Journal of Human Hypertension (2008), 1–7

www.nature.com/jhh

ORIGINAL ARTICLE

The effect of lowering blood pressure by magnesium supplementation in diabetic hypertensive adults with low serum magnesium levels: a randomized, double-blind, placebo-controlled clinical trial

F Guerrero-Romero and M Rodríguez-Morán
Biomedical Research Unit of the Mexican Social Security Institute, Research Group on Diabetes and Chronic Illnesses, and Nucleus of Research and Clinical Diagnosis (NIDIAC), Durango, Mexico

To test the blood pressure (BP)-lowering effect of oral magnesium supplementation (that is, magnesium chloride ($MgCl_2$) solution) in diabetic hypertensive adults with hypomagnesaemia not on diuretic treatment but receiving concurrent captopril, we conducted a double-blind, placebo-controlled trial. Eighty-two subjects between 40 and 75 years of age were randomly enrolled. Over 4 months, subjects in the intervention group received 2.5 g of $MgCl_2$ (50 ml of a solution containing 50 g of $MgCl_2$ per 1000 ml of solution) equivalent to 450 mg of elemental magnesium, and control subjects inert placebo. The primary trial end point was a reduction in systolic (SBP) and diastolic (DBP) blood pressure. Complete follow-up was achieved for 79 of the 82 randomized subjects. SBP (-20.4 ± 15.9 versus -4.7 ± 12.7 mm Hg, $P=0.03$) and DBP (-8.7 ± 16.3 versus -1.2 ± 12.6 mm Hg, $P=0.02$) showed significant decreases, and high-density lipoprotein-cholesterol (0.1 ± 0.6 versus -0.1 ± 0.7 mmol l^{-1}, $P=0.04$) a significant increase in the magnesium group compared to the placebo group. The adjusted odds ratio between serum magnesium and BP was 2.8 (95%CI: 1.4–6.9). Oral magnesium supplementation with $MgCl_2$ significantly reduces SBP and DBP in diabetic hypertensive adults with hypomagnesaemia.
Journal of Human Hypertension advance online publication, 20 November 2008; doi:10.1038/jhh.2008.129

Keywords: magnesium; diabetes; hypomagnesaemia

Introduction

Magnesium is an essential cofactor of high-energy phosphate bonds in enzymatic pathways involved in the metabolism and synthesis of protein, and plays a key role in regulating insulin action, insulin-mediated glucose uptake, vascular tone and blood pressure homoeostasis.[1–4] Magnesium also can stimulate both tyrosine kinase[1] and cell membrane calcium ATPase activity, as well as modulate calcium binding and release from the sarcoplasmic reticulum, resulting in an enhanced ability to pump calcium from the cell, essentially acting as a calcium blocker.[5,6] Thus, magnesium may be aetiologically related to insulin resistance, type 2 diabetes and hypertension.[1,3]

Correspondence: Dr M Rodríguez-Morán, Biomedical Research Unit, Instituto Mexicano del Seguro Social, Siqueiros 225 esq/castañeda, 34000, Durango, Dgo. 34000, Mexico.
E-mail: rodriguez_moran@hotmail.com
Received 12 July 2008; revised 18 September 2008; accepted 20 September 2008

Clinical evidence regarding the inverse association between magnesium and blood pressure (BP) has emerged largely from cross-sectional and longitudinal population studies;[7,8] however, data from clinical trials on the effects of lowering BP by magnesium supplementation have been inconsistent, with some studies showing a significant reduction in the BP[9–12] but not others.[13–15]

Even though the incidence of hypomagnesaemia among patients with type 2 diabetes can reach 13.5–47.7%[16] and that hypomagnesaemia has been linked to hypertension,[3,17] there are no earlier reports based on randomized, placebo-controlled trials about the efficacy of magnesium supplementation in the treatment of hypertension in patients with type 2 diabetes.[3] In this study, we tested the hypothesis that magnesium supplementation (that is, magnesium chloride ($MgCl_2$) solution) exerts a BP-lowering effect in diabetic hypertensive adults with low serum magnesium levels who are not on diuretic treatment but are receiving concurrent captopril.

Materials and methods

With protocol approval by the Mexican Social Security Institute (MSSI) Research Committee and after obtaining subject informed consent, a randomized, double-blind, placebo-controlled trial[18,19] was carried out from July 2006 to August 2007.

