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Magnesaemia in dialysis patients – the unappreciated feature of mineral metabolism

Stężenie magnezu w osoczu u pacjentów dializowanych – niedoceniany aspekt gospodarki elektrolitowej

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S u m m a r y

Magnesium plasma concentration are seldom controlled in dialysis patients. This article addresses the role of magnesium as the fourth most abundant cation, the consequences of hypo- and hypermagnesaemia, and the prevalence of hypo- and hypermagnesaemia in patients on dialysis. In people with CKD and in dialysed patients, plasma level of magnesium could be above normal, because of the lack of excretion by the kidneys, normal or below normal, as a result of diminished reabsorption and/or removal of magnesium during dialysis. In general population the hypomagnesaemia is a significant predictor of increased cardiovascular morbidity and mortality, and dietary magnesium intake is inversely associated with mortality risk. More and more experimental studies report a protective effect of magnesium on cardiovascular system, including inhibitory effects of magnesium on vascular calcification. Mechanism of this protective magnesium activity is intensely studied. Recently published data obtained from a large group of dialysed patients correlated the higher concentration of magnesium in plasma (including mild hypermagnesaemia) with lower mortality, and lower vascular calcification, which confirmed the earlier observations made on smaller groups of patients. Thus, it seems necessary to monitor the concentration of magnesium in dialysed patients, and prevent its deficiency. Though mild hypermagnesaemia appears of no consequences to the dialysis patients' health, and even could be protective, the lack of large interventional clinical trials does not allow, at present, to promote magnesium supplementation to increase its level above normal with an intention to prevent vascular calcification and reduce mortality.

S t r e s z c z e n i e

Stężenia magnezu w osoczu pacjentów dializowanych nie monitoruje się rutynowo, mimo że zaburzenia metabolizmu tego jonu są bardzo częste w tej grupie chorych. W artykule omówiono rolę magnezu jako ważnego, czwartego co do ilości kationu w organizmie oraz częstość występowania i konsekwencje hipo- i hipermagnezemii u pacjentów dializowanych. U pacjentów z niewydolnością nerek oraz dializowanych stężenie magnezu w osoczu może być zarówno podwyższone (z uwagi na brak czynności wydalniczej nerek), prawidłowe, jak i obniżone (z powodu zmniejszonego wchłaniania w przewodzie pokarmowym i usuwania magnezu do płynu dializacyjnego podczas dializy). W populacji ogólnej i u chorych z chorobami sercowo-naczyniowymi wykazano niekorzystny wpływ hipomagnezemii na chorobowość i śmiertelność, i odwrotnie – korzystny efekt suplementacji magnezu. W wielu badaniach eksperymentalnych *in vitro* i *in vivo* na modelach zwierzęcych wykazano ochronny wpływ magnezu na układ sercowo-naczyniowy, w tym na hamowanie kalcyfikacji naczyń. Mechanizmy tego protekcyjnego działania magnezu są intensywnie badane. W dużych badaniach obserwacyjnych publikowanych ostatnio potwierdzono wcześniejsze doniesienia o dodatniej korelacji pomiędzy wyższymi stężeniami magnezu u chorych dializowanych, w tym łagodnej hipermagnezemii, a mniejszą chorobowością i śmiertelnością oraz mniejszym stopniem kalcyfikacji naczyń. Stężenie magnezu powinno być zatem rutynowo oznaczane u chorych dializowanych i należy zapobiegać jego niedoborom. Wydaje się, że chociaż łagodna hipermagnezemia wydaje się pozbawiona ryzyka dla pacjentów, a nawet może mieć znaczenie ochronne dla układu krwionośnego chorych, to z uwagi na brak dużych badań interwencyjnych rutynowa suplementacja magnezu nie może być zalecana pacjentom leczonym hemodializami.

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Disorders of magnesium homeostasis are common, but seldom monitored in dialysis patients. Mild hypermagnesaemia in this particular group of patients is present more often than in general population, but hypomagnesaemia can also ensue. Can we identify implications for the CRF patients of those disorders and should we monitor the concentration of magnesium in plasma in RRT patients, and try to normalize it?

