be evaluated in previous study. Only in a study\(^ {26}\), patients in standard formula group arm showed a significantly higher incidence of diarrhea than patients in specific diabetes formula. Our study did not detect significant differences between formulas.

In conclusion, a high monounsaturated fatty acid diabetes-specific supplement improved glucose, HbA1c and albumin levels. A diabetes-specific supplement with lower fat percentage than the first improved weight and protein levels without metabolic effects.

### References