Participants, aged 40–75 years, were recruited from outpatients at the Primary Level Medical Care Office at Durango, Mexico. Diabetic hypertensive adults with low serum magnesium levels not on diuretic treatment but receiving concurrent captopril were candidates for inclusion in the study. They were not admitted to the study if any of the following criteria were present: chronic diarrhoea, alcohol intake (equal to or more than 30 g day^{-1}), use of diuretics and/or calcium antagonist drugs, previous oral magnesium supplementation, ischaemic diseases and renal damage. For this purpose, before randomization, all patients were clinically evaluated and laboratory test were performed to verify that they had no exclusion criteria. In this regard, renal damage was defined by the presence of albuminuria equal or greater than 300 mg per 100 ml.

On the basis of previous results from healthy subjects of our population,[20] decreased serum magnesium levels were defined by magnesium concentrations $\leqslant 0.74$ mmol l^{-1}.

The primary trial end point was a reduction in the systolic (SBP) and diastolic (DBP) BP to the levels lower than 140 and 90 mm Hg, respectively.

Sample size estimation was based on a statistical power of 80% with a 0.05 α and an expected BP decrease of 75 and 35% for the subjects receiving magnesium supplementation and placebo, respectively. The required sample size to detect a treatment effect was of 35 subjects per group. To compensate for patients with limited data, we planed to enroll 40 patients per group. Computer-generated random numbers were used to assign participants to the oral magnesium supplementation or placebo groups. The final distribution was 42 subjects with magnesium supplementation and 40 subjects in the placebo group (Figure 1). Because $MgCl_2$ solution shows a higher bioavailability than other commercial magnesium preparations,[21] the $MgCl_2$ solution (50 g of $MgCl_2$ by 1000 ml of solution 5% solution) was the magnesium supplement used. Under fasting conditions, subjects in the magnesium group drank 50 ml of a solution containing 50 g of $MgCl_2$ in 1000 ml of solution (5% solution) to receive 2.5 g of $MgCl_2$ daily, equivalent to 450 mg of elemental magnesium, that correspond to approximately 7% in excess (for compensate the hypomagnesaemia) to the recommended dietary allowance for adult men and postmenopausal women (420 mg).[22,23]

Subjects were assigned on an individual basis to magnesium and placebo groups. They remained in the same allocation through the period of intervention.

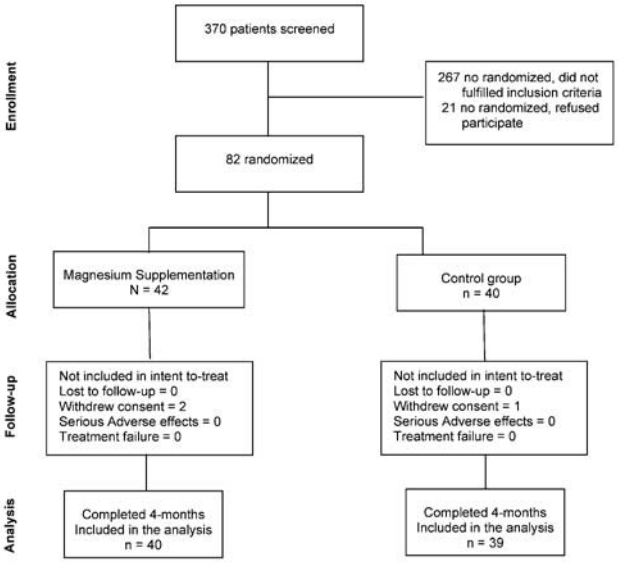

Figure 1 Study participant flow diagram. The diagram includes the number of patients actively followed at different times during the trial.

All personnel and participants were blinded to treatment assignment during duration of the study.

One week before beginning the trial, subjects were withdrawn from antihypertensive pharmacological treatment and other drugs. According to the age and physical condition of each participant, all the subjects were advised to perform mild-to-moderate physical activity with a goal of 30 min of physical activity at least three times per week. Glibenclamide was started and individually adjusted to achieve glucose control. In addition, subjects who were receiving hypolipemiant treatment started with pravastatin or fibrates that were maintained without changes during the study. Subjects in both groups received 25 mg of captopril daily, which remained without changes during the study period.

At baseline and after 4 months of treatment, anthropometric measurements, fasting plasma glucoseFPG, haemoglobin A1c level and lipid profile were measured. BP and serum magnesium levels were measured every month. SBP and DBP were obtained by trained personnel who were blinded to the participant's treatment assignment.

Adherence to pharmacological treatment and lifestyle intervention were assessed every month by personal interview, tablet count and measurement of remaining solution.