Data obtained from a large group of patients in Japan show correlation between higher concentration of magnesium in plasma and lower mortality, which confirms the earlier observations made on smaller groups of patients (1-5). A number of experiments conducted during last 15 years showed beneficial effect of magnesium in preventing vascular calcification. In general population and in CVD patients' hypomagnesaemia was correlated with higher mortality, and higher magnesium levels correlated with better outcomes.

Because of that, many of investigators suggest the necessity of the regular monitoring of the magnesium plasma concentration in dialysis patients.

Magnesium is the fourth most abundant cation in the body, and the second intracellular cation. Almost half of magnesium is located in bones. Only 1-2% is present in extracellular space. About 25-30% of magnesium in serum is bound to proteins, mainly albumin, 5-10% is complexed with nonprotein anions such as bicarbonate, phosphate and citrate; the rest is free, mostly ionized.

In general population, the total and ionized serum magnesium normal concentrations usually range 0.65-1.05 mmol/L and 0.45-0.74 mmol/L, respectively (1 mEq/l = 0.5 mmol about 1.2 mg/dl). Serum magnesium concentration does not strictly reflect the total amount of magnesium in the body.

Kidneys have an important role in magnesium homeostasis: regulation of magnesium excretion is determined by filtration and reabsorption (6, 7). In people with normal renal function ~95% of the 74-100 mmol (1800-2400 mg) of magnesium filtered daily, is reabsorbed in tubules, with the remaining ~5% being excreted in urine. Magnesium reabsorption takes place both in the thick ascending limb (via the paracellular pathway), and in the distal convoluted tubule (via the transcellular route involving transient receptor potential cation channel subfamily melastatin member 6 – TRPM6). In hypermagnesaemia, the fractional excretion of magnesium is high, and it is low in hypomagnesaemia.

In moderate CKD, the increase in fractional excretion of magnesium compensates for the loss of renal function, thus serum levels are maintained within the normal range, but in more advanced renal failure the mechanism becomes inefficient and thus the hypermagnesaemia is quite common. There are many additional factors affecting magnesium concentration in plasma, and magnesium body content (diuretics, proton pump inhibitors, phosphate binders, poor nutrition, acidosis and followed reduced absorption), so in people with CKD the magnesium balance can become negative and lower its plasma concentration.

In dialysed patients the magnesium concentration in dialysate is one of the major determinants of magnesium balance. Ionised magnesium crosses the dialyser and peritoneal membranes freely, and the amount eliminated depends on both the ultrafiltration and the diffusible magnesium concentration gradient between serum and dialysis fluid. Ionized magnesium ranges between 60 and 70% of the total serum value depending on protein concentration and percentage of the complexed magnesium. In most cases, a dialysate magnesium concentration of ~0.5 mmol/L ($\times$ 0.962 = 0.46 mmol/L) or lower, results in a diffusive elimination of magnesium.

Mild hypermagnesaemia has been described when using magnesium dialysate concentration of 0.75 mmol/L, in both PD and HD patients, but when lower dialysate concentrations (0.5 and/or 0.25 mmol/L) were used, the results were not that much consistent.

Besides the dialysate concentration, number of factors like diuretics, nutrition, and disorders of gastrointestinal tract, affect the magnesium balance in HD/PD patients. In recent years the role of commonly used proton pump inhibitors, is stressed (8). Proton pump inhibitors decrease the activity of TRPM6 (which is expressed in distal tubule and also in the small intestine brush border membrane, where it increases intestinal magnesium uptake in face of low magnesium intake), and predispose to hypomagnesaemia (9).

Mineral magnesium is involved in several important biochemical reactions, including all ATP transfer reactions (10). Magnesium directly influences vascular tone, baseline tension and vascular responsiveness to vasoconstrictor agents (11).

Magnesium affects calcium ion concentration and its availability at critical sites, acting as a physiologic calcium channel blocker (12). Increased levels of extracellular magnesium inhibit calcium influx. And conversely, reduced extracellular magnesium activates calcium influx via calcium channels. Low intracellular magnesium concentrations stimulate inositol-triphosphate (IP-3)-mediated mobilization of intracellular calcium and reduce Ca^{2+}-ATPase activity. Thus, calcium efflux and sarcoplasmic reticular calcium reuptake are reduced, leading to cytosolic accumulation of calcium and increased intracellular calcium concentration, which is the crucial factor for vasoconstriction. Increased intracellular levels of magnesium result in decreased intracellular free calcium concentration, promoting vasodilation.

