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Ionized Magnesium Deficiency in Elderly Hypertensive Patients – A Pilot Study

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ABSTRACT

Objective: According to recent publications, a magnesium deficiency is found in up to 50% of the elderly, depending on co-morbidities, drugs and nutritional status. In addition, it is well known that magnesium insufficiency is a pathogenic factor in the development of hypertension. Calcium-magnesium antagonism, sodium-magnesium antiport, disturbed vitamin D metabolism and disrupted magnesium channels are of interest in this context. Magnesium metabolism is of particular interest in elderly hypertensive patients. Ionized magnesium is the active form and this parameter was thus also measured.

Design and methods: We studied 45 patients with essential hypertension and normal renal function. None of the patients received diuretics or magnesium. No-one with diabetes was included in the study. The patients (23 men, 22 women) were all aged over 65 years. Measurements of magnesium were performed either in serum (Cobas, Roche, Germany) or ionized in blood (NOVA, Rödermark, Germany).

Results: Considering the serum magnesium concentrations alone, only 1 person had values below 1.5 mg/dL, all the other elderly hypertensive patients had normal serum magnesium concentrations.

In contrast, ionized magnesium concentrations were significantly decreased in 15 of the 45 patients (30%), with values below 0.5 mmol/L ($p<0.01$). However, we found no correlation between total serum and ionized blood magnesium (ns, Pearson or Spearman rank test, p value 0.91 and 0.41 respectively). Blood pressure was well controlled with values below 150/90 mmHg.

Conclusions: There is no correlation between serum and ionized blood magnesium concentrations. This is of particular importance, as a normal serum magnesium concentration does not exclude a deficiency of ionized magnesium. As ionized magnesium is the vasoactive form, it is more useful to determine ionized magnesium concentrations when assessing body magnesium stores. In elderly hypertensive patients with well-controlled blood pressure, nearly 30% showed an ionized magnesium deficiency despite normal serum magnesium values.

INTRODUCTION

The interest in magnesium has increased in almost all fields of medicine over recent years. Magnesium is an essential mineral for living organisms and the human body must receive an adequate supply [1,2]. Magnesium overload or intoxication has relatively little clinical relevance. However, magnesium deficiency in humans occurs frequently and cannot always be fully compensated with a normal diet (Table 2). The primary effect of magnesium deficiency is a reduction in the activity of pacemaker enzymes involved in the metabolic pathways of energy production. Impaired energy production affects membrane function, intracellular calcium relocation, electrolyte gradients, the production of secondary messengers and cell synthesis. This, in turn, affects organ function and alters the extent to which the body can react to external and internal stress. When there is also ill health, the limited energy status affects the patient's prognosis and exacerbates clinical signs of disease, such as arrhythmias, hypertension, pre-eclampsia, allergic reactions, etc. [1-5]. The value of oral or parenteral magnesium therapy is well documented in a variety of disorders, for which various magnesium products and supportive measures are available.

Table 1: Causes of hypomagnesaemia.

Increased Mg^{++} sequestration from the extracellular space
- increased Mg^{++} uptake in the bones
- Mg^{++} precipitation in the tissues
- increased Mg^{++} uptake into the intracellular space
- respiratory alkalosis
Increased Mg^{++} excretion by the kidneys
- diuretics, cisplatin
- expansion of the extracellular space
- pharmaceuticals
- congenital defects of tubular Mg^{++} reabsorption
Reduced Mg^{++} uptake from the gastrointestinal tract
- proton pump inhibitors, metformin
- malnutrition/inadequate dietary supply
- malabsorption
- parenteral nutrition
Alcoholism

More recently it has been reported that, besides other electrolyte imbalances, magnesium deficiency may also promote the development of high blood pressure. Numerous studies have presented relevant data on red blood cells, lymphocytes, platelets, cell membranes and smooth muscle cells. Many of these publications have come from our own research group. The diagnosis of magnesium deficiency by means of laboratory tests is often difficult, as the serum magnesium concentration accounts for only about 1% of the total body magnesium. However, new analytical methods now allow us to measure ionized magnesium concentrations easily. Ionized magnesium is the actual vasoactive form of magnesium that is important in the development of hypertension. Elderly people in particular often have a magnesium deficiency. The causes of this are numerous and include poor dietary intake, interactions between medicines and comorbidities [1-5]. It was therefore of interest for us to measure the serum magnesium levels and ionized magnesium concentrations in a group of elderly patients with essential hypertension.