Hypertension was defined by SBP and DBP equal to or higher than 140 and/or 90 mm Hg, respectively.[24]

Measurements

Brachial artery BP was measured in seated participants after they had rested for 5 min with the use of a baumanometer (Microlife AG, Heerbrugg Switzerland) and stethoscope (3M Littman Classic II, Neuss,

Germany). An appropriately sized cuff was placed on the left arm, pulse occlusion pressure was determined, and the cuff was inflated to 20 mm Hg above that pressure. SBP was defined as the first appearance of sound (Korotkoff phase 1), and DBP by the disappearance of sound (Korotkoff phase 5). The technique of BP measurement and stages of hypertension were defined by criteria scheduled in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[24]

Height and weight were taken using the standard protocols with the subjects in light clothing and without shoes. Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference was the minimum circumference at umbilicus level.

Assays

Serum magnesium concentrations were measured by colorimetric method; the intra- and inter-assay variations were 1.0 and 2.5%, respectively. Serum glucose was measured by the glucose-oxidase method; the intra- and inter-assay variations were 2.5 and 4.0%, respectively. Triglycerides were measured enzymatically, and the high-density lipoprotein (HDL) cholesterol fraction was obtained after precipitation by phosphotungstic reagent. The respective intra- and inter-assay coefficients of variation were 1.7 and 3.1% for triglycerides and 1.3 and 2.6% for HDL cholesterol.

Statistical analysis

All data analysis was carried out according to our pre-established plan. The preplanned intention-to-treat analysis of the primary study end point was performed on all randomly allocated participants who satisfactorily completed follow-up (Figure 1).

For comparison of normally distributed variables, we used a two-tailed, unpaired, Student *t*-test (or Mann–Whitney *U*-test for skewed data) to establish the differences between the groups. The χ^2 test with continuity correction or Fisher's exact test, when appropriate, was used for testing differences between categorical variables.

The relationship between variations of serum magnesium levels (independent variable) and BP (dependent variable) was established by calculating the odds ratio (OR) using multivariate logistic regression analysis. Values of SBP and DBP less than 140 and 90 mm Hg, respectively, were the primary trial and the expected outcome. The model was adjusted by age, sex, body mass index and waist circumference.

A 95% confidence interval ($CI_{95\%}$) was considered, and *P*-value <0.05 defined the level of statistical significance. Data analysis was performed using the SPSS 10.0 statistical package (SPSS Inc., Chicago, IL, USA, 1998).

Results

A total of 370 patients were screened between July 2006 and January 2007; of these, 267 subjects did not satisfactorily fulfill the inclusion criteria. Among the 103 (27.8%) with hypomagnesaemia, 21 refused to participate. Therefore, a total of 82 individuals were randomized to receive either $MgCl_2$ solution or placebo. A total of 42 and 40 individuals were allocated in the magnesium and placebo groups, respectively. Three subjects (3.6%) withdrew consent (two in the $MgCl_2$ group and one in placebo group; Figure 1). The magnesium supplement was well tolerated, and there were no serious adverse events or side effects. Mild abdominal pain and occasional diarrhoea that did not require discontinuation of magnesium or additional treatment was present in six (14.3%) patients; of these, four were in the $MgCl_2$ group and two were in the placebo group. There were no protocol deviations or forced withdrawals due to elevated BP in the study group. A total of 49 (62%) participants required treatment with pravastatin or fibrates (22 and 27 individuals in the groups of magnesium and placebo, respectively, $P=0.28$)

A total of 40 and 39 subjects in the magnesium and placebo groups, respectively, who satisfactorily completed the follow-up, were included in the analysis of data. Both groups achieved appropriate adherence to pharmacological treatment (92.5 versus 92.3% of subjects in the magnesium and placebo groups, $P=0.98$) and lifestyle changes (95 versus 92.3% of subjects in the magnesium and placebo groups, $P=0.67$).

Glibenclamide (an average of 15 mg daily in both groups) required no changes during the period of study for all participants.

General characteristics of the enrolled population are shown in Table 1. There were no differences by sex, age, duration of diabetes, duration of hypertension and anthropometric measurements between the magnesium and placebo groups.

At baseline, SBP and DBP as well as lipid profile, fasting plasma glucose, haemoglobin A1c level and serum electrolyte concentrations were similar, without significant statistical differences between the groups. Sodium concentration was slightly higher ($P=0.048$) in the magnesium group compared to the placebo group.

Table 2 shows the outcomes by randomized groups. The SBP and DBP showed a significant decrease and HDL-cholesterol a significant increase in the magnesium group compared to the placebo group. Fasting plasma glucose and haemoglobin A1c level exhibited an important reduction; however, there were no significant statistical differences between the groups. Serum concentrations of calcium, potassium and sodium remained without significant changes in both the magnesium and placebo groups.

