Hypomagnesaemia and risk for metabolic glucose disorders: a 10-year follow-up study

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ABSTRACT

Background Although several lines of evidence suggest that hypomagnesaemia is a risk factor for developing type 2 diabetes, there are no studies regarding the association between hypomagnesaemia and the risk for developing impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Our objective was to examine the association between serum magnesium levels and the risk for developing IFG, IGT and type 2 diabetes.

Materials and methods A total of 1122 individuals (20–65 years of age) were enrolled between 1996 and 1997, and 817 individuals re-examined about 10 years later. New-onset IFG (5·6–7·0 mmol L−1 fasting glucose), IGT (7·8–11·1 mmol L−1 glucose 2-h postload), and type 2 diabetes were determined from the number of subjects who had these conditions at the second examination without evidence that they were present at the first one. The relative risk of new-onset metabolic glucose disorders and diabetes (dependent variables) was computed using Poisson regression model adjusted for age, sex, family history of diabetes, waist circumference and homeostasis model assessment for insulin resistance index. Serum magnesium levels of < 0·7 4 mmol L−1 (independent variable) defined the exposed group.

Results At baseline, 420 (51·4%) individuals had hypomagnesaemia. New-onset IFG and IGT was identified in 276 (33·8%) individuals. The relative risk for IFG, IGT and IFG + IGT was 1·11 (95% confidence interval, 0·5–5·1), 1·38 (95% confidence interval, 1·1–6·3) and 1·49 (95% confidence interval, 1·1–4·9), respectively. New-onset diabetes was identified in 78 (9·5%) individuals (relative risk 2·54; 95% confidence interval, 1·1–4·1).

Conclusions Hypomagnesaemia is independently associated with the development of IGT, IFG + IGT and type 2 diabetes, but not with the development of IFG.

Keywords Hypomagnesaemia, impaired fasting glucose, impaired glucose tolerance, risk, type 2 diabetes.

Introduction

Epidemic growth of type 2 diabetes leading to an increased risk of cardiovascular disease and death is a major global health challenge [1]. It has been estimated that the worldwide number of adults with diabetes will rise to 300 million in the year 2025 [2]. To face up to this challenge, the primary prevention remains as the main strategy; however, because the pathogenesis of the disease is complex and current public health programs are insufficient, finding new strategies of prevention is needed.

In the last decade, several lines of evidence have demonstrated that magnesium plays an important role in the pathogenesis of diabetes, suggesting that hypomagnesaemia is a risk factor for developing the disease [3,4]. In vitro and in vivo studies have showed that magnesium deficiency deteriorates the insulin secretion and that magnesium supplementation prevents the development of diabetes in rat models [5,6]. Furthermore, it has been demonstrated that hypomagnesaemia promotes disorders of the tyrosine-kinase activity on insulin receptor and increases the intracellular calcium concentration, events related to the development of insulin resistance [7].

In addition, short-term randomized clinical trials have provided evidence that magnesium supplementation improves insulin sensitivity in nondiabetic individuals and reduces the serum glucose levels in diabetic subjects [8–10], and large follow-up studies suggest that low dietary magnesium intake is associated to the risk of developing type 2 diabetes [11–13].

At end of the 1990s, Kao et al., showed a graded, inverse, independent relationship between serum magnesium levels and incident type 2 diabetes in white, middle-aged adults [3]. However, to the best of our knowledge, there are no follow-up
studies regarding the association between hypomagnesaemia and the risk for developing metabolic glucose disorders, a finding that could be useful for the implementation of further strategies in preventing the disease. In this study, we examined the association between hypomagnesaemia and the risk for developing impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes.

Materials and methods
The Mexican Diabetes Prevention study is a randomized clinical trial for testing strategies to prevent or delay the development of type 2 diabetes in high-risk individuals. For this purpose, the Multidisciplinary Research Group on Diabetes (GRUMID) that includes researchers from 14 clinical centres, four medical research units, and two biomedical research centres from the Instituto Mexicano del Seguro Social (IMSS), the largest healthcare institution in Mexico, randomly enrolled individuals from urban and rural communities.

A total of 1122 individuals, representative of the general population for gender and age (20–65 years) [14], were enrolled between 1996 and 1997 and re-examined about 10 years later. The applied questionnaires covered demographic characteristics, family history of diabetes, and clinical condition. Measurements included blood pressure, weight, height, waist, and overnight fasting and 2-h postload plasma glucose and insulin levels as well as serum magnesium levels and lipid profile.

