Original Research

Clinical Efficacy of Magnesium Supplementation in Patients with Type 2 Diabetes

Kuninobu Yokota, MD, Mitsutoshi Kato, MD, Frank Lister, PhD, Hirokazu Ii, DC, Toshiyuki Hayakawa, PhD, Tetsuya Kikuta, DC, Shigeru Kageyama, MD, and Naoko Tajima, MD

Department of Internal Medicine (K.Y., N.T.), Kato Medical Clinic (M.K.), Department of Anatomy (T.H.), Department of Clinical Pharmacology & Therapeutics (S.K.), Jikei University School of Medicine, Matier Co. Ltd. (H.I., T.K.), Tokyo, JAPAN, WA Salt Supply, AUSTRALIA (F.L.)

Key words: magnesium supplementation, type 2 diabetes mellitus, hypertension, insulin-resistance, hypertriglyceridemia, life style-related diseases

Effects of magnesium (Mg) supplementation on nine mild type 2 diabetic patients with stable glycemic control were investigated. Water from a salt lake with a high natural Mg content (7.1%) (MAG21) was used for supplementation after dilution with distilled water to 100mg/100mL; 300mL/day was given for 30 days. Fasting serum immunoreactive insulin level decreased significantly, as did HOMA□R (both $p < 0.05$). There was also a marked decrease of the mean triglyceride level after supplementation. The patients with hypertension showed significant reduction of systolic ($p < 0.01$), diastolic ($p = 0.0038$), and mean ($p < 0.01$) blood pressure. The salt lake water supplement, MAG21, exerted clinical benefit as a Mg supplement in patients with mild type 2 diabetes mellitus.

INTRODUCTION

It has recently been pointed out that magnesium (Mg) deficiency is related to life style-related diseases, such as diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease. Patients with diabetes mellitus often are Mg deficient, expressed by hypomagnesemia and [1,2,3] with which insulin resistance (characteristic of patients with type 2 diabetes) is related. Thus, Mg supplementation in patients with type 2 diabetes should be clinically beneficial. “Bitterns” are the main component of natural salt which is used as a coagulator of “tofu” (bean-curd) and we focused our attention on bitterns with a high Mg content as a Mg supplement for type 2 diabetes mellitus.

METHODS

Subjects

Six male and three female mild type 2 diabetes mellitus patients, with stable glycemic control by diet therapy alone or by oral hypoglycaemic agents other than insulin, were selected for study after obtaining their informed consent. Their mean age was 51.6 ± 2.6 (mean ± S.E.) years. Patients with other Mg metabolism disorders such as renal disease, arrhythmia, and ischemic heart disease were excluded. Estimated duration of diabetes was 4.7 ± 0.5 years on average, and the average body mass index (BMI) was 26.1 ± 1.1 kg/m^2. Six of the patients had hypertension, defined as blood pressure of 140 and/or 90 mmHg or over, that was being treated by antihypertensive agents. There were five cases of hyperlipidemia, defined as total cholesterol of 220 mg/dL or over, and/or total triglyceride of 150 mg/dL or over. In addition, there were two cases of hyperuricemia. Five patients were treated by diet therapy alone, one patient by an α-glucosidase inhibitor, two patients by a sulfonylurea, one patient by nateglinide, and one patient by a biguanaide.

Methods

The components of MAG21 solution, that was used for Mg supplementation in this study, are shown in Table 1. This is a low sodium chloride solution from a salt lake with a high Mg

Address reprint requests to: Dr. Kuninobu Yokota, 3-15-8 Nishi-shinbashi Minato-ku 105-0003, JAPAN. E-Mail: yokota@jikei.ac.jp.