Magnesium is also cofactor for acetylcholine-induced endothelium-dependent relaxation. Alterations in extracellular magnesium are able to modify the formation and release of nitric oxide, this way altering arterial smooth muscle tone.

In general population the hypomagnesaemia is a significant predictor of increased cardiovascular morbidity and mortality, favours reduction of HDL and increase of LDL and TG, increases oxidative stress and inflamma-

tion, platelet aggregation and insulin resistance (13). Data from recent trial: a study on the Atherosclerosis Risk in Communities (ARIC) cohort (> 14,000 participants), reported an independent association between low magnesium levels and incident heart failure (14). Dietary magnesium intake was inversely associated with mortality risk in people at high risk of CVD in Spanish prospective randomized trial (> 7,200 patients) (15) and in general population (16).

Manifestations of severe hypomagnesaemia include: ataxia, tetany, tremors, depression, muscle fibrillation, and irritability. In less severe cases (mild to moderate) hypomagnesaemia can lead to general weakness, vertigo, electrocardiographic changes (QT prolongation, ST segment shortening), increase in myocardial irritability, reduced myocardial contractility, positive Trousseau and Chvostek signs, hypertension, neuromuscular hyper-excitability with hyper-reflexia, abnormal skeletal function, increased renin and aldosterone secretion and increased incidence of osteoporosis.

Manifestations of severe hypermagnesaemia include: muscle paralysis, apnoea, heart block and cardiac arrest (Mg > 5 mmol/l). Moderate hypermagnesaemia (> 3 mmol/l) can cause: somnolence, areflexia, hypocalcaemia, hypotension, bradycardia electrocardiographic changes (prolongation of PR and QT intervals, increase in QRS duration), pruritus. Hypermagnesaemia > 2 mmol/l can cause hyporeflexia, drowsiness, but that of less than 2 mmol/l is asymptomatic (17, 18).

In RRT patients hypermagnesaemia is seldom above 1.5 mmol/L.

The anxiety about the negative impact of hypermagnesaemia on RRT patients was concerned with bone abnormalities. Even so, the studies assessing the amount of magnesium in bones in patients on RRT are scarce and with the extremely inconsistent results (19-24). It is worth to point out that magnesium constitute only tiny fraction of bone mass – about 0.5%. In several studies authors found the elevated magnesium concentrations in trabecular and cortical bones (20-22), but other group did not find it (25).

Because of its inhibiting effect in mineralisation and influence on PTH secretion, it was suggested that magnesium could be involved in pathogenesis of renal osteodystrophy. On the other hand it was proved that the deficiency of magnesium leads to osteoporosis (26-28).

It was demonstrated that magnesium plasma concentration influence PTH secretion: high magnesium activates extracellular CaSR leading to decreased PTH secretion. On the other hand in patients with severe hypomagnesaemia, at levels < 0.5 mmol of magnesium, secretion of PTH is suppressed (29, 30), and calcium-dependent regulation can be restored by elevating magnesium concentrations. Low Mg levels may reduce serum vitamin D levels and cause vitamin D deficiency (31).

Magnesium deficiency can exacerbate inflammation and in this way lead to osteoporosis. In the rat and/or mouse the Mg deficiency results in increased skeletal substance P, which in turn stimulates production of cytokines. With the use of immunohistocytochemistry, it was found that Mg deficiency resulted in an increase in substance P, TNF alpha and IL-1beta (23).

Several small clinical trials were assessing the influence of Mg on the bone using bone biopsy. In one study, after increasing the serum Mg concentration from 0.96 ± 0.2 mmol/l to 1.54 ± 0.2 mmol/L by using a magnesium phosphate binder for 8 and 20 months, bone histomorphometry (performed in 9 patients) showed no change in mineralization or osteoid formation (21).

However, in another study, diminishing serum magnesium from 1.24 ± 0.15 mmol/L to 1.03 ± 0.6 mmol/L by changing the dialysate magnesium concentration from 0.5 mmol/L to 0.25 mmol/L, resulted after one year in significant reduction of the biopsy proven osteomalacia pattern (32).