Measurements
In the mid-1990s, participants were invited to the Biomedical Research Unit of the IMSS in Durango, Mexico, for collection of clinical and anthropometric data as well as to undergo an oral glucose tolerance test (OGTT).

While in the standing position, the subjects’ weight and height were measured, with the subjects in light clothing and without shoes, using a fixed scale with stadiometer (Tanita TBF-215, Tokyo, Japan). The increments of weight and height measurements were 0·1 kg and 0·01 m, respectively. Body mass index was calculated as weight (kilograms) divided by height (metres) squared. Waist circumference was measured to the nearest centimetre with a flexible steel tape measure while the subjects were in the standing position. The anatomical landmarks used were: laterally, midway between the lowest portion of the rib cage and iliac crest, and anteriorly midway between the xiphoid process of sternum and the umbilicus.

Using Baumanometer (Microlife AG, Heerbrugg, Switzerland) and stethoscope (3M Littman Classic II, Neuss, Germany), blood pressure was measured. The technique for measurement of blood pressure was the recommended in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [15].

Venous blood samples were drawn after an overnight fasting of 10–12 h and 2-h post 75-g glucose load for measuring plasma glucose, insulin and serum magnesium levels. At baseline, those participants with metabolic disorders of glucose and/or hypomagnesaemia were informed about their potential risk, received dietary advice, and were invited to undergo medical vigilance in the outpatient health centres of the IMSS. Subjects who at baseline had diabetes were not included in the follow-up.

The same data obtained between 1996 and 2007 were collected by trained personnel of the Biomedical Research Unit of Durango, keeping that the data collection procedures were identical in the two occasions. Diagnosis of hypomagnesaemia was based on data obtained at the first and second examination. New-onset metabolic glucose disorders and diabetes were determined from the number of subjects who had this condition at the second examination without evidence that they were present at the first one.

Definitions
Hypomagnesaemia was defined by serum magnesium concentration of < 0·74 mmol L⁻¹ [16].

Metabolic glucose disorders included the following categories: (i) IFG, (ii) IGT and (iii) IFG + IGT. Diagnosis of IFG was based on fasting plasma glucose (FPG) of ≥ 5·6 mmol L⁻¹ and < 7·0 mmol L⁻¹; diagnosis of IGT was based on 2-h postload serum glucose levels of ≥ 7·8 mmol L⁻¹ and < 11·1 mmol L⁻¹; and diagnosis of IFG + IGT was based on FPG of ≥ 5·6 mmol L⁻¹ and < 7·0 mmol L⁻¹, and 2-h postload serum glucose levels of ≥ 7·8 mmol L⁻¹ and < 11·1 mmol L⁻¹. Diagnosis of diabetes was established by glucose concentration 2-h postload ≥ 11·1 mmol L⁻¹ [17]. Furthermore, subjects who at the end of follow-up were taking hypoglycaemic drugs or receiving insulin, were considered as new-onset diabetes irrespective of their FPG levels. Subjects with IFG and IGT were required to have serum glucose concentration 2-h postload < 7·8 mmol L⁻¹ and FPG < 5·6 mmol L⁻¹, respectively.

Assays
Plasma glucose levels were determined with the Synchron CX4 System™ of Beckman Coulter (Fullerton, CA, USA) using a timed endpoint method. The intra- and interassay coefficients of variation for glucose measurements were 1·1% and 1·11%, respectively.

Serum magnesium concentrations were measured by colorimetric method with the Data Pro Plus Random Access Clinical Analyzer (Arlington, TX, USA); the intra- and interassay variations were 1·0% and 2·5%, respectively.

The protocol was approved by the Scientific Research Committee of the IMSS. Before to the study, all the subjects gave their informed consent.
Statistical analysis

SPSS version 10.0 (SPSS Inc., Chicago, IL, USA) was used for data management and statistical analysis. The bivariate analysis was performed using unpaired Student’s t-test for numerical data (Wilcoxon test for nonparametric distributed numeric data) and \( \chi^2 \)-test for testing differences between nominal variables.

We computed incidence rate (IR) (number of events/person-time) and relative risk (RR) (IR exposed/IR non-exposed) for each category of metabolic glucose disorders and diabetes. In all analyses, serum magnesium levels < 0.74 mmol L\(^{-1}\) defined the exposed group.