Journal of the American College of Nutrition, Vol. 23, No. 5, 506S–509S (2004)
Published by the American College of Nutrition

Table 1. Diagram of Componential Analysis of MAG21 (Pure Natural Concentrated Magnesium Chloride from Lake Deborah)

Magnesium	10,300 mg	Selenium	0.73 ppb	Calories	0 kcal
Potassium	633 mg	Silicon	1.43 ppm	Protein	0 g
Sodium	584 mg	Phosphorus	0.26 ppm	Lipids	0 g
Calcium	4.6 mg	Molybdenum	0.15 ppm	Carbohydrate	0 g
Zinc	47 μg	Iron	0.14 ppm	Specific gravity	1.293
Copper	26 μg	Chromium	2.7 ppb		
Manganese	11 μg			Amount Per 100 mL	

Japan Food Research Laboratories No. 101031748.
RIKEN (The Institute of Physical and Chemical Research), Japan. No. 11-526.

content, Lake Deborah West, which is located north-east of Perth in Western Australia.

MAG21, with specific gravity of about 1.3, is a clear, and slightly viscous, mildly acidic water of pH 6.2. It is salt water with a high concentration of "bitterns" and a low sodium content of 0.84% and Mg content as high as 7.1%. MAG21 also contains small amounts of other trace elements, such as zinc, manganese, etc. When diluted to 1% solution, it becomes an ionized alkaline water of pH 8.9. MAG21 is produced in the "Mg chloride evaporation ponds," that are filled with lake water for evaporation by solar heat and concentrated.

In this study, MAG21 as Mg supplementation liquid is diluted with distilled water so that Mg concentration is 100mg/100 mL, and 300 mL/day was ingested for 30 days. Fasting morning blood was drawn before and after the tests. Total serum Mg and urinary Mg concentrations, potassium (K) and calcium (Ca), fasting plasma glucose (FPG) and fasting immunoreactive insulin (FIRI), glycated hemoglobin (HbA_1c), glycated albumin (GA), 1,5-anhydroglucitol (1,5-AG), and total cholesterol (TC), triglyceride (TG), and high density lipoprotein cholesterol (HDL-C) were measured. Insulin resistance was determined by the homeostasis model assessment index (defined as HOMA-R = FPG(mg/dL) $\times$ FIRI(μU/mL)/405 [4]), which is commonly used for measuring insulin sensitivity.

The therapeutic regimens of subjects taking MAG21 was not changed. Prescribed antihypertensive agents were taken at fixed times. Blood pressure level in the sitting position, at a given time after taking the drug, was measured 3 times after 10 minutes' rest, and the average of the three measurements was used. All the data were compared with regards to the measurements of each parameter before and after the tests. Paired Student's t-test was used for statistical analysis, and each value was expressed as mean (M) $\pm$standard error (S.E.). A p value of less than 0.05 was considered indicative of statistical significance.

RESULTS

MAG21 did not cause adverse effects such as diarrhea in any of the subjects. Changes of K and Ca levels were not observed, but total serum Mg (2.1 $\pm$ 0.06 to 2.3 $\pm$ 0.07 mg/dL, $p < 0.01$), urinary Mg concentration (5.2 $\pm$ 0.87 to 9.2 $\pm$ 1.79 mg/dL, $p < 0.01$), and urinary Mg excretion rate (2.4 $\pm$ 0.50 to 3.6 $\pm$ 0.84, respectively, $p < 0.01$) significantly increased after supplementation. There was no significant change in FPG after MAG21 supplementation, but FIRI significantly decreased (8.08 $\pm$ 1.84 to 5.89 $\pm$ 1.03 μU/mL, $p < 0.01$), therefore insulin resistance index, HOMA-R, was reduced (2.73 $\pm$ 0.49 to 2.05 $\pm$ 0.29, $p < 0.05$). None of the three indices, namely, HbA_1c, GA, and 1,5 AG showed statistically significant differences before and after supplementation (data were not shown). There was no significant change in TC, while HDL-C showed a slight increase after the supplementation, but the increase was not statistically significant. On the other hand, a marked decrease of mean TG level was noted after the supplementation, although a change was not statistically significant (Table 2). The changes of blood pressure (BP) levels are also shown in Table 2. The mean BP levels of all the subjects did not show a significant hypotensive effect after supplementation, but six patients with hypertension showed significant reduction of the systolic BP (136.3 $\pm$ 2.7 to 130.8 $\pm$ 2.8 mmHg, $p < 0.01$), diastolic BP (83.0 $\pm$ 5.14 to 79.0 $\pm$ 5.9