Finally in a study on bone biopsies from 100 HD patients authors did not find any increased amount of magnesium in bone, despite the increased magnesium/calcium ratio. This increased ratio was not correlated with osteomalacia (vs. increased bone aluminium, lead and strontium concentrations and aluminium/calcium ratio) (33).

After 18 month of taking magnesium as a main phosphate binder in 7 HD patients with coronary hart disease authors did not find any impact on vertebral BMD (34).

The inconsistencies mentioned above explain, why at present, the role of magnesium in affecting bone metabolism remains unclear.

The relationship between low magnesium concentration and haemodynamic instability – tendency to hypotension, arrhythmia, and worse cardiac contractility in HD patients is well known (35, 36). The NDT 2007 Guideline 3.2.4a states clearly: "In patients with frequent episodes of IDH, low (0.25 mmol/l) magnesium dialysate should be avoided, especially in combination with low-calcium dialysate (Level II)".

But the attention paid lately to magnesium in patients on RRT is on raise because of increasing number of experimental studies reporting inhibitory effects of magnesium on vascular calcification in normal and/or uremic animals (37-39) and in *in vitro* models (40). What is even more interesting – the increasing number of epidemiologic studies shows correlations between higher serum magnesium levels, and lower incidence of CVD and mortality (1-5).

Many studies pointed out that higher serum magnesium is correlated with diminished vascular calcification (VC), and lower magnesium with more increased VC (2, 3, 41). In one of the earliest studies in 44 CAPD patients (follow up of 27 months) the relationship of serum levels of Ca, P, P/Mg, Ca X P/Mg and iPTH to the development or regression of peripheral arterial Mg and Ca X P/Mg were significantly higher. Authors conclude that in end-stage renal disease, hypermag-

nesaemia may retard the development of arterial calcifications (2).

A large study conducted on 142,555 haemodialysis patients from nationwide registry-based cohort in Japan with the objective to determine whether hypomagnesaemia is an independent risk for increased mortality, showed that in this population hypomagnesaemia was significantly associated with an increased risk of mortality in haemodialysis patients (1). Moreover, among patients with serum phosphate levels of ≥ 6.0 mg/dl, the cardiovascular mortality risk significantly decreased with increasing serum magnesium levels.

Simultaneously, the mechanism of possible protective role of magnesium on vascular calcification was examined in experimental studies.

The process of vascular calcification in people on RRT is still being investigated. One of the most important factors triggering VC is hyperphosphataemia. Hyperphosphataemia along with the loss of inhibitors of mineralization leads to the formation of Ca/P nanocrystals, which are taken up by vascular smooth muscle cells (VSMCs). Magnesium inhibits transformation of amorphous Ca/P to apatite and, by forming Mg-substituted whitlockite crystals, which result in smaller, more soluble deposits (9, 42-44), and in this way prevents atherosclerosis. Nevertheless, in a study published lately, the authors exclude a physicochemical role of magnesium in altering the calcium/phosphate crystal growth, composition or structure suggesting that magnesium beneficial role in attenuating VC should be linked to an active cellular role (45).

Inorganic phosphate (Pi) accumulate within the cells, inter alia, via an uptake through Pit-1 and Pit-2. After lysosomal degradation of nanocrystals Ca and Pi are released into the cell. Ca/P nanocrystals and Pi induce expression of genes, which promote the osteogenic transformation process and supress the expression of factors that inhibit calcification leading to transdifferentiation of VSMCs to osteoblast-like cells. Mg functions as a Ca-channel antagonist and thus inhibits the entry of Ca into the cells. Mg enters the cell via TRPM7 and prevents osteoblastic conversion and calcification of VSMCs, by diminishing enhanced expression of RUNX2 and BMP2 and neutralizing phosphate-induced inhibition of MGP and BMP7 (39, 46, 48, 49).

In addition, magnesium acts on the calcium-sensing receptor (CaSR).

In experimental investigations the effect of magnesium on calcification induced by β-glycerophosphate (BGP) in bovine vascular smooth muscle cells (BVSMCs) were examined.

Magnesium prevented calcium deposition in the cells and in higher levels led to inhibition of BGP-induced alkaline phosphatase activity as well as to a decreased expression of genes associated with the process of trans differentiation of BVSMCs into osteoblast-like cells. Furthermore, estimated calcium entry into the cells decreased with increasing magnesium concentrations in the media. In addition, higher magnesium concentrations prevented cell damage (apoptosis) induced by BGP as well as progression of already established (47).