Table 2: Important magnesium-dependent enzymes and proteins.

- $Na^{+}K^{+}$-ATPase
- Ca^{++}-ATPase
- H^{+}-ATPase
- Mg^{++}-ATPase
- K^{+} channels
- Adenylate cyclase
- Mg^{++}-dependent nucleic acid polymerases
- Pyruvate dehydrogenase
- Propionyl-CoA carboxylase
- Phosphoenolpyruvate carboxykinase
- Hexokinase and other glycolytic enzymes
- Ornithine carbamoyltransferase
- Membrane proteins

PATIENT POPULATION AND METHODS

We studied 45 patients with essential hypertension and normal renal function (serum creatinine 1.1 ± 0.1 mg/dL). 23 men and 22 women participated in the study. The mean age was 69.4 ± 4.4 years. None of these patients took magnesium supplements. All patients had essential hypertension that was being treated with the usual antihypertensive agents (betablockers, calcium antagonists or Renin-Angiotensin-Aldosterone System (RAAS) blockers). None of the patients had been given diuretics for at least 4 weeks before the start of the study. The patients gave their written informed consent.

Serum magnesium concentrations were measured in mg/dL using a Cobas instrument from Roche, Germany. The analysis of the measurements of the ionized magnesium concentration was carried out with a Prime Plus system from NOVA Rödermark, Germany. This is a point-of-care device. Besides ionized magnesium and calcium, it determines blood gases, glucose, haemoglobin and serum creatinine. The tests use either

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capillary blood or about 1 mL of whole blood and the complete measurement process takes about 1 minute. The results of the ionized magnesium measurements are given in mmol/L. and are presented as mean ± standard deviations. The statistical analyses were performed with Anova.

RESULTS

The mean serum magnesium concentration in elderly hypertensive patients was 1.97 ± 0.17 mg/dL. The normal range is 1.7-2.55 mg/dL. Only one male patient had values less than 1.5 mg/dL. All the other subjects had normal serum magnesium concentrations. The mean ionized magnesium concentration in these elderly hypertensive patients was 0.58 ± 0.1 mmol/L. The normal range was 0.54-0.8 mmol/L. In contrast to the serum magnesium levels, there were statistically significant lower concentrations of ionized magnesium in 15 of the 45 patients (< 0.5 mmol/L) ($p<0.01$), corresponding to 30% of the patients. There was no correlation between the serum levels and the ionized magnesium (ns, Pearson or Spearman rank order correlation, p-value 0.91 and 0.41 respectively). Blood pressure was well controlled and remained below 150/90 mmHg in all patients.

The results are presented in Figure 1.

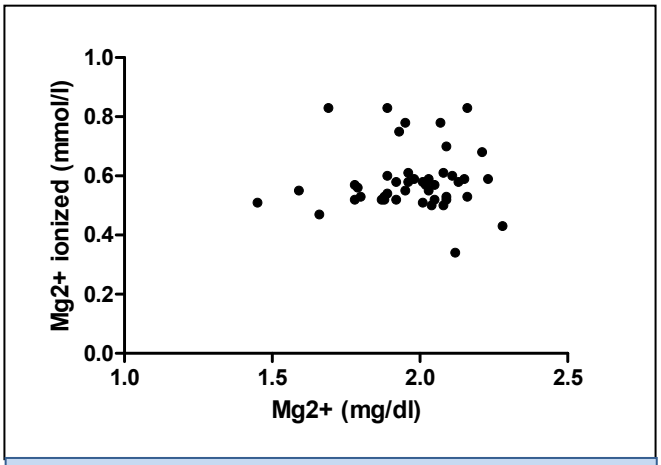

Figure 1: Ionized magnesium concentrations and serum magnesium levels in 45 elderly hypertensive patients.