Table 2. Laboratory Evaluation before and after Supplementation with MAG21

	Before	After
FPG (mg/dL)	149.4 $\pm$ 13.8	147.4 $\pm$ 12.0
FIRI (μU/mL)	8.08 $\pm$ 1.84	5.89 $\pm$ 1.03[a]
HOMA-R	2.73 $\pm$ 0.49	2.05 $\pm$ 0.29[b]
Lipids		
TC (mg/dL)	205.3 $\pm$ 8.98	207.9 $\pm$ 12.07
HDL-C (mg/dL)	51.7 $\pm$ 5.36	53.7 $\pm$ 4.82
TG (mg/dL)	255.4 $\pm$ 80.5	178.8 $\pm$ 38.3
BP (blood pressure) N = 6 cases with hypertension		
SBP (mmHg)	136.3 $\pm$ 2.68	130.8 $\pm$ 2.79[c]
DBP (mmHg)	83.0 $\pm$ 5.14	79.0 $\pm$ 5.86[d]
MBP (mmHg)	100.8 $\pm$ 3.34	96.3 $\pm$ 3.98[e]

FPG = fasting plasma glucose, FIRI = fasting immunoreactive insulin, HOMA-R = homeostasis model insulin resistance index: FPG(mg/dL) $\times$ FIRI(μU/mL)/405 = FPG(mmol/L) $\times$ FIRI(μU/mL)/22.54), TC = total cholesterol, HDL-C = high density lipoprotein cholesterol, TG = triglyceride, SBP = systolic blood pressure; DBP = diastolic blood pressure, MBP = mean blood pressure.
[a] $p < 0.01$ compared to before supplementation, [b] $p < 0.05$ compared to before, [c] $p < 0.01$ compared to before, [d] $p = 0.038$ compared to before, [e] $p < 0.01$ compared to before.

mmHg, $p = 0.0038$), and mean BP (100.8 ± 3.3 to 96.3 ± 4.0 mmHg, respectively $p < 0.01$).

DISCUSSION

It has recently been pointed out that magnesium (Mg) deficiency is related to life style-related diseases, and this chronic deficiency of Mg is speculated to play an important role in the increased incidence of the diseases. These diseases have drastically increased in Japan today. A notable change in diet during the past 50 years in Japan is an increase of fat intake, in addition, various factors have contributed to chronic Mg deficiency among the Japanese including: (1) decreased intake of food grains rich in Mg; (2) discontinuation of intake of various minerals, Mg in particular, from the sea salt, because of the abolishment of "the Sea Farm law" in 1971; (3) vegetables grown on nonfertile land nowadays; and (4) decreased consumption of seafood. As a consequence, the amount of decrease of Mg intake in the Japanese population seems to be speculated as at least 100mg/day compared with 50 years before.

Diabetes mellitus is the most common disease, in which a high frequency of hypomagnesemia [1,2,3] due mainly to an increase of urinary Mg excretion, is often detected, as is the pathological state of insulin resistance, that is especially common in patients with type 2 diabetes. In this study insulin sensitivity estimated by HOMA-R [4] in patients with mild type 2 diabetes was significantly improved with supplementation with MAG21. The mechanism by which insulin resistance develops is complicated and still remains unclear, but decreased tyrosine kinase activity due to Mg deficiency is reported as one of the mean by which insulin resistance is expressed [5]. Mg supplementation with MAG21 may have increased enzyme activity.

Although there was no significant change in the level of three glycemic control indices before and after supplementation, the HbA_1c and GA levels after supplementation were either similar or showed a tendency to decrease in five patients, and 1,5-GA level after supplementation was either similar or showed tendency to slightly increase in five patients. If the supplementation period were much longer, more favorable results might have been seen.