Other group provided *in vitro* evidence for a protective role of magnesium on Pi-induced calcification in a primary cell culture model of human aortic vascular smooth muscle cells (HAVSMC) (37).

Lately it was determined that magnesium in levels only slightly increased, significantly reduced VSMC calcification and expression of the osteogenic transcription factors Cbfa-1 and osterix, and up-regulated expression of the natural calcification inhibitors matrix Gla protein (MGP) and osteoprotegerin (OPG). High phosphate induced activation of Wnt/β-catenin pathway, as demonstrated by the translocation of β-catenin into the nucleus, increased expression of the frizzled-3 gene, and increased downregulation of Dkk-1 gene, a specific antagonist of the Wnt/β-catenin signalling pathway. The addition of magnesium inhibited phosphate-induced activation of Wnt/β-catenin signalling pathway. Furthermore, TRPM7 silencing using siRNA resulted in activation of Wnt/β-catenin signalling pathway. Inhibition of Wnt/β-catenin by magnesium is one potential intracellular mechanism by which this anticalcifying effect is achieved (48).

The effect of magnesium in animal models has been also investigated. In Abcc6-knockout mice, a model of pseudoxanthoma elasticum with diffuse connective tissue and arterial calcification, an increase in dietary magnesium intake led after 12 months to a marked decrease in the calcium content of vascular tissues (36, 49).

In rats with chronic renal failure induced by an adenine diet for 4 weeks, the aortic calcium content was examined after one week of treatment with CaMg in comparison to sevelamer and vehicle. The percentage of calcified area of the aorta was significantly lower in sevelamer and CaMg group than vehicle-treated animals. The presence of aortic calcification was associated with increased *sox9*, *bmp-2*, and *matrix gla* protein expression, but this did not differ in the treatment groups. Thus, treatment with either CaMg or sevelamer effectively controlled serum phosphate levels in CRF rats and reduced aortic calcification. Therefore, phosphate binders in which part of the calcium is replaced by magnesium might be a good alternative for calcium acetate/carbonate in dialysis patients with vascular calcification (50). It is also safe for bones (38).

In spite of quite strong evidence from experimental and observational studies that magnesium could prevent VC and diminish mortality, there is lack of large intervention clinical trials.

The interventions trials are sparse and conducted in small group of patients.

In one study including 7 patients with coronary artery disease, magnesium carbonate/calcium carbonate (elemental Mg: 86 mg/elemental Ca 100 mg) was administered as the principal phosphate binder for

a period of 18 months and changes in coronary artery calcification and vertebral-bone mineral density were measured at baseline, 6, 12, and 18 months. Electron beam computed tomography results demonstrated a small not statically significant increase in absolute CAC scores, and a small none significant change in V-BMD. Authors conclude that magnesium may have a favourable effect on CAC (33).

In the second one-which included 47 HD patients, the effect of magnesium citrate 610 mg/d vs. calcium acetate as a phosphate binder was examined on carotid intima media thickness measured by ultrasound. At the end of 2 months bilateral carotid IMT was significantly improved in patients treated with magnesium citrate compared to initial values (51).

The last study involved 36 HD patients who received magnesium carbonate plus calcium acetate as a phosphate binder (Mg group), and the 36 who received calcium acetate alone (Ca group), during 12 months. In 9/32 (28.12%) patients of the Mg group and in 12/27 (44.44%) patients of the Ca group, the arterial calcifications worsened ($p = 0.276$). Moreover, in 4/32 (15.6%) patients in the Mg group and in 0/27 (0%) patients in the Ca group, the calcification improved ($p = 0.040$), which suggests that serum magnesium was an independent predictor for the lack of progression of the arterial calcifications (52).

The CALMAG study with magnesium/calcium a phosphate binder accessed the safety of issues, and Mg/Ca compound was not inferior to sevelamer (53).

CONCLUSIONS

In conclusion it seems necessary to monitor the concentration of magnesium in dialysed patients, and prevent its deficiency. Mild hypermagnesaemia is not dangerous to the patients, could be protective, but the lack of large clinical trials does not allow at present to supplement magnesium in order to increase magnesium level above normal and possibly prevent vascular calcification and mortality.

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