Table 1 General characteristics at baseline of subjects randomly allocated to receive magnesium chloride, 2.5 g daily (magnesium group), or placebo by 4 months ($n = 79$)

	Overall (n = *79*)	*Magnesium* (n = *40*)	*Placebo* (n = *39*)	P-*value**
Male/female (%)	48.1/51.9	47.5/52.5	48.7/51.3	0.91
Age (years)	59.5 ± 8.9	58.9 ± 8.5	60.5 ± 9.4	0.41
Body mass index (kg m^{-2})	29.5 ± 5.3	29.9 ± 5.2	29.0 ± 5.1	0.43
Waist circumference (cm)	107.5 ± 11.0	108.8 ± 9.7	107.0 ± 11.8	0.18
Duration of hypertension (years)	7.4 ± 9.0	8.5 ± 10.5	6.2 ± 7.2	0.23
Duration of diabetes (years)	10.4 ± 6.1	10.4 ± 6.3	10.5 ± 6.0	0.92

**P*-value between magnesium and placebo groups.

Table 2 Baseline and final characteristics of subjects randomly allocated to receive magnesium chloride, 2.5 g daily (Magnesium group), or placebo by 4 months ($n = 79$)

	Magnesium (n = *40*)			*Placebo* (n = *39*)			*Difference in change***	P-*value*‡
	Baseline	*Final*	*Change*	*Baseline*	*Final*	*Change*		
Body mass index	29.9 ± 5.2	29.4 ± 4.7	−0.5 ± 1.7	29.0 ± 5.1	28.6 ± 4.9	−0.4 ± 1.5	−0.2 (−0.9 to 0.1)	0.35
Systolic blood pressure (mm Hg)	161.1 ± 26.0	140.7 ± 11.9	−20.4 ± 15.9†	154.5 ± 21.2	149.8 ± 20.6	−4.7 ± 12.7	−16.1 (−27.1 to −5.1)	0.03
Diastolic blood pressure (mm Hg)	88.4 ± 14.5	79.7 ± 7.1	−8.7 ± 16.3†	84.9 ± 12.4	83.8 ± 9.7	−1.2 ± 12.6	−7.9 (−12.6 to −3.1)	0.02
Fasting plasma glucose (mmol l^{-1})	13.6 ± 3.7	9.3 ± 1.6†	−4.3 ± 4.0†	12.6 ± 4.0	9.3 ± 1.8	−3.3 ± 4.2†	−0.8 (−5.1 to 4.3)	0.27
Hemoglobin bA1c level (%)	13.4 ± 3.9	8.9 ± 1.8	−4.5 ± 3.8†	11.9 ± 3.9	8.7 ± 2.2	−3.2 ± 2.1†	−1.3 (−3.0 to −0.4)	0.06
Triglycerides (mmol l^{-1})	2.9 ± 1.4	2.8 ± 1.8	−0.1 ± 2.2	2.6 ± 1.8	2.5 ± 1.3	−0.1 ± 1.9	0 (−6.4 to 6.5)	0.91
HDL-cholesterol (mmol l^{-1})	1.0 ± 0.4	1.1 ± 0.4	0.1 ± 0.6	0.9 ± 0.5	0.8 ± 0.4	−0.1 ± 0.7	0.2 (−0.8 to 1.2)	0.04
Calcium (mmol l^{-1})	2.6 ± 0.3	2.8 ± 0.4	0.2 ± 0.3	2.7 ± 0.5	2.8 ± 0.3	0.1 ± 0.3	0.1 (−0.7 to 0.9)	0.11
Sodium (mmol l^{-1})	153.6 ± 7.1	153.1 ± 8.6	−0.6 ± 0.9	147.9 ± 5.5*	148.2 ± 6.1	−0.3 ± 0.6	−0.4 (−4.4 to 2.8)	0.25
Potassium (mmol l^{-1})	5.1 ± 0.5	5.3 ± 0.9	−0.03 ± 0.4	5.2 ± 0.7	5.0 ± 0.9	−0.02 ± 0.6	−0.01 (−0.3 to 0.3)	0.46
Magnesium (mmol l^{-1})	0.62 ± 0.10	0.81 ± 0.11	0.18 ± 0.10	0.61 ± 0.10	0.68 ± 0.11	0.08 ± 0.14	0.10 (0.03 to 0.17)	0.002

**P*-value <0.05 between magnesium and placebo groups at baseline.
**Mean (95% confidence interval).
†*P*-value <0.05 between baseline and final condition within group.
‡*P*-value of difference between groups.