The average level of TG markedly decreased after MAG21 supplementation in patients with a higher level of TG before supplementation. Since decreased activity of lipoprotein lipase (LPL) due to Mg deficiency causes hypertriglyceridemia in diabetics [6], the reduced TG levels after Mg supplementation with MAG21 might reflect its increase of LPL activity.

The change of blood pressure in patients with hypertension was statistically significant. Antihypertensive effect due to Mg supplementation may have been caused by the antagonistic action of Mg on calcium [7] mainly through the reduction of insulin resistance [5]. Reports of clinical studies on Mg supplementation have focused mainly on hypertension, and Mg oxide [8], Mg hydrate [9], and Mg aspartate [10] were often used in the studies. We could find no references reporting the effect of Mg supplementation with this pure natural Mg chloride, the main component of "bitterns." In this study, the effect of short-term Mg supplementation at 300mg/day with MAG21 was assessed in diabetics. Although the daily quantity of Mg is considerably lower and the supplementation period is also shorter than those used in other studies, favorable effects have been demonstrated. The reason may be that MAG21 is pure and already in solution, so that Mg absorption from the intestinal tract may be relatively high.

Mg is an essential mineral, that tends to be chronically deficient in people today, so its Mg supplementation must be clinically useful, in particular for patients with life style-related diseases. We hope that the clinical effect of supplementation with pure natural Mg, such as MAG21 will be studied further in the future.

CONCLUSION

Salt lake water with a high Mg content, MAG21, has shown clinical benefit, as a Mg supplement in patients with mild type 2 diabetes.

ACKNOWLEDGMENTS

We thank M. Shiraishi (Department of Clinical Laboratory, Jikei University School of Medicine) and H. Akiyama (SRL Co, Ltd. Tokyo) for performing the assays of materials.

REFERENCES

1. Mather HM, Nisbet JA, Burton GH, Poston GJ, Bland JM, Bailey PA, Pilkington TRE: Hypomagnesaemia in diabetes. Clin Chem Acta 95:235–242, 1979.
2. Resnick LM, Altura BT, Gupta RK, Laragh JH, Alderman MH, Altura BM: Intracellular and extracellular magnesium depletion in type 2 (non insulin-dependent) diabetes mellitus. Diabetologia 36:767–770, 1993.
3. Yokota K, Kato M, Shiraishi M, Kageyama S, Sakurai T, Ishibashi K, Yamamoto J, Mimura A, Aihara K, Yokose T, Tajima N: Abnormalities of serum ionized magnesium in the patients with type 2 diabetes. In: Advances in magnesium research: Nutrition and Health, eds. Rayssiguier, Y., Mazur, A. & Durlach, J. pp.381–383, 2001. London: John Libbey & Co Ltd.
4. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and

β-cell function from fasting plasma glucose and insulin concentration in man. Diabetologia 28:412–419, 1985.

5. Paolisso G, Barbagallo M: Hypertension, diabetes mellitus, and insulin resistance. The role of intracellular magnesium. Am J Hypertens 10:346–355, 1997.
6. Rayssiguier Y, Gueux E: Magnesium and lipids in cardiovascular disease. J Am Coll Nutr 5:507–519, 1986.
7. 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 65:729–745, 1987.
8. Sanjuliani AF, Fagundes VG, Francischetti EA: Effects of magnesium on blood pressure and intracellular ion levels of Brazilian hypertensive patients. Intern J Cardiol 56:177–183, 1996.
9. Widman L, Wester PO, Stegmayr BK, Wirell M: The dose-dependent reduction in blood pressure through administration magnesium. A double blind placebo controlled cross-over study. Am J Hypertens 6:41–45, 1993.
10. Dyckner T, Wester PO: Effect of magnesium on blood pressure. Br Med J 286:1847–1849, 1983.

Received August 5, 2004.