DISCUSSION

As long ago as 1960, our research group first showed that the intracellular sodium concentrations in red blood cells were raised in patients with primary essential hypertension. At first, both we and other researchers assumed that this raised sodium concentration, which was later also demonstrated in the vessel walls of hypertensive rats, was key to the development of high blood pressure. It was assumed that the sodium gradient of the muscle cells was decisive for the tone of the vessel walls and thus for the blood pressure. Later studies, however, showed not only the intracellular sodium concentration to be raised in essential hypertension, but also the intracellular calcium activity. From today's perspective, this increase in intracellular calcium may ultimately be significant for the increased vascular tone in hypertensive patients and therefore responsible for the development of high blood pressure [1-7]. Several factors come into consideration for the increase in intracellular calcium activity in hypertension. One of these factors may be the accumulation of sodium in the cells, but we can assume that other electrolytes may also affect the intracellular calcium concentration. The first to be mentioned in this context is potassium. It has been known for a long time that hypokalaemia has a negative effect on the pharmacotherapeutic control of high blood pressure. On the other hand, both animal and clinical studies have shown that the administration of potassium lowers the blood pressure.

Numerous studies have demonstrated that magnesium deficiency not only leads to a reduction in the intracellular magnesium concentration, but also simultaneously increases the intracellular sodium and calcium concentrations and reduces the potassium levels. A series of studies on electrolyte balance has also shown that intracellular calcium activity is central to the pathogenesis of essential hypertension. Increased calcium activity may result from a potassium or magnesium deficiency as well as from an increased sodium supply, with major therapeutic consequences. Along with other research groups, we have described a sodium-magnesium antiport in red blood cell membranes. On the one hand, hypokalaemia or hypomagnesaemia is unfavourable in this respect. On the other hand, it is conceivable that the blood pressure can be lowered by giving magnesium supplements, even when extracellular magnesium concentrations are normal. This would influence intracellular calcium activity via the calmodulin complex and muscle filament contraction, which is also magnesium- and phosphate-dependent through Adenosine Triphosphate (ATP) consumption, as we were able to demonstrate in smooth muscle cells. As a physiological calcium antagonist, magnesium should

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therefore be used in the treatment of high blood pressure. Even though it is not to be expected that the administration of magnesium alone would return the blood pressure to normal levels in the case of WHO grade II or III hypertension, its concomitant administration may allow the dose of other antihypertensive agents to be reduced and, as a result, the numerous adverse drug reactions to antihypertensive therapy would certainly also decrease [8-16].

The detailed associations between Type 2 Diabetes (T2D) and total stroke and magnesium intake as well as the dose–response has been documented in a recent meta-analysis. A total of 41 prospective cohort studies comprising 53 cohorts, 1 912 634 participants and 76 678 cases were eligible for inclusion in the systematic review and meta-analysis. The magnitude of the risk was significantly reduced by 22% for T2D (RR 0.78 (95% CI 0.75 to 0.81); p<0.001; AR reduction 0.120%), 11% for total stroke (RR 0.89 (95% CI 0.83 to 0.94); p<0.001; AR reduction 0.281%) and 12% for ischaemic stroke (RR 0.88 (95% CI 0.81 to 0.95); p=0.001; AR reduction 0.246%) when comparing the highest magnesium intake to the lowest. The inverse association still existed when studies on T2D were adjusted for cereal fibre (RR 0.79; p<0.001) and those on total stroke were adjusted for calcium (RR 0.89; p=0.040).

Another large-scale meta-analysis from 2013 documented a dose-dependent effect of magnesium monotherapy on both the systolic and diastolic blood pressures. Likewise, magnesium deficiency may have unfavourable effects on the development of arteriosclerosis. Increased intima-media thickness in the common carotid artery has recently been reported. Magnesium deficiency also affects the pulse pressure (the difference between the systolic and diastolic blood pressure). A high pulse pressure (i.e. > 66 mmHg) promotes the occurrence of hypertension, arteriosclerosis, strokes and heart attacks. Magnesium deficiency also plays a significant role here [8-19].