During the 4 months of treatment, serum magnesium concentrations in the magnesium group, compared to the placebo group, gradually increased reaching significance in the third month (Figure 2); and BP gradually decreased reaching significance in the fourth month of treatment (Figure 3). There was a significant inverse correlationship between the increase in serum magnesium and the decrease in SBP ($r = -0.245$, $P = 0.005$) and DBP ($r = -0.143$, $P = 0.02$).

The adjusted OR (by age, sex, body mass index and waist circumference) that computes the relationship between the improvement in the serum magnesium levels and reduction in BP was 2.8 (95% CI: 1.4–6.9). After additional adjustments of the logistic regression analysis by risk factors such as physical activity (OR 2.65; 95% CI 1.2–15.4), haemoglobin A1c level (OR 2.42; 95% CI 1.2–9.7), triglycerides level (OR 2.51; 95% CI 1.7–18.1) and HDL-cholesterol level (OR 2.11; 95% CI 1.5–11.4), the improvement of serum magnesium levels remained strongly associated with BP reduction.

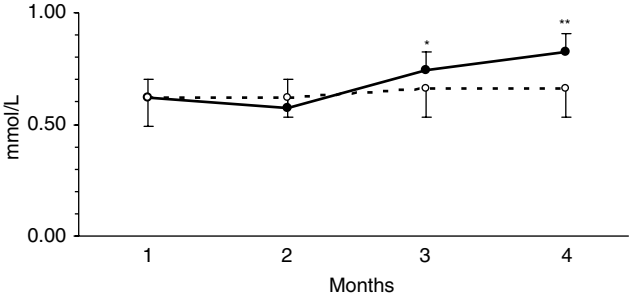

Figure 2 Mean and standard deviation of serum magnesium concentrations in the 40 subjects who received magnesium chloride (black circles) and the 31 placebo recipients (white circles). Magnesium levels, in the subjects who received magnesium supplementation, showed a gradual increase that reach significance at the third month of treatment. *$P = 0.001$; **$P < 0.00001$.

Discussion

Results of this study demonstrate that magnesium supplementation significantly reduces BP in

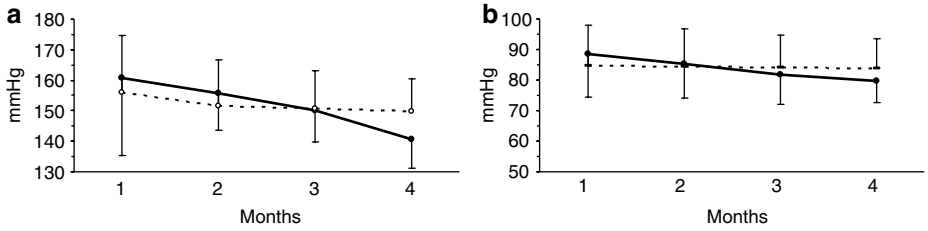

Figure 3 Systolic (SBP) (**a**) and diastolic (DBP) (**b**) blood pressures in the subjects who received magnesium supplementation (black circles) or placebo (white circles). At the end of 4 months of treatment, systolic and diastolic blood pressures significantly decreased in the magnesium supplementation group reaching significance at the fourth month of treatment. $^{*}P<0.0001$.

diabetic hypertensive adults not on diuretic treatment receiving concurrent captopril.

From the earliest 1980s, the important role of magnesium on BP regulation[25,26] has been supported in the following years by experimental studies that show the possible mechanisms involved in the antihypertensive effects of magnesium.[27] Among these, it has been reported that magnesium inhibits the effect of calcium from vascular smooth muscle sarcoplasmic reticulum by competition for a calcium receptor on a calcium-regulated efflux channel,[28] essentially acting as a calcium blocker. Recently, two cation channels of the transient receptor potential melastatin cation channel family have been identified as magnesium transporters and implicated as a signalling kinase involved in vascular smooth muscle cell growth, apoptosis, adhesion, contraction, cytoskeleton organization and migration, as well as important processes involved in vascular remodelling associated with hypertension and other vascular diseases.[29]

