Dietary magnesium supplements improve B-cell response to glucose and arginine in elderly non-insulin dependent diabetic subjects

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Abstract. Hypomagnesemia and low erythrocyte magnesium content are both common findings in non-insulin-dependent diabetic subjects. Moreover, intracellular magnesium may play a crucial role in modulating B-cell response to glucose by interfering with potassium permeability. Eight elderly, moderately obese, non-insulin-dependent diabetic subjects were treated with either magnesium supplementation (3 g/day) to the diet or placebo. Both treatment schemes lasted 4 weeks and were separated by a 'wash-out' of 3 weeks. At the end of each treatment period, an iv glucose tolerance test (0.33 g/kg for 3 min) and an iv arginine (5 g) test were performed to determine the B- and A-cell responses. Dietary magnesium supplementation vs placebo produced a slight but significant decrease in basal plasma glucose (8.6 ± 0.3 vs 8.0 ± 0.1 mmol/l, p < 0.05) and an increase in acute insulin response after iv glucose (37.1 ± 2.3 vs –14.7 ± 0.9 pmol·l⁻¹·(10 min)⁻¹, p < 0.01) and after iv arginine (151 ± 22 vs 81 ± 15 pmol·l⁻¹·(10 min)⁻¹, p < 0.01), respectively. Plasma glucagon levels were unaffected by chronic dietary magnesium supplementation as well under basal conditions as in response to arginine. Net increase in acute insulin response after iv glucose and after iv arginine was significantly correlated to the net increase in erythrocyte magnesium content after dietary magnesium supplementation. We conclude that magnesium administration may be a useful adjuvant to the classic hypoglycemic agents in the treatment of non-insulin-dependent diabetic subjects.

In healthy subjects, plasma and erythrocyte magnesium levels are stable; in diabetic subjects, hypomagnesemia and low erythrocyte magnesium content are common findings. Mather et al. (2) and Vanroelen et al. (3) described a substantial hypomagnesemia in a large series of diabetic patients and reported a close relationship between hypomagnesemia and poor metabolic control. We have previously shown that insulin induces opposite changes in plasma and erythrocyte magnesium levels (4). A low erythrocyte magnesium content, a condition associated with insulin resistance, is also found in the elderly (5).

In the light of these findings the aim of the present study was to investigate the effects of magnesium administration on the B- and A-cell responses to iv glucose and to iv arginine in elderly, moderately obese, non-insulin-dependent diabetic patients.

Patients and Methods

Subjects

Eight elderly, moderately obese, non-insulin-dependent (Type II) diabetic patients were studied (Table 1). The patients stopped taking oral hypoglycemic agents or other drugs at least 3 weeks before the experiments. They were on a weight-maintaining diet containing 312 ± 12 mg/day magnesium and at least 250 g/day carbohydrates. All subjects gave their informed consent and the study was approved by the Ethical Committee of our Institution.
Table I.
Clinical characteristics of the subjects studied.

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>Duration of diabetes (years)</th>
<th>Plasma glucose (mmol/l)</th>
<th>Plasma insulin (pmol/l)</th>
<th>Therapy</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>69</td>
<td>27</td>
<td>11</td>
<td>8.6</td>
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<td>2</td>
<td>M</td>
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<td>32</td>
<td>14</td>
<td>7.8</td>
<td>57</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>65</td>
<td>30</td>
<td>6</td>
<td>8.5</td>
<td>7</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>72</td>
<td>31</td>
<td>7</td>
<td>8.1</td>
<td>86</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>59</td>
<td>29</td>
<td>3</td>
<td>8.3</td>
<td>64</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>63</td>
<td>34</td>
<td>8</td>
<td>8.6</td>
<td>71</td>
<td>S+B</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>71</td>
<td>30</td>
<td>9</td>
<td>9.0</td>
<td>71</td>
<td>S+B</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>72</td>
<td>31</td>
<td>10</td>
<td>9.1</td>
<td>86</td>
<td>S</td>
</tr>
</tbody>
</table>

BMI = body mass index; D = diet; B = biguanides; S = sulfonylureas.
All data were recorded at the start of the pre-study period.

Experimental design
The design was a double-blind, randomized, cross-over study (Fig. 1). Each subject was followed for a pre-study period of 3 weeks before the daily administration of either placebo or magnesium supplementation (Mag 2 3 g/day, Lirca Synthelabo, Italy). Each treatment period lasted 4 weeks. There was a wash-out period of 3 weeks between placebo and magnesium supplementation periods. At the end of each treatment period and after an overnight fast of at least 12 h, the following experimental protocols were performed randomly on different days: a) iv glucose (0.33 g/kg for 3 min); b) arginine (5 g iv).

All tests were performed with the subjects in the supine position. Two 19-gauge polyethylene catheters were inserted iv, one in each arm; one was used for all infusions, the other for blood sampling.