To compute the RR of new-onset metabolic glucose disorders and diabetes (dependent variables), Poisson regression was used. Serum magnesium levels < 0.74 mmol L\(^{-1}\) (independent variable) defined the exposed group. We computed crude IRs (number of events/person-time) and crude RRs (IR exposed/IR non-exposed). Individuals who progressed to IFG, IGT or IFG + IGT during the 10-year follow-up were among the subjects with normal glucose tolerance at baseline, whereas progressors to diabetes were among the subjects who at baseline exhibited IFG, IGT or IFG + IGT. Persons-year for estimating the IR was different in the progressors to metabolic glucose disorders or diabetes. In addition, the Poisson regression model was adjusted for age, sex, family history of diabetes, waist circumference and the homeostasis model assessment for insulin resistance (HOMA-IR) index for estimating the association between the risk of developing metabolic glucose disorders and diabetes in relation with serum magnesium levels. The adjusted Poisson regression analysis also was used to examine the threshold of developing metabolic glucose disorders, for serum magnesium concentrations ranging from 0.35 to 1.15 mmol L\(^{-1}\).

A 95% confidence interval was computed and a two-sided \( P \)-value of < 0.05 defined the level of statistical significance.

Results

Of the 1122 individuals seen at the first examination, 90 (8.0%) had diabetes and were not included. Contact was re-established and participation obtained 10 years later in 817 (72.8%) individuals, for a total of 8735 person-years of follow-up. Of these, a total of 3351 and 5384 person-years of follow-up were completed for the subjects who at baseline had normal glucose tolerance or metabolic glucose disturbances, respectively.

Among the subjects who satisfactorily completed the follow-up period, at baseline 420 (51.4%) individuals had hypomagnesaemia. A total of 460 (56.3%) individuals exhibited metabolic glucose disorders, of these 273 (65.0%) and 187 (47.1%) in the exposed and non-exposed groups \( (P < 0.001) \), respectively.

Percentage of hyperglycaemia (67.9% vs. 45.1%, \( P < 0.0001 \)) and insulin resistance (41.0% vs. 21.2%, \( P < 0.0001 \)) was higher in the individuals with hypomagnesaemia. Individuals in the

### Table 1: Baseline characteristics of the subjects who satisfactorily completed the follow-up period

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of the subjects who satisfactorily completed the follow-up period</th>
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<tbody>
<tr>
<td><strong>NGT</strong></td>
<td>IFG</td>
</tr>
<tr>
<td><strong>Exposed</strong></td>
<td>Non-exposed</td>
</tr>
<tr>
<td>N</td>
<td>36 (29-47)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>89 (85-90)</td>
</tr>
<tr>
<td>Body mass index (kg m(^{-2}))</td>
<td>29.7 (28-32)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>81 (78-84)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>116.5 (105-126)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>70 (62-77)</td>
</tr>
<tr>
<td>2-h postload glucose (mmol L(^{-1}))</td>
<td>4.5 (4.0-5.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>66 (61-72)</td>
</tr>
<tr>
<td>Fasting insulin (pmol L(^{-1}))</td>
<td>54.6 (34.8-76.2)</td>
</tr>
<tr>
<td>HOMA-IR index</td>
<td>1.5 (1.2-1.9)</td>
</tr>
<tr>
<td>Serum magnesium (mmol L(^{-1}))</td>
<td>0.42 (0.37-0.48)</td>
</tr>
</tbody>
</table>

Data are median (interquartile range). Serum magnesium levels < 0.74 mmol L\(^{-1}\) defined the exposed group. \( P < 0.05 \) between exposed and non-exposed individuals within each category of glucose metabolic disorder.

MAGNESIUM AND GLUCOSE DISORDERS
non-exposed group exhibited higher percentage of family history of diabetes (69.6% vs. 56.2%, \( P < 0.0001 \)).

As shown in Table 1, the mean fasting glucose, insulin and 2-h postload glucose levels were higher in the subjects with hypomagnesaemia. Obesity and blood pressure were similar in both groups.

**New-onset metabolic glucose disorders**

At the second examination, new-onset metabolic glucose disorders were identified in 276 (33.8%) individuals, for a crude IR of 824 per 10 000 person-years. The crude IRs for IFG, IGT and IFG + IGT in the total population who at baseline had normal glucose tolerance were 516, 472 and 385 per 10 000 person-years, respectively.

The new-onset state of metabolic glucose disorders was more frequent in the individuals with hypomagnesaemia (crude IR = 815 per 10 000 persons-year) than in the non-exposed group (crude IR = 558 per 10 000 persons-year, \( P < 0.001 \)).

The crude IRs for IFG, IGT and IFG + IGT in the group with hypomagnesaemia were 281, 301 and 233 per 10 000 person-years, respectively. In the non-exposed group, the crude IRs for IFG, IGT and IFG + IGT were 236, 170 and 152 per 10 000 person-years, respectively.