The effect of magnesium supplementation on SBP and DBP in this study was higher than reported in previous studies using different magnesium salts,[9–12,30,31] but similar with a previous non-randomized study with $MgCl_2$ in which both SBP and DBP decreased significantly, by a mean of 13 ± 9 mm Hg.[32] It has been reported that $MgCl_2$ shows a higher bioavailability than other commercial magnesium preparations,[21] circumstance that could be involved in a better response using this salt for magnesium supplementation. In addition to the salt used, differences in the reduction of BP between our results and those of others could be explained also by methodological issues. In this regard, we conducted a randomized clinical trial that compared the effect of magnesium supplementation among hypertensive subjects receiving concurrent captopril; however, in other studies, the effect of magnesium supplementation has been evaluated in randomized clinical trials that compared magnesium versus placebo.[10–13,31] It has been suggested that magnesium may attenuate the biological actions of angiotensin II,[33] which inhibits norepinephrine release,[34] and that a direct calcium antagonist effect of magnesium at the cellular level might be involved in the BP effects of magnesium;[35] furthermore, it has also been reported that captopril increases cytosolic-free magnesium levels[36] and that the BP reduction with oral magnesium supplementation is significantly higher among patients with elevated levels of plasma rennin activity.[37] In this regard, it is possible that the greater reduction of BP that we observed could be related with a synergic action of $MgCl_2$ and captopril and/or that our patients have high levels of plasma rennin activity. Further research is needed to clarify the exact mechanisms of magnesium regulation in the cardiovascular system and the implications in the pathogenesis of hypertension.

On the other hand, taking into account the age and the duration of diabetes and hypertension of our target population maybe the atherosclerosis, that promotes stiffness and decrease elasticity of the wall of arteries,[38,39] is involved in the high variability of the BP response that we observed in both groups.

However, the benefits of oral magnesium supplementation in hypertensive subjects are controversial.[8–15,40] Inconsistencies between the studies showing the efficacy or the lack of effect of oral magnesium on high BP can be explained based on several issues; among the most important are differences in the type and doses of supplemental magnesium used, magnesium status, duration of intervention and the stage of hypertension. Because differences in the methodology imply differences in the external validity of the studies, comparing results could be inappropriate. Nonetheless, a conclusion can be addressed, and it is that oral supplementation with magnesium seems to be effective for lowering BP in hypertensive diabetic subjects with magnesium depletion.[15]

Our results demonstrate that oral magnesium supplementation is useful in the treatment of hypertension in hypomagnesemic adults with diabetes, a well-known condition that facilitates the development of magnesium deficiency and hypertension.[6,8] In addition, our data supports the statement that magnesium supplementation should be considered as an alternative or adjuvant for treatment of hypertension in patients with risk factors for hypomagnesaemia and should be instituted for patients with magnesium deficiency and hypertension.

Furthermore, at the end of 4 months of treatment, HDL cholesterol significantly improved in the magnesium group compared to the placebo group. Further research is warranted to appropriately establish the benefit of magnesium supplementation on HDL cholesterol levels.

The main limitation of this study was not measuring intracellular magnesium content or ionized magnesium. As magnesium is a predominantly intracellular ion, its serum measurements are not representative of magnesium status or the intracellular pool. Intracellular magnesium depletion could be seen with normal serum concentrations but not the opposite.[41] Therefore, we included only patients with decreased serum magnesium levels. The possibility of normal intracellular magnesium in the study population, which might be a source of bias, is minimal and does not influence our conclusions. Furthermore, because our stringent inclusion criteria, the results of this study cannot be extrapolated to all patients seen in general clinical practice.

On the other hand, the main strength of this study is the homogeneous population enrolled including only hypomagnesemic diabetic patients with an average BP greater than 140 mm Hg.

The use of diuretics in subjects with diabetes and hypertension deserves particular attention. Because the occurrence of diabetes and hypertension are multiplicative risk factors for macro- and microvascular disease and determinants of cardiovascular outcomes,[42] the tight control of BP and glycemia in diabetic hypertensive patients is strongly recommended for preventing cardiovascular events.[43] In clinical practice, it is almost impossible to control the BP in diabetic patients without the use of diuretics.[42] Although diuretics are frequently needed to control BP in patients with diabetes, their use contributes to the development of hypokalaemia and hypomagnesaemia.[44,45] This finding emphasizes the possible benefit of oral magnesium supplementation in diabetic hypertensive adults on diuretic therapy. In this study, the enrolled patients did not receive diuretic treatment; further research is needed to appropriately demonstrate the efficacy of magnesium supplementation in the diabetic subjects receiving diuretic therapy.

In text table, oral magnesium supplementation with $MgCl_2$ significantly reduces SBP and DBP in hypertensive adults with type 2 diabetes and low serum magnesium levels.

What is known about topic

- Magnesium is related with the physiopathology of type 2 diabetes and hypertension.
- There is an inverse association between magnesium and blood pressure.
- Data from clinical trials on the blood pressure lowering-effects of magnesium supplementation are inconsistent.

