

Original article

Oral magnesium supplementation improves glycaemic status in subjects with prediabetes and hypomagnesaemia: A double-blind placebo-controlled randomized trial

F. Guerrero-Romero, L.E. Simental-Mendía, G. Hernández-Ronquillo, M. Rodríguez-Morán*

Biomedical Research Unit of the Mexican Social Security, Institute at Durango, Durango, Mexico

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Abstract

Aim. – This study evaluated the efficacy of oral magnesium supplementation in the reduction of plasma glucose levels in adults with prediabetes and hypomagnesaemia.

Methods. – A total of 116 men and non-pregnant women, aged 30 to 65 years with hypomagnesaemia and newly diagnosed with prediabetes, were enrolled into a randomized double-blind placebo-controlled trial to receive either 30 mL of MgCl₂ 5% solution (equivalent to 382 mg of magnesium) or an inert placebo solution once daily for four months. The primary trial endpoint was the efficacy of magnesium supplementation in reducing plasma glucose levels.

Results. – At baseline, there were no significant statistical differences in terms of anthropometric and biochemical variables between individuals in the supplement and placebo groups. At the end of follow-up, fasting (86.9 ± 7.9 and 98.3 ± 4.6 mg/dL, respectively; $P=0.004$) and post-load glucose (124.7 ± 33.4 and 136.7 ± 23.9 mg/dL, respectively; $P=0.03$) levels, HOMA-IR indices (2.85 ± 1.0 and 4.1 ± 2.7 , respectively; $P=0.04$) and triglycerides (166.4 ± 90.6 and 227.0 ± 89.7 , respectively; $P=0.009$) were significantly decreased, whereas HDL cholesterol (45.6 ± 10.9 and 46.8 ± 9.2 mg/dL, respectively; $P=0.04$) and serum magnesium (1.96 ± 0.27 and 1.60 ± 0.26 mg/dL, respectively; $P=0.005$) levels were significantly increased in those taking MgCl₂ compared with the controls. A total of 34 (29.4%) people improved their glucose status (50.8% and 7.0% in the magnesium and placebo groups, respectively; $P<0.0005$).

Conclusion. – Our results show that magnesium supplementation reduces plasma glucose levels, and improves the glycaemic status of adults with prediabetes and hypomagnesaemia.

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Keywords: Clinical trial; IFG; IGT; Magnesium; Prediabetes

1. Introduction

Lifestyle changes related to globalization have resulted in remarkable changes in human behaviour and increased the number of obese people, with a consequent increase in the incidence and prevalence of type 2 diabetes (T2D). Thus, the disorder ranks high on the international agenda as a global pandemic threat to human health and the global economy [1].

* Corresponding author. Canoas 100, Col. Los Angeles, 34067 Durango, Dgo, Mexico. Tel.: +52 6188 12 0997.

E-mail address: rodriguez.moran.martha@gmail.com (M. Rodríguez-Morán).

It is well known that, in the natural history of T2D, the development of insulin resistance is among the early underlying mechanisms and that normal glucose tolerance shows a gradual impairment that mirrors the failure of beta-cell function to compensate for the increased insulin resistance. There are also pathophysiological mechanisms that lead to prediabetic hyperglycaemic states, defined as the presence of impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), or both.

Although not all prediabetic individuals progress to diabetes, identification of prediabetes provides an opportunity for early interventions to prevent or delay the progression of disease [2], thus supporting the hypothesis that the natural history of diabetes can be changed through routine screening combined with

management aimed at keeping glucose levels as close to normal as possible [3].

The above-mentioned hypothesis is of particular importance when taking into account the study by Danaei et al. [4], which analyzed data from 2.7 million adults participating in health surveys and epidemiological studies worldwide, and showed rising glycaemic levels in the populations of developed and developing countries, resulting in the increase in rates of prediabetes.

Magnesium is an essential cofactor in the enzymatic processes of the high-energy phosphate and glucose metabolic pathways [5–7] involved in the development of hyperglycaemia. With this in mind, low serum magnesium levels in individuals with prediabetes are significantly lower than in those with normal glucose tolerance [8]. In addition, it has been shown that oral magnesium supplementation reduces insulin resistance and improves beta-cell function to compensate for variations in insulin sensitivity [9,10].