Impaired glucose tolerance (25.1% and 13.7%, \( P = 0.006 \)) and IFG + IGT (19.4% and 12.3%, \( P = 0.03 \)), but not IFG (23.4% and 19.0%, \( P = 0.11 \)), were more frequent among the subjects in the exposed than in the non-exposed group.

**New-onset type 2 diabetes**

At the second examination, 10 years after the first one, new-onset diabetes was identified in 78 individuals for a crude IR of 145 per 10 000 person-years; of these, 61 and 17 individuals in the exposed and non-exposed groups, respectively.

The crude IR of new-onset state of diabetes was significantly more frequent in the individuals with hypomagnesaemia (crude IR = 105 per 10 000 persons-year) than in the non-exposed group (crude IR = 29 per 10 000 persons-year, \( P < 0.001 \)).

Individuals in the non-exposed group who developed diabetes were significantly older (57.7 ± 11.5 years vs. 47.5 ± 11.2 years, \( P = 0.002 \)) and had higher frequency of family history of diabetes (82.3% vs. 50.8%, \( P = 0.04 \)) than progressors to diabetes in the exposed group. On the other hand, progressors to diabetes in the exposed group had higher fasting insulin (171.6 ± 44.4 vs. 86.4 ± 36.6 pmol L\(^{-1} \), \( P < 0.0001 \)), HOMA-IR index (5.7 ± 2.2 vs. 2.4 ± 1.2, \( P < 0.0001 \)), and low serum magnesium levels (0.53 ± 0.12 vs. 0.91 ± 0.16 pmol L\(^{-1} \), \( P < 0.0001 \)) than progressors to diabetes in the non-exposed group.

Most progressors to diabetes in the non-exposed group (64.7%) were in the IFG + IGT category.

Table 2 shows results from Poisson regression models examining the incidence of new-onset metabolic glucose disturbances and type 2 diabetes in relation with serum magnesium levels. RRs indicated that individuals with hypomagnesaemia were at increased risk for IGT, IFG + IGT and type 2 diabetes. Adjusted by confounders, hypomagnesaemia remained significantly associated to the risk of IGT, IFG + IGT and type 2 diabetes, but not with IFG.

The adjusted Poisson regression models for analysing the threshold of developing metabolic glucose disorders for different serum magnesium levels show that individuals with severe hypomagnesaemia (serum magnesium ≤ 0.50 mmol L\(^{-1} \)) have an increased risk for IFG. The opposite showed that individuals with serum magnesium concentrations ≥ 1.05 mmol L\(^{-1} \) decreased the risk for developing IGT, IFG + IGT and type 2 diabetes (Fig. 1).

**Discussion**

Our results confirm the previously published work of others demonstrating the association between hypomagnesaemia and
incident type 2 diabetes. Furthermore, our results show that hypomagnesaemia (serum magnesium levels of < 0.74 mmol L⁻¹) predicts incident IGT and IFG + IGT, but not IFG, that severe hypomagnesaemia (serum magnesium of ≤ 0.50 mmol L⁻¹) predicts IFG, and that individuals with serum magnesium levels of ≥ 1.05 mmol L⁻¹ decreased their risk for developing IGT, IFG + IGT and type 2 diabetes.

Strengths of our study included a randomized population sampling, a longitudinal design of 10-year follow-up, a large sample size, and that glucose metabolism status was determined by OGTT, minimizing the possibility of bias selection, increasing the reliability of the statistical analysis, and the precision of the diagnosis of metabolic glucose disorders.

Limitations of our study that deserve to be mentioned are: First, measures of magnesium were limited to serum compartment. As magnesium predominantly is an intracellular ion and only the free or ionized fraction of magnesium is biologically active, we cannot exclude the possibility of pseudo-hypomagnesaemia [18]. However, we should keep in mind that the correlation between serum ionized and total magnesium in healthy subjects is 0.75 [19], and that although significant intracellular magnesium depletion could be seen with normal serum concentrations, once serum magnesium declines it is unlikely to find normal intracellular levels of magnesium [20]. Although misclassification of individuals with and without hypomagnesaemia could be a source of bias, it is limited to those individuals with hypomagnesaemia and normal intracellular magnesium status. In addition, the low intra- and interassay variation of magnesium in this study and the lack of consensus regarding the measurement of magnesium status increase the reliability of our results [21]. Nevertheless, the possibility that measurement of magnesium in serum compartment was a source for underestimating the association between magnesium status and development of metabolic glucose disorders should be kept in mind. Second, we did not measure baseline food and water intake of magnesium. Questionnaires may provide reliable dietary information [11], but since finding the source of hypomagnesaemia in the targeted population was not an original objective in this study, they were not applied.
Magnesium, the second most abundant intracellular cation, is an essential cofactor of high-energy phosphate bounds enzymatic pathways involved in the energetic metabolism and modulation of glucose transport across cell membranes [21–23].