What this study adds

- This report is the first randomized placebo-controlled trial on the efficacy of magnesium supplementation in the treatment of hypertensive type 2 diabetic patients.
- Oral magnesium supplementation is useful in the treatment of uncomplicated hypertension in hypomagnesaemic patients with type 2 diabetes.

Acknowledgements

We gratefully acknowledge the commitment and dedication of the physicians, chemists and participant personnel of the Biomedical Research Unit of the Mexican Security Institute at Durango in charge of the patient enrolment and follow-up. This study was supported by grants from the Fundación IMSS, AC from Mexico.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1 Barbagallo M, Dominguez LJ. Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. *Arch Biochem Biophys* 2007; **458**: 40–47.
2 Paolisso G, Scheen A, D'Onofrio F, Lefèbvre P. Magnesium and glucose homeostasis. *Diabetologia* 1990; **33**: 511–514.
3 Barbagallo M, Dominguez LJ, Resnick LM. Magnesium metabolism in hypertension and type 2 diabetes mellitus. *Am J Ther* 2007; **14**: 375–385.
4 Guerrero-Romero F, Rodríguez-Morán M. Complementary therapies for diabetes: the case for chromium, magnesium, and antioxidants. *Arch Med Res* 2005; **36**: 250–257.
5 Altura BM, Altura BT. Role of magnesium in the pathogenesis of hypertension updated: relationship to its actions on cardiac, vascular smooth muscle, and endothelial cells. In: Laragh JH, Brenner BM (eds.). *Hypertension: Pathophysiology, Diagnosis, and Management*, 2nd edn, Raven Press: New York, NY, 1995, pp 1213–1242.
6 Altura BM, Altura BT. Magnesium ions and contraction of vascular smooth muscles: relationship to some vascular diseases. *Fed Proc* 1981; **40**: 2672–2679.
7 Joffres MR, Reed DM, Yano K. Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu heart study. *Am J Clin Nutr* 1987; **45**: 469–475.
8 Ascherio A, Hennekens Ch, Willett WC, Sacks F, Rosner B, Manson J *et al.* Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension* 1996; **27**: 1065–1072.
9 Motoyama T, Sano H, Fukuzaky H. Oral magnesium supplementation in patients with essential hypertension. *Hypertension* 1989; **13**: 227–232.
10 Witteman JC, Grobbee DE, Derkx FH, Bouillon R, de Bruijn AM, Hofman A. Reduction of blood pressure with oral magnesium supplementation in women with mild to moderate hypertension. *Am J Clin Nutr* 1994; **60**: 129–135.
11 Yokota K, Kato M, Lister F, Ii H, Hayakawa T, Kikuta T *et al.* Clinical efficacy of magnesium supplementation in patients with type 2 diabetes. *J Am Coll Nutr* 2004; **23**: 506S–509S.
12 Kawano Y, Matsuoka H, Takishita S, Omae T. Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. *Hypertension* 1998; **32**: 260–265.