Although several trials have demonstrated that an increase of magnesium intake with the customary diet reduces the risk of impaired glucose and the progression of prediabetes to diabetes [11,12], there are no reports based on randomized controlled clinical trials evaluating the role of magnesium supplementation in the improvement of prediabetes. Yet, such an approach could be of particular importance, given that foods containing magnesium (unprocessed foods such as whole grains, nuts and green leafy vegetables) are uncommon in Westernized diets. Thus, the objective of the present study was to evaluate the efficacy of oral magnesium supplementation in reducing plasma glucose in individuals with prediabetes and hypomagnesaemia.

2. Methods

With the approval of our protocol by the Mexican Social Security Institute Research Committee and after obtaining our participants' informed consent, a randomized double-blind placebo-controlled trial was carried out.

Men and non-pregnant women, aged 30 to 65 years and newly diagnosed with impaired fasting glucose (IFG), were eligible to participate in the study. A standardized interview and clinical examination were performed to determine the presence of chronic diarrhoea, alcohol intakes ≥ 30 g/day, smoking, high blood pressure, diagnosis of chronic diseases, and diuretic therapy as well as intakes of oral supplements and/or vitamins, all of which were exclusion criteria. In addition, eligible subjects underwent an oral glucose tolerance test (OGTT), and those with 2-h post-load plasma glucose levels ≥ 200 mg/dL (11.1 mmol/L) and those with serum magnesium levels ≥ 1.8 mg/dL (0.74 mmol/L) were also excluded.

The included subjects were randomly allocated to receive either 30 mL of MgCl_2 5% solution (equivalent to 382 mg of magnesium) as a single bolus or 30 mL of NaHCO_3 0.1% solution as a single bolus once daily for four months. Computer-generated random numbers were used for assigning participants to either the oral magnesium supplementation or the placebo group.

Based on a total daily caloric intake of 30 kcal/kg of ideal body weight, the subjects in both groups were advised to follow

a diet that was 55% carbohydrates, 25% lipids and 20% proteins, as well as engage in physical activity for at least 30 min three times a week.

Adherence to the magnesium supplementation, diet and exercise were assessed every month by personal interview and by measurement of unused MgCl_2 and placebo solutions, and additionally by the participants' changes in serum magnesium levels. All participants and personnel assessing outcomes were blinded to group assignment.

Screening was performed in 543 subjects: 340 (62.6%) women and 203 (33.4%) men; 410 (75.5%) subjects were not included because they either did not fulfil the inclusion criteria or they met criteria for exclusion. Thus, a total of 133 (24.5%) people with newly diagnosed prediabetes were enrolled and randomly allocated to the study groups. A total of 17 (12.8%) participants dropped out, or were lost to follow-up, withdrew their consent or changed their residence; of these, seven and 10 were from the intervention and control groups, respectively (Fig. 1). Side-effects were related to mild abdominal pain and mild diarrhoea, and were documented in 7.6 and 6.0% of the intervention and control groups, respectively ($P=0.94$, Fig. 1). In both groups, the mild abdominal pain and mild diarrhoea were totally resolved within 24 h of stopping the administration of the magnesium chloride or placebo.

At baseline and after 16 weeks of treatment, anthropometric variables, fasting and 2-h post-load plasma glucose, and serum magnesium were measured.

2.1. Definitions

Hypomagnesaemia was defined as serum magnesium concentrations ≤ 1.8 mg/dL (≤ 0.74 mmol/L) [13]. Prediabetes was defined as the presence of fasting plasma glucose (IFG levels ≥ 100 but < 126 mg/dL [≥ 5.6 but < 7.0 mmol/L]) or IGT [2-h post-load plasma glucose levels ≥ 140 but < 200 mg/dL (≥ 7.7 but < 11.1 mmol/L)], or IFG + IGT. Normoglycaemia was defined as fasting plasma glucose < 100 mg/dL (< 5.6 mmol/L) and 2-h post-load plasma glucose levels < 140 mg/dL (< 7.7 mmol/L) [14]. The homoeostasis model assessment for insulin resistance (HOMA-IR) index was calculated using the following formula: Fasting insulin (U/mL) $\times$ fasting glucose (mmol/L)/22.5 [15].

2.2. Measurements

Height and weight were measured in fasting conditions with subjects wearing light clothing and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Waist circumference (WC) was measured, using a flexible steel tape and with participants standing, as the smallest circumference at a level midway between the lowest margin of the rib cage and superior border of the iliac crest. Blood pressure was measured according to recommendations proposed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [16].

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