From the early 1980s, the importance that magnesium has on improving insulin sensitivity and insulin-mediated glucose uptake has been suggested [24]. Evidences showing the advantages of an appropriate dietary magnesium intake in the reduction of the risk of type 2 diabetes and on the improvement of insulin homeostasis [13] as well as regarding the potential benefits of dietary magnesium supplementation as adjuvant in the management of diabetes [9,23] and prediabetes [10] are rapidly accumulating.

Large longitudinal studies on population-based sampling strategies consistently show the strong association between deficient dietary magnesium intake and the increase incidence of diabetes [3,11–13], suggesting that higher intake of magnesium may reduce new-onset diabetes among middle-aged individuals [12].

To date, only Kao et al., based on a 6-year follow-up study that enrolled nondiabetic middle aged adults, from the Atherosclerosis Risk in Communities (ARIC) study, has evaluated the association between serum magnesium levels and incident type 2 diabetes [3]. They found a strong association between hypomagnesaemia and the risk for diabetes in white middle-aged participants. Our results, showing a strong association between hypomagnesaemia and new-onset type 2 diabetes are consistent with previous report by Kao et al. [3]. However, because all participants in our study were from the same ethnic group, we did not test possible differences attributable to ethnicity, as suggested by Kao et al. [3], for explaining the lack of association between hypomagnesaemia and the incidence of diabetes in the African American participants in the ARIC Study. Further studies are needed to determine the role of ethnicity in the pathways of glucose and energy metabolism that are dependents of magnesium.

Furthermore, ours results show for the first time an association between hypomagnesaemia and new-onset of IGT and IFG + IGT. Magnesium depletion results in defective tyrosine-kinase activity and reduction of autophosphorylation on the beta-subunit at the insulin receptor level that decrease insulin sensitivity and deteriorate glucose uptake [7,25], promoting the development of metabolic glucose disturbances. In this regard, the association between hypomagnesaemia and new-onset IGT could be explained, but the lack of association between hypomagnesaemia and incidence of IFG was unexpected.

Why is hypomagnesaemia associated with IGT but not with IFG? First, analysis of data from the Baltimore Longitudinal Study of Aging suggests the presence of at least two distinct phenotypic pathways in the evolution of type 2 diabetes [26]. The more common pathway seems to be the development of abnormal postload glucose with normal FPG levels. This pathway is characterized by a prolonged decrease in glucose tolerance with slow progression from normal glucose tolerance to IGT to diabetes. Only a few subjects on this pathway show IFG. A less common pathway includes development of IFG and, more rarely, development of diabetic FPG levels. This pathway is featured by slower progression from normal glucose tolerance to diabetes and most subjects developed IGT. These two phenotypes, abnormal postload glucose alone or abnormal FPG in combination with abnormal postload glucose, are present in the progression from normal glucose tolerance to diabetes but often the two pathways remained exclusive [26]. Second, although both IFG and IGT are prediabetic states with similar risk factors, IGT is a more advanced stage of alteration in the glucose metabolism, with a significant decrease of insulin sensitivity and insulin secretion than the IFG [27]. Finally, studies in Pima Indians showed that individuals with isolated IFG had a greater impairment in the first-phase insulin secretion and higher basal hepatic endogenous glucose output than subjects with isolated IGT [28], suggesting that abnormal FPG and postload glucose levels are not necessarily part of a continuum in the evolution of diabetes [26]. It is possible that magnesium’s influence on glucose metabolism could be different according to the pathway involved. Interestingly, when we analysed the threshold for different serum magnesium concentrations, individuals with severe hypomagnesaemia were at increased risk for IFG, suggesting that other mechanisms such as secondary hypocalcaemia, impairment in endocrine function, increased inflammatory response, and interference with the generation of cAMP may contribute in detriment of the metabolic glucose pathways [29]. Further research is needed in this regard.

On the other hand, our results also indicate a protective role of serum magnesium levels of up to 1.05 mmol L⁻¹, a finding that agrees with previous reports that show the beneficial effect of magnesium supplementation in the improvement of insulin sensitivity in nondiabetic subjects [10,23,30].

In summary, our data show that hypomagnesaemia is independently associated with the development of IGT, IFG + IGT and type 2 diabetes. Because serum magnesium levels are easy to detect and hypomagnesaemia is easy to correct, our finding may have implications in the planning of strategies for the prevention of diabetes.

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