13 Ferrara LA, Iannuzzi R, Castaldo A, Iannuzzi A, Dello Russo A, Mancini M. Long-term magnesium supplementation in essential hypertension. *Cardiology* 1992; **81**: 25–33.
14 Cappuccio FP, Markandu ND, Beynon GW, Shore AC, Sampson B, MacGregor GA. Lack of effect of oral magnesium on high blood pressure: a double blind study. *Br Med J (Clin Res Ed)* 1985; **291**(6490): 235–238.
15 Zemel PC, Zemel MB, Urberg M, Douglas FL, Geiser R, Sowers JR. Metabolic and hemodynamic effects of magnesium supplementation in patients with essential hypertension. *Am J Clin Nutr* 1990; **51**: 665–669.
16 Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2007; **2**: 366–373.
17 Altura BM, Altura BT, Gebrewold A, Ising H, Günther T. Magnesium deficiency and hypertension: correlation between magnesium-deficient diets and microcirculatory changes *in situ*. *Science* 1984; **223**: 1315–1317.
18 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Ann Intern Med* 2001; **134**: 657–662.
19 Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D *et al.* The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001; **134**: 663–694.
20 Guerrero-Romero F, Rodríguez-Morán M. Relationship between serum magnesium levels and C-reactive protein concentration, in non-diabetic, non-hypertensive obese subjects. *Int J Obes Relat Metab Disord* 2002; **26**: 469–474.
21 Firoz M, Graber M. Bioavailability of US comercial magnesium preparations. *Magnes Res* 2001; **14**: 257–262.
22 Laires MJ, Moreira H, Monteiro CP, Sardinha L, Limão F, Veiga L *et al.* Magnesium, insulin resistance and body composition in healthy postmenopausal women. *J Am Coll Nutr* 2004; **23**: 510S–513S.
23 Ford ES, Mokdad AH. Dietary magnesium intake in a national sample of US adults. *J Nutr* 2003; **133**: 2879–2882.
24 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL *et al.* The National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206–1252.
25 Altura BM, Altura BT. Interactions of Mg and K on blood vessels—aspects in view of hypertension. Review of present status and new findings. *Magnesium* 1984; **3**: 175–194.
26 Altura BM, Altura BT, Carella A, Turlapaty PD. $Ca2^{+}$ coupling in vascular smooth muscle: $Mg2^{+}$ and buffer effects on contractility and membrane $Ca2^{+}$ movements. *Can J Physiol Pharmacol* 1982; **60**: 459–482.
27 Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, Nishio A. $Mg2^{+}$–$Ca2^{+}$ interaction in contractility of vascular smooth muscle: $Mg2^{+}$ versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. *Can J Physiol Pharmacol* 1987; **654**: 729–745.
28 Stephenson EW, Podolsky RJ. Regulation by magnesium of intracellular calcium movement in skinned muscle fibers. *J Gen Physiol* 1977; **69**: 1–16.
29 Touyz RM. Transient receptor potential melastatin 6 and 7 channels, magnesium transport and vascular biology: implications in hypertension. *Am J Physiol Heart Circ Physiol* 2008; **294**(3): H1103–H1118.
30 Jee SH, Miller III ER, Guallar E, Singh VK, Appel LJ, Klag MJ. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. *Am J Hypertens* 2002; **15**: 691–696.
31 Kawasaki T, Itoh K, Kawasaki M. Reduction in blood pressure with a sodium-reduced, potassium- and magnesium-enriched mineral salt in subjects with mild essential hypertension. *Hypertens Res* 1998; **21**: 235–243.
32 Shafique M, Misbah-ul-Ain, Ashraf M. Role of magnesium in the management of hypertension. *J Pak Med Assoc* 1993; **43**: 77–78.
33 Atarashi K, Takagi M, Matsuoka H, Sugimoto T. Effects of magnesium on changes in blood pressure and plasma aldosterone induced by angiotensin II. *Am J Hypertens* 1990; **3**(6 Part 1): 488–490.
34 Shimosawa T, Takano K, Ando K, Fujita T. Magnesium inhibits norepinephrine release by blocking N-type calcium channels at peripheral sympathetic nerve endings. *Hypertension* 2004; **44**: 897–902.
35 Lind L, Lithell H, Pollare T, Ljunghall S. Blood pressure response during long-term treatment with magnesium is dependent on magnesium status. A double-blind, placebo-controlled study in essential hypertension and in subjects with high-normal blood pressure. *Am J Hypertens* 1991; **4**: 674–679.
36 Barbagallo M, Dominguez LJ, Resnick LM. Protective effects of captopril against ischemic stress: role of cellular Mg. *Hypertension* 1999; **34**(4 Part 2): 958–963.
37 Motoyama T, Sano H, Fukuzaki H. Oral magnesium supplementation in patients with essential hypertension. *Hypertension* 1989; **13**: 227–232.
38 Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M *et al.* Arterial stiffness and the development of hypertension. The ARIC study. *Hypertension* 1999; **34**: 201–206.
39 Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation* 1995; **91**: 1432–1443.
40 Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. *JAMA* 1992; **267**: 1213–1220.
41 Reinhart R, Marx J, Haas R, Desbiens N. Intracellular magnesium of mononuclear cells from venous blood of clinical healthy subjects. *Clin Chim Acta* 1988; **48**: 2415–2420.
42 Zanella MT, Kohlmann Jr O, Ribeiro AB. Treatment of obesity, hypertension, and diabetes syndrome. *Hypertension* 2001; **38**: 705–708.
43 Snow V, Weiss KB, Mottur-Pilson C, Clinical Efficacy Assessment Subcommittee of the American College of Physicians. The evidence base for tight blood pressure control in the management of type 2 diabetes mellitus. *Ann Intern Med* 2003; **138**: 587–592.
44 Zanella MT, Plavnik FL, Kohlmann Jr O, Ribeiro AB. Hypokalemia, glucose intolerance and hyperinsulinemia during diuretic therapy. *Hypertension* 1992; **19**(Supp II): II-26–II-29.
45 Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2007; **2**: 366–373.