Analytical procedures
Each blood sample for hormone determination was collected in a tube containing 0.3 ml EDTA-Trasylol solution (Trasylol, Bayer, 5 × 10⁶ ml/l and disodium-EDTA 3.2 mmol/l); the plasma was assayed in duplicate for insulin and glucagon. Upon blood withdrawal, samples were immediately placed at 5°C. At the end of each experiment, plasma was separated in a refrigerated centrifuge (5°C) and stored at −20°C until assay. Plasma glucose was determined immediately after each experiment using a Beckman Auto Analyzer (Beckman Instr, Co, USA) and the glucose-oxidase method (coefficient of variation 2.1 ± 0.9%). Plasma insulin (Bio-Data Kit, Italy; coefficient of variation 4.2 ± 1.4%) and glucagon (Byk-Gulden mat Kit, using 30K antiserum; coefficient of variations 4.4 ± 1.1%)

Plasma samples obtained during each experiment from each subject were assayed in one assay to eliminate inter-assay variations. Plasma and erythrocyte magnesium levels were determined in triplicate by atomic absorption spectrophotometry using a Perkin-Elmer apparatus (Perkin-Elmer Co, Norwalk, CT) (6).

![Diagram](https://via.placeholder.com/150)

Fig. 1.
Experimental design of the study.
Calculations and statistical analysis

The first phase of acute insulin response (AIR) to glucose and arginine pulse, and acute glucagon response (AGR) to arginine were calculated as the incremental area under the curve from 0 to 10 min after glucose and arginine pulses, respectively. Total plasma glucose, and insulin and glucagon area under the curve were calculated by an Apple II desk computer programme using the trapezoidal method. Glucose disappearance (Kg) was calculated as the absolute value of the slope of the regression line to log of plasma glucose concentration to time in min from 10–60 after glucose pulse multiplied by 100. Net increases in AIR and in erythrocyte magnesium content were calculated as the differences between the values recorded after placebo and magnesium supplementation, respectively.

After preliminary analysis of variance (ANOVA), the statistical comparison of the results was performed by two-tailed t-test for paired data and Pearson's coefficient of correlation (r). A p-value < 0.05 was chosen as the limit of significance. All data are presented as mean ± SEM.

Results

Body mass index, fasting plasma glucose, insulin, glucagon and magnesium levels, and erythrocyte magnesium content were not significantly different throughout the pre-study period. At the end of treatment periods (Table 2), fasting plasma glucose was slightly but significantly lower after magnesium supplementation. In contrast, the differences in body mass index (BMI), basal plasma insulin, and glucagon levels did not achieve statistical significance in any of the conditions studied. Plasma and erythrocyte magnesium levels were significantly enhanced after magnesium administration in comparison to placebo.

Table 2.

Metabolic data of the patients after placebo (A) and chronic dietary magnesium supplementation (B).

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>30.5 ± 0.8</td>
<td>31 ± 0.7</td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>8.6 ± 0.3¹</td>
<td>8.0 ± 0.1</td>
</tr>
<tr>
<td>Plasma insulin (pmol/l)</td>
<td>66 ± 8</td>
<td>70 ± 7</td>
</tr>
<tr>
<td>Plasma glucagon (ng/l)</td>
<td>130 ± 33</td>
<td>135 ± 29</td>
</tr>
<tr>
<td>Plasma Mg²⁺ (mmol/l)</td>
<td>0.74 ± 0.07¹</td>
<td>0.88 ± 0.09</td>
</tr>
<tr>
<td>Erythrocyte Mg²⁺ (mmol/l)</td>
<td>1.79 ± 0.07²</td>
<td>2.08 ± 0.05</td>
</tr>
</tbody>
</table>

All metabolic determinations were performed after overnight fast (12 h). All results are means ± SEM. ¹ p < 0.05; ² p < 0.01.

After placebo administration, glucose pulse did not evoke significant AIR (~14.7 ± 0.9 pmol·l⁻¹·(10 min)⁻¹) (Fig. 2). Under the same conditions, glucose disappearance (Kg) was 0.42 ± 0.08%. On the contrary, after dietary magnesium supplementation, the glucose pulse caused a slight but significant increase in both AIR (37.1 ± 2.3 pmol·l⁻¹·(10 min)⁻¹, p < 0.01) and Kg (0.79 ± 0.05%, p < 0.01). The net increase in AIR and erythrocyte magnesium content appeared to be significantly and positively correlated (r = 0.65, p < 0.05) at the end of the magnesium administration period. Glucose-induced glucagon suppression was unaffected by placebo or magnesium administration.

Arginine pulse produced an increase in AIR (81 ± 15 vs 151 ± 22 pmol·l⁻¹·(10 min)⁻¹) and in total insulin area under the curve (2.3 ± 0.2 vs 4.8 ± 0.3 pmol/l·l⁻¹·min⁻¹, p < 0.01), which were both significantly higher after magnesium than placebo.
magnesium administration (Fig. 3). On the contrary, AGR (98 ± 21 vs 99 ± 31 mg·L⁻¹·min⁻¹, NS) and total glucagon area under the curve (2.9 ± 0.2 vs 3.0 ± 0.3 pg·L⁻¹·min⁻¹, NS) were both unaffected by magnesium administration. Total plasma glucose area under the curve (255 ± 43 vs 178 ± 38 mmol·L⁻¹·min⁻¹, p < 0.05) was significantly lower after magnesium than placebo administration.

Net increases in AIR and erythrocyte magnesium content were significantly and positively correlated (r = 0.71, p < 0.01) at the end of the magnesium administration period.

Discussion

Previous studies have reported low plasma and erythrocyte magnesium levels in non-insulin-de-
glucose metabolism and enhanced B-cell response to nutrients or a combination of both possibilities cannot be excluded.

In conclusion, the present study shows that dietary magnesium supplementation can enhance insulin secretion, thus contributing to the improvement of metabolic control in non-insulin-dependent diabetic subjects.

References


Received November 7th, 1988.
Accepted February 27th, 1989.

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