Association of blood pressure and metabolic syndrome components with magnesium levels in drinking water in some Serbian municipalities

Zorica Rasic-Milutinovic, Gordana Perunicic-Pekovic, Dragana Jovanovic, Zoran Gluvic and Milce Cankovic-Kadijevic

ABSTRACT

Chronic exposure to insufficient levels of magnesium (Mg) in drinking water increases the risk of magnesium deficiency and its association with hypertension, dyslipidemia and type 2 diabetes mellitus. The aim of the study was to assess the potential association of mineral contents in drinking water with blood pressure and other components of metabolic syndrome (MetS) (BMI as measure of obesity, triglycerides, glucose, and insulin resistance, index-HOMA IR), in a healthy population. This study was conducted in three randomly selected municipalities (Pozarevac, Grocka and Banovci), and recruited 90 healthy blood donors, aged 20–50 years. The Pozarevac area had a four times higher mean Mg level in drinking water (42 mg L^{-1}) than Grocka (11 mg L^{-1}). Diastolic blood pressure was lowest in subjects from Pozarevac. Serum Mg (sMg) was highest, and serum Ca^{2+}/Mg (sCa/Mg) lowest in subjects from Pozarevac, and after adjustment for confounders (age, gender, BMI), only total cholesterol and sMg levels were independent predictors of diastolic blood pressure, sMg levels were independent predictors of triglycerides, and sCa/Mg predicted glucose levels. These results suggest that Mg supplementation in areas of lower magnesium levels in drinking water may be an important measure in the prevention of hypertension and MetS in general.

Key words | calcium, drinking water, hypertension, magnesium, magnesium deficiency, metabolic syndrome

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INTRODUCTION

Hypertension is the leading cause of cardiovascular morbidity and mortality of individuals worldwide. Although the exact etiology is unknown, the fundamental hemodynamic abnormality in hypertension is increased peripheral resistance, due primarily to changes in vascular structure and function. Many studies support a role for Mg in the development of hypertension, with reports demonstrating, for the most part, an inverse correlation between body Mg levels and blood pressure, hypotensive actions of dietary Mg supplementation and hypertensive effects of Mg deficiency (Resnick *et al.* 2000; Touyz 2003; Sontia & Touyz 2007).

Obesity and dietary macronutrients clearly play a role in the risk for hypertension and metabolic syndrome (MetS), but the role of micronutrients in this process is not clear. Several epidemiological studies suggest a close relation between water hardness, and risk for cardiovascular disease (CVD) (Rylander 1996; Nerbrand *et al.* 2003; Kousa *et al.* 2004; Monarca *et al.* 2006; Kousa *et al.* 2008). Regarding individual minerals, several studies have been reported where hypertensive subjects were treated with nutritional doses of Mg (Bucher *et al.* 1996; Jee *et al.* 2002; Rylander & Amaud 2004). The results suggested a dose-dependent reduction in blood pressure from the Mg intervention, as well as supplementation of Mg together with other minerals, among persons with a low body burden of Mg and Ca (Rubenowitz *et al.* 1998).

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Magnesium is an essential element that has numerous biological functions in the cardiovascular system. At the subcellular level, Mg regulates contractile proteins, modulates transmembrane transport of Ca, Na and K, and acts as an essential cofactor in the activation of ATPase, which controls the metabolic regulation of energy-dependent cytoplasmic and mitochondrial pathways (Altura & Altura 1995; Cowan 2000).

Magnesium serves as a co-factor for enzymes involved in a variety of physiological processes including lipid metabolism and it has recently been shown that increased magnesium intake may be associated with reduced risk of developing the metabolic syndrome (He *et al*. 2006). The favorable effect of increased magnesium intake on type 2 diabetes and risk of diabetes has been attributed to an effect of magnesium on insulin sensitivity (Kao *et al*. 1999; McCarty 2005).

The hardness of ground water, defined by concentrations of Ca and Mg, is different in various parts of Serbia. Until now, no research has been conducted into the relation between drinking water quality and the presence of hypertension, MetS, and CVD. Dietary Mg intake as a supplement, including in fortified foods and bottled water, is marginal and in a whole population a small alteration in Mg intake may increase deficiency. Unfortunately, the real dietary intakes of calcium and magnesium from both food and water sources in Serbia is unknown. It has been estimated that drinking-water can contribute to 40–100 mg of Mg per day (Marier 1990), up to 30% of the estimated average requirement for adults. Magnesium deficiency in the body is reflected by a decrease in serum magnesium (sMg) levels, and sMg has been considered as the first indicator of magnesium deficiency (Dunn & Walser 1966).

Although most epidemiological and experimental studies support the role of low magnesium in the pathophysiology of hypertension and metabolic disarrangement, data from clinical studies have been less convincing. The present study attempts to elucidate the role of magnesium in the regulation of blood pressure and discusses the implications of magnesium in some components of MetS in a healthy young to middle-aged population in three municipalities of Serbia.

MATERIAL AND METHODS

Study design

The study was a randomized, cross-sectional, epidemiological, with three groups of subjects, 90 healthy blood donors, aged 18–52 years (mean 34.57 ± 10.56), 30 from each of the three municipalities in Serbia (Banovci, Grocka and Pozarevac). One of the municipalities, Pozarevac, was characterized by hard water, and the other two by softer water, particularly Grocka. The present study was designed to determine whether a relationship exists between water hardness and blood pressure in healthy people, and to evaluate potential mechanisms leading to hypertension.

Descriptions of hardness correspond roughly with ranges of mineral concentrations, and total water hardness according to the scale of degree of General Hardness (dGH) (defined as 10 mg of calcium oxide per liter of water) could be from: 0–4 dGH (very soft), 4–8 dGH (soft), 8–12 dGH (slightly hard), 12–18 dGH (moderately hard), 18–30 dGH (hard), and >30 dGH (very hard).

Total water hardness, magnesium and calcium concentrations, electroconductivity and total dissolved solids were measured in water samples from public water supply systems as part of the National Monitoring Programme of Drinking Water Quality from Public Water Supply Systems from 2003 to 2004. Water samples from individual wells were not taken into consideration.

Sampling and chemical analyses of drinking water from water supply systems were performed at the following laboratories: at the Institute of Public Health in Belgrade, the Institute of Public Health in Sremska Mitrovica and the Institute of Public Health in Pozarevac. All laboratories were accredited and authorized according to SRPS ISO/IEC 17025 and SRPS ISO 9001 standards. Laboratory procedures for sample management, analytical methods, and quality control measures (accuracy, precision, and detection limits) were standardized by Serbian laws (Book of Regulations for Water Sampling 87/33 1987; Book of Regulations on the Hygienic Correctness of drinking water 98/42 1998). Following these protocols, water Ca and Mg levels were analyzed by inductively coupled plasma optical

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emission spectrometry (ICP-OES). Total water hardness was measured by gravimetric methods. Water conductivity was measured directly using a conductivity probe. Total dissolved solids are determined gravimetrically (APHA 1995). Descriptions of hardness correspond roughly with ranges of mineral concentrations.

Subjects

Subjects were recruited by referrals from primary care physicians. They were evaluated and recruited by physicians of the Institute of Blood Transfusion in Belgrade. A complete history and physical examination were performed. Heights and weights of participants were measured in centimeters and kilograms and body mass index, (BMI, kg m^{-2}) was calculated. Participants were asked about the main source of water they use for drinking.

Blood pressure

Blood pressure was recorded by standard mercury sphygmomanometer, before the blood samples were taken. Two separate recordings were made after 5 min of supine rest. The blood pressure, systolic, diastolic and mean arterial pressure, was reported as the average of these recordings.

Blood samples

Blood samples were taken after overnight fasting for at least 8 h to measure serum concentrations of Mg, Ca, Na, K, P, creatinine, glucose, lipids, insulin, red blood cells, white blood cells, platelets, and haematocrite values.

Laboratory tests

The analyses were performed at the Biochemical laboratory of Clinical Hospital Zemun, Belgrade. Serum minerals Na, K, Ca, were measured by ion-meter AVL- 988–3, and P and Mg were measured with colorimetric assay by IL 650 analyzer. Glucose levels, total cholesterol, and triglycerides were measured by commercial enzymatic tests. Insulin level was measured with immunofluorescence assay by IMMULITE 1000.

Statistical analysis

Data are expressed as means ± SD. Differences between groups were analyzed by general model ANOVA and *post hoc* multiple comparisons were performed using LSD test when ANOVA testing was significant ($p < 0.05$). For variables with skewed distribution, the values were log-transformed and a normal distribution was confirmed by the Komolgorov–Smirnov goodness-of-fit test ($p > 0.15$). Correlation analysis was performed by calculating Pearson's correlation coefficient. By multivariate linear regression analysis we evaluate the relative importance of factors possibly contributing to the variation in risk factor levels. All statistical analyses were done with the SPSS statistical software package (version 15.0; SPSS, Chicago, USA).

RESULTS

All participants use water from public water supply system as the main source of drinking water consumption. The total hardness of water, defined as the sum of Ca and Mg, the levels of Ca and Mg separately, as well as the ratio of Ca/Mg, of three municipalities is presented in Table 1. The water from the water supply from Pozarevac municipality had the highest degree of hardness. The median content of Ca in this water supply system was 99.79 mg L^{-1}, almost twice than of the water supply system from Grocka, or Banovci. The median content of Mg in the water supply from Pozarevac was significantly higher, and the ratio of Ca/Mg was significantly lower than the level in the water supply from Grocka. The median content of Mg in the

Table 1 | The hardness of drinking water from three municipalities

	Pozarevac	Grocka	Banovci
Total hardness (dGH)	23.71	11.15[a]	13.87[a]
Calcium (mg L^{-1})	99.79	58.85[a]	49.7[a]
Magnesium (mg L^{-1})	42.25	11.8[a]	54.92
Ca/Mg	2.36	4.98[a]	0.9
Water conductivity	761	752.7	667.2
Total dissolved solids ($T = 105\ ^{\circ}C$)	546.0	503.1	434.6

[a]Significant difference compared with Pozarevac, $p < 0.05$.

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water supply system did not differ between Pozarevac and Banovci, and neither did the ratio of Ca/Mg (Table 1).

There were no significant differences between groups of subjects according to the age, gender, or nutritional status. The subjects were not obese (BMI < 30 kg m^{-2}). The mean systolic blood pressure did not differ between groups. There were significant differences between groups for diastolic blood pressure; it was the lowest in subjects from Pozarevac (Table 2).

There were no differences between groups for mean level of sCa^{2+}. The mean sMg was the highest in the group from Pozarevac, and the ratio sCa^{2+}/Mg was the lowest in the serum of the same subjects (Table 2). The mean value of serum triglycerides, as well as creatinine, was the lowest in the subjects from Pozarevac (Table 2). There were no differences between three groups for serum glucose, insulin, HOMA IR and HOMA Beta.

Table 3 shows the Pearson's correlation between all clinical and laboratory data of subjects from three geographic areas. We observed an inverse association between diastolic blood pressure and mean levels of serum Mg. Diastolic blood pressure directly correlated with the ratio of serum Ca^{2+}/Mg, total cholesterol, triglycerides, and creatinine (Table 3). There was negative correlation between serum triglycerides and sMg. Glucose level positively correlated with sMg, but the other parameters of insulin resistance or obesity (insulin level, HOMA IR, BMI) did not significantly correlate with sMg levels. HOMA Beta, the parameter of beta-cell function, also did not correlate with sMg levels (Table 3).

To determine independent predictors of diastolic blood pressure in healthy blood donors we examined the regression of all predictors using a stepwise multivariate linear regression process, and 23% of the variation in diastolic blood pressure was explained by the sMg and cholesterol levels, after adjustment for age, gender, BMI, the ratio of sCa^{2+}/Mg, Na, and triglycerides (Table 4). About 20% of the variation in serum triglycerides, could be explained by sMg levels, together with BMI, and after adjustment for age, and gender (Table 5). Eighteen percent

Table 2 | Characteristics of healthy blood donors from three municipalities

Variables	Pozarevac mean ± SD	Grocka mean ± SD	Banovci mean ± SD	Significance p_1; p_2
Age (year)	40.88 ± 9.47	39.33 ± 4.84	37.21 ± 3.85	0.42; 0.08
Gender (male/female)	23/7	19/11	22/8	
BMI (kg m^{-2})	24.65 ± 4.72	25.44 ± 5.37	25.91 ± 3.67	0.54; 0.29
SBP (mmHg)	124.50 ± 7.80	125.00 ± 5.30	126.96 ± 5.72	0.87; 0.49
DBP (mmHg)	78.30 ± 4.87	81.66 ± 5.86	82.50 ± 4.33	**0.03**; 0.08
MAP	93.70 ± 4.68	96.11 ± 5.17	97.08 ± 4.50	0.18; 0.05
sCa^{2+}(mmol L^{-1})	1.06 ± 0.04	1.10 ± 0.02	1.07 ± 0.05	0.13; 0.38
sMg (mmol L^{-1})	0.87 ± 0.09	0.71 ± 0.05	0.73 ± 0.05	**0.01**; **0.04**
sCa/sMg	1.23 ± 0.13	1.54 ± 0.10	1.48 ± 0.12	**0.02**; 0.06
sNa (mmol L^{-1})	137.52 ± 2.29	141.11 ± 0.42	141.84 ± 2.4 5	**0.04**; 0.96
sCholesterol (mmol L^{-1})	5.47 ± 0.95	5.62 ± 1.05	5.22 ± 0.93	0.70; 0.97
sTriglycerides (mmol L^{-1})	1.20 (1.05–1.95)	2.00 (0.95–3.60)	1.40 (1.00–1.80)	**0.04**; 0.05
sGlucose (mmol L^{-1})	4.11 ± 0.75	3.95 ± 0.95	4.25 ± 0.67	0.10;0.05
sInsulin (mU L^{-1})	15.7 (11.65–20.65)	19.45 (8.34–30.97)	16.30 (14.20–24.40)	0.81;0.89
HOMA IR	2.90 (0.60–3.86)	2.79 (0.93–5.72)	3.30 (2.46–4.88)	0.72;0.68
HOMA Beta	79.27 (57.10–92.78)	96.23 (64.23–162.21)	82.35 (56.5–87.35)	0.20;0.73
s-Creatinine (μmol L^{-1})	72.96 ± 6.98	78.66 ± 12.46	84.10 ± 8.93	**0.01**; **0.03**

p_1 = difference between the mean (median) value of variables from Pozarevac and Grocka.
p_2 = difference between the mean (median) value of variables from Pozarevac and Banovci.

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Table 3 | Correlations (Pearson correlation coefficient *r*) between serum calcium, magnesium, sodium, cholesterol, triglycerides, glucose, insulin, HOMA IR, HOMA Beta and blood pressure

	age	BMI	sCa	sMg	sCa/Mg	sNa	sCh	sTg	sGlucose	sInsulin	HOMA IR	HOMA B	sCreatinine	SBP	DBP
age	1	0.438**	0.145	−0.106	0.161	−0.272	0.344**	0.227*	0.194*	0.129	0.139	0.162	0.240*	0.225*	0.400*
BMI		1	0.104	−0.099	0.135	0.161	0.244*	0.353**	0.161	0.428**	0.351**	0.387**	0.318**	0.412**	0.293*
sCa^{2+}			1	−0.256*	0.369**	0.100	0.175	0.046	−0.233*	0.029	−0.219	0.215	−0.011	0.137	0.128
sMg				1	−0.698 **	−0.415**	−0.149	−0.205*	0.207*	0.023	−0.072	−0.099	−0.326**	−0.226*	−0.262*
sCa^{2+}/Mg					1	0.377**	0.214*	0.175	−0.282*	−0.052	−0.174	0.140	0.256*	0.287*	0.254*
sNa						1	−0.083	0.020	−0.266*	0.210	0.232	0.147	0.197	0.224*	0.098
sCh							1	0.324**	−0.085	0.204	0.229	0.257*	0.137	0.216*	0.358*
sTg								1	0.79	0.313*	0.311*	0.302*	0.342**	0.198	0.291*
sGlucose									1	0.254*	0.564**	0.292*	0.012	−0.175	0.013
sInsulin										1	0.887**	0.848	−0.072	−0.028	0.028
HOMA IR											1	0.573	0.087	0.132	0.035
HOMA B												1	0.062	0.070	0.035
sCreatinine													1	0.249*	0.404*
SBP														1	0.352*
DBP															1

*$p < 0.05$;
**$p < 0.01$.

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Table 4 | Independent predictors of diastolic blood pressure in healthy blood donors from three municipalities

	Standardized coefficient beta	T	Significance
(Constant)		9.790	0.000
sCholesterol	0.225	2.361	0.02
sMg	−0.194	−2.122	0.03

Adjusted for gender, BMI, triglycerides, Ca/Mg ratio, $R^2 = 23\%$.

Table 5 | Independent predictors of serum triglycerides in healthy blood donors from three municipalities

	Standardized coefficient beta	T	Significance
(Constant)		−1.323	0.182
BMI	0.344	3.633	0.001
sMg	−0.174	−1.901	0.05

Adjusted for age and gender, $R^2 = 20\%$.

Table 6 | Independent predictors of serum glucose in healthy blood donors from three municipalities

	Standardized coefficient beta	T	Significance
(Constant)		5.499	0.000
sCa^{2+}	−0.481	−4.358	0.000
sInsulin	0.240	2.179	0.03

Adjusted for age, gender, and BMI, $R^2 = 27\%$.

of the variation of serum glucose was explained with sCa^{2+}, and sInsulin, after adjustment for confounders, as age, gender and BMI (Table 6).

DISCUSSION

There is increasing evidence that low intakes of Mg are associated with various metabolic diseases, including hypertension, cardiac arrhythmia, cardiovascular disease and diabetes mellitus (Jee *et al.* 2002; Kousa *et al.* 2004; Rasic-Milutinovic *et al.* 2004). The extensive reviews of epidemiological studies on drinking water composition and CVD supported the hypothesis that soft drinking water with the low supply of Mg from drinking water increased the risk of CVD mortality and possibly played a role in developing CVD (Sauvant & Pepin 2002).

The present study shows an inverse association between the diastolic blood pressure and hardness of drinking water, and that the serum level of Mg is an independent predictor of diastolic blood pressure in normotensive healthy subjects. It supports the previously presented hypothesis that water hardness and particularly Mg content may have a role in the etiology of hypertension (Sontia & Touyz 2007).

A large retrospective study which assessed Mg and Ca content in drinking water in subjects who died from hypertension compared with those who died from other causes demonstrated that magnesium levels in drinking water were inversely related to the risk of death from hypertension (Yang & Chiu 1999). Many clinical studies have shown some forms of hypomagnesemia (serum and/or tissue) in hypertensive patients, with significant inverse correlations between magnesium concentration and blood pressure. A number of factors influence circulating concentrations of Mg. Age, gender, educational level, obesity, smoking habits, alcohol consumption and physical exercise are known to affect the intake of Mg, Ca, and Na. Data from the Vanguard study demonstrated that independently of weight reduction, diet-induced changes in systolic blood pressure were significantly related to changes in urinary excretion of magnesium, potassium and calcium relative to sodium (Nerbrand *et al.* 2003). In agreement with previous studies, after adjustment for age, gender, and BMI, the serum concentration of Mg in our subjects is still negatively associated with systolic and diastolic blood pressure, stronger with the latter. Magnesium depletion may be due to dysregulation of factors controlling magnesium status: intestinal hypoabsorption of magnesium, reduced uptake and mobilization of bone magnesium, urinary leakage, or hyperadrenoglucocorticism by decreased adaptability to stress (Runyan *et al.* 2005). Long-term magnesium deficiency in experimental animals potentiates responses to vasoconstrictor agents, attenuates responses to vasodilator agents, increases vascular tone and elevates blood pressure. However, our subjects are healthy people of younger age, normotensive, not obese, with mean serum levels of Mg within referent range, but they differ between the groups according to the hardness of drinking water from the areas separately, as well as according to serum levels of Mg. The subjects from Pozarevac, the area with the hardest drinking water, show the highest level of serum Mg, the lowest level

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of serum ratio Ca^{2+}/Mg, lower level of serum Na, and the lowest level of diastolic blood pressure.

Systolic blood pressure did not differ between the groups. There was a difference for the ratio of serum Ca^{2+}/Mg between the subjects from the hardest drinking water, Pozarevac, and the softest drinking water, Grocka. Our data are in agreement with the findings of human Mg balance studies, which indicated that mild to moderate deficits in Mg intake increase intracellular ionized Ca with increased release of pro-inflammatory peptides, enhancement of oxidative stress and increased vascular tone (Kramer *et al.* 2003). As food is the major source of magnesium and calcium intake, the main limitation of our study is the lack of individual data on dietary and water intake. However, we assumed that the dietary habits of participants did not differ between the investigated areas.

Exact molecular mechanisms of Mg vascular actions are unclear, but Mg probably influences intracellular free Ca concentration, which is fundamental in myocardial regulation, endocrine and renal secretion, and smooth muscle contraction. In vascular smooth muscle cells, Mg antagonizes Ca by inhibiting transmembrane calcium transport and calcium entry. It also acts intracellularly as a Ca antagonist thereby modulating its vasoconstrictor actions, a major determinant of vascular contraction (Touyz & Schiffrin 1999; Touyz 2003; Weglicki *et al.* 2005). Low magnesium causes an increase in intracellular Ca, with associated vascular contraction and increased tone. Intracellular Mg depletion has been demonstrated in many tissues (heart, lungs, kidney, bone, and muscle) and cell types (vascular smooth muscle cells, erythrocytes, platelets, and lymphocytes) in both human and experimental hypertension (Altura & Altura 1995; Touyz 2003; Kisters *et al.* 2004).

Magnesium is important as a co-factor in lipid metabolism. The rate limiting step in cholesterol synthesis, at HMG-CoA reductase, can be activated through magnesium requiring enzymes (Rosanoff & Seelig 2004). It has been suggested that low magnesium may impair HMG-CoA reductase inactivation via phosphorylation. Magnesium is also important for the activity of the extracellular enzymes lecithin-cholesterol acyl transferase and lipoprotein lipase (Rosanoff & Seelig 2004). Our results agreed with the statement that low Mg might have the impact on the physiological processes that affect serum lipid levels, because we showed an independent effect of sMg on triglyceride levels, and positive correlation between sCa^{2+}/Mg and serum cholesterol.

Insulin increases cellular glucose uptake by coordinating signaling and trafficking pathways that facilitate GLUT4 exocytosis (Lanner *et al.* 2008). At present, we know that mitochondria have numerous outputs that may be linked to the antagonism of insulin-stimulated GLUT4 exocytosis. For example Ca, ATP, pH, and ROS are all linked to insulin resistance. Calcium is required for GLUT4 vesicle trafficking and fusion. Adequately high levels of serum Ca, and consequently intracellular Ca homeostasis, in our subjects obviously participate in maintaining glucose homeostasis, as we concluded from negative association between sCa and serum glucose level.

The Atherosclerosis Risk in Communities study has prospectively linked high sMg levels with reduced risk for type 2 diabetes (Kao *et al.* 1999). Consistently, individuals with type 2 diabetes or metabolic syndrome tend to have lower sMg levels than otherwise healthy individuals (Guerrero-Romero & Rodriguez-Moran 2002; Walti *et al.* 2003; Evangelopoulos *et al.* 2008). In addition, specific risk factors like BMI, fasting glucose and insulin, blood pressure, fasting triglycerides, total cholesterol, and HOMA IR have been reported to negatively correlate with sMg levels (Evangelopoulos *et al.* 2008).

However, our results in healthy individuals, in agreement with those of Randell *et al.* (2008), did not show any significant association between glucose, insulin, HOMA IR, HOMA Beta and sMg level. Finally, Hunt & Johnson (2006) compiled magnesium balance data from 20 controlled feeding studies and concluded that large numbers of people consume the levels of magnesium and calcium that are insufficient to support even the most conservative estimates of their physiological needs. It is also possible that if the beneficial effect associated with drinking water minerals is indeed confirmed, that could be due to other essential elements present at low but important concentrations in the drinking-water, rather than to calcium and magnesium. The strongest correlation was confirmed between vanadium and magnesium (Powell *et al.* 1987).

In conclusion, the data from clinical trials of magnesium therapy in hypertension have been disappointing. However, increasing evidence indicates that low magnesium intake

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may play a pathophysiological role in the development of hypertension. Therefore, there is a need for more suitable analytical epidemiological studies that have wider objectives (Calderon & Hunter 2009). Our study results demonstrate that areas with hard drinking water and adequate supply of Mg from drinking water may prevent hypertension, and participate in maintaining normal triglyceride levels in healthy adults.

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