

REVIEW

Is the Importance of Magnesium in Chronic Kidney Disease Underappreciated?

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