The total magnesium content in a healthy person weighing 70 kg is about 2000 mval or 24 g. In terms of quantity, magnesium therefore lies in fourth place after the alkali metal ions sodium and potassium and the other biologically important alkaline earth metal ion calcium. Taking the mval as the unit of measurement, the magnesium content in the body is about half that of sodium or potassium. Some 50-60% of the total magnesium content can be found in the bones and about 30% in the muscles; 1% of the total magnesium is present in the extracellular space. In skeletal muscle, the distribution of magnesium between the intra- and extracellular compartments runs in part parallel to the K^+ gradients across the cell membrane. The serum Mg^{++} concentration lies between 0.8 and 1.2 mmol/L. Approximately 60% of this is present as free ions, 15% is bound to complexes, e.g. in the form of phosphates or citrates, and 25-32% is bound to proteins, especially albumin. The red blood cell/serum magnesium concentration gradient is about 2.5 [1,2].

In the cells, magnesium is responsible for the activation of some 600 enzymes and transport proteins (Table 2). Addressing some of the cytosolic and mitochondrial enzymes in particular: Na^+-K^+-ATPase requires magnesium, as do Ca^{++}-ATPase and H^+-ATPase, while the rectifying behaviour of certain Ca^{++} and K^+ channels is regulated on the cytosolic side by magnesium. The average daily intake of magnesium is 10-15 mmol, with some 60-79% subsequently excreted in the faeces and 21-40% in the urine. Magnesium is absorbed in the small intestine. Isotope studies with 28Mg have confirmed this, although the factors that promote or suppress absorption have still not been fully clarified. Increasing the supply of magnesium does not lead to a linear increase in its absorption or in its excretion via the kidneys. The higher the oral supply of magnesium is, the lower its absorption. The physiological magnesium level is a relevant starting point here. More magnesium is absorbed, if there is a magnesium deficiency, while less is absorbed in the case of magnesium saturation. With a normal magnesium balance, therefore, even high oral doses of magnesium cannot achieve magnesium storage much above the upper level of normal. Following absorption in the intestine, magnesium is eliminated mainly via the kidneys. Renal excretion is extremely rapid to prevent a significant rise in the blood levels. Amongst other things, this explains the long exchange time between the magnesium pool in the cells and the extracellular magnesium [1,2].

The filtration of magnesium is incomplete due to protein binding. The Gibbs-Donnan effect means that there is a slight further decrease in the concentration on the Bowman's capsule (filtrate) side. Reabsorption of magnesium in the proximal tubule is coupled to Na^+ reabsorption and therefore also increases in the case of hypovolaemia. Conversely, magnesium

absorption decreases with hypervolaemia. In addition, mineralocorticoids and glucocorticoids have effects on magnesium excretion. An increased secretion of mineralocorticoids and glucocorticoids leads to an increase in magnesium excretion, whilst the converse is true when there is a deficiency of these hormones. Magnesium absorption in the loops of Henle is reduced by an increase in the extracellular Ca^{++} concentration. We assume that there is competition between Ca^{++} and Mg^{++} with respect to absorption in the loops of Henle. Magnesium transport in the loops of Henle is coupled to chloride transport. All diuretics that lead to increased K^{+} excretion (thiazides, loop diuretics, carbonic anhydrase inhibitors) simultaneously increase magnesium excretion, but K^{+}-sparing diuretics do not. The precise reasons for this are unknown [1-3].

Besides the actions of steroids, the hormonal effects of parathyroid hormone must also be mentioned. Parathyroid hormone increases magnesium absorption, although it is partially or completely antagonised by the opposing effects of hypercalcaemia. This also explains the different findings with respect to magnesium excretion in primary hyperparathyroidism. Magnesium excretion is slightly reduced both in Addison's disease and with the administration of an aldosterone antagonist (spironolactone). However, as a rule, this observation has practically no clinical relevance. Since up to almost 79% of the magnesium intake may be lost with bowel motions ('stool ions'), problems with magnesium absorption from the intestine may arise in the case of diarrhoea. When there is an intracellular magnesium deficiency, increased neuromuscular excitability in the intestinal smooth muscle (which may result in diarrhoea) reduces the absorption of magnesium even further [7].

Independent magnesium transport channels have gained interest in recent years, especially TRPM7 and 6. The TRMP7 channel, in particular, is of great importance in blood pressure regulation [6]. These channels were first discovered in the intestine, but have since also been found in the kidney and the heart. They have been well documented in publications over the last couple of years. Interactions with vitamin D also exist [1,2].

The study presented here involving elderly hypertensive patients demonstrated a deficiency of ionized magnesium in about 30% of the patients, even though the serum magnesium levels were apparently within the normal range. These findings provide further evidence for the weakness of routine lab tests for magnesium to date. Furthermore, publications on geriatric populations indicate that magnesium deficiency occurs frequently (in up to 50%). The severity of the magnesium deficiency and the clinical picture depend on nutritional status, concomitant medication (e.g. diuretics, proton pump inhibitors, metformin or psychotropic drugs) and existing diseases (such as diabetes, chronic inflammatory bowel disease or chronic kidney disease) [1,2,7].

It is therefore clear that a magnesium imbalance may exist in elderly hypertensive patients, so that replacement therapy with oral magnesium supplements (about 4 to 10 mg magnesium per kg bodyweight daily) is of benefit. Likewise, determination of the ionized magnesium concentration is a relevant lab test that offers considerable advantages over the usual methods for measuring the serum magnesium concentration.

CONCLUSION

Magnesium is present in almost all organs of the body and plays an important role in carbohydrate and protein metabolism as well as in nearly all enzymatic processes. It is an essential mineral that has to be supplied in the diet. Dietary habits can aggravate the negative impact of drugs on magnesium status. In the US and the UK, the magnesium content of vegetables and fruit have lost in the past 100 years large amounts of minerals and other micronutrients. It is estimated that vegetables (e.g. cabbage, lettuce, spinach) have dropped magnesium levels by around 80–90%. For instance modern dietary practices such as vegetable cooking and grain bleaching can cause a loss of up to 80% of magnesium content. Magnesium intoxication is rare. Magnesium deficiency is characterised by cerebral involvement (pressure headaches, dizziness, ataxia, drowsiness), by cardiac arrhythmias, muscle involvement with tetany and smooth muscle spasms, hypertension and raised pulse pressure as well as by the development of arteriosclerosis. Serum Mg^{++} levels are of only limited value in assessing the integrity of the magnesium balance. Magnesium-rich foods are recommended in the treatment of magnesium deficiency, while various magnesium products, mineral waters, spa waters and magnesium-enriched salts are also available (Table 3).

Table 3: Indications for Mg therapy.

- Mg-deficiency
- Normocalcaemic tetany
- Calf muscle cramps, neonatal seizures
- Tachycardic arrhythmias (ventricular arrhythmias)
- Digitalis intoxication
- Calcium stones (relapse prevention therapy)
- Extraosseous calcifications (myositis ossificans)
- Vascular spasms (cardiac, cerebral?)
- Eclampsia
- High blood pressure (e.g. physiological Ca-antagonist)
- Diabetes Typ 1 and 2
- Migraine
- Hearing loss
- Dysmenorrhoea
- Arteriosclerosis
- Hyperlipidaemia

In the present study on elderly patients with essential hypertension, we did not find a significant correlation between the serum magnesium concentration and ionized magnesium. About 30% of the elderly hypertensive patients over the age of 65 had a deficiency of ionized magnesium despite a normal serum magnesium level. Elderly patients often have an ionized magnesium deficiency. The determination of ionized magnesium offers considerable advantages in the diagnostic investigation of magnesium deficiency.

REFERENCES

1. Gröber U, Schmidt J, Kisters K. (2015). Magnesium in Prevention and Therapy. Nutrients. 23: 8199-8126.
2. Gröber U, Schmidt J, Kisters K. (2018). Important drug-micronutrient interactions: A selection for clinical practice. Crit Rev Food Sci Nutr Dez. 23: 1-19.
3. Kisters K, Gröber U. (2018). Magnesium and thiazide diuretics. Magnes Res. 31: 143-145.
4. Kisters K, Gremmler B, Schmidt J, Gröber U, Tokmak F. (2017). Positive effect of magnesium orotate therapy in hypertension heart disease. Metabolism. 7: 1-4.
5. Rosanoff A, Plessert MR. (2013). Oral magnesium supplements decrease high blood pressure (SBP<155 mmHg) in hypertensive subjects on antihypertensive medications: a targeted meta-analysis. Magnes Res. 26: 93-99.
6. Touyz RM, Yao G. (2004). Presence of functionally active Mg** uptake channels. TRPM6 and TRPM7 in vascular smooth muscle cell from WKY and SHR - differential regulations by aldosterone an angiotensin II. Am J Hypertens. 5: 176.
7. Vorman J. (2016). Magnesium: Nutrition and Homoeostasis. Public Health. 3:329-340.
8. Kisters K, Spieker C, Tepel M, Zidek W. (1993). New data about effects of oral physiological magnesium supplementation on several cardiovascular risk factors (lipids and blood pressure). Magnes Res. 4: 335-360.
9. Kisters K, Tepel M, Spieker C, Dietl KH, Barenbrock M, et al. (1997). Decreased cellular magnesium concentrations in a subgroup of hypertensives–cell models for the pathogenesis of primary hypertension. Hum Hypertens. 11: 367-372.
10. Kisters K, Tepel M, Spieker C, Zidek W, Barenbrock M, et al. (1998). Decreased cellular magnesium concentrations in a subgroup of hypertensives. Membrane model for the pathogenesis of primary hypertension. Am. J. Hypertens. 11: 1390-1393.
11. Kisters K, Krefting ER, Spieker C, Zidek W, Dietl KH, et al. (1998). Increased sodium/magnesium exchange in vascular smooth muscle cells from SHR. Clin Sci. 95: 583-587.
12. Kisters K, Krefting ER, Hausberg M, Kohnert K, Honig A, et al. (2000). Importance of decreased intracellular phosphate and magnesium concentrations and reduced ATPase activities in SHR. Magnes. Res. 13: 183-188.
13. Kisters K, Wessels F, Küper H, Tokmak F, Krefting ER, et al. (2004). Increased calcium and decreased magnesium concentrations and an increased calcium/magnesium ratio in spontaneously hypertensive rats versus Wistar-Kyoto rats: relation to arteriosclerosis. Am J Hypertens. 17: 59-62.
14. Kisters K, Gremmler B, Hausberg M. (2005). Magnesium and arterial stiffness. Hypertension. 47: e3.
15. Kisters K, Hoffmann O, Hausberg M, Funke C, Kozianka J, et al. (2005). Magnesium und Pulsdruck bei Hypertonie. Nieren-Hochdruckkrh. 10: 455- 457.
16. Kisters K, Gremmler B, Hausberg M. (2006). Preventing pregnancy induced hypertension: the role of calcium and magnesium. J. Hypertens. 24: 201.
17. Gröber U. (2019). Magnesium and Drugs. Int J Mol Sci. 20: 2094.
18. Gröber U. (2020). Common drugs as micronutrient disruptors: A selection for clinical practice. Ann Epidemiol Public Health. 3: 1014-1031.
19. Zhao B, Zang L, Zhao J, Wu Q, Dong Y, et al., (2020). Association of Magnesium Intake With Type 2 Diabetes and Total Stroke: An Updated Systematic Review and Meta-Analysis. BMJ Open. 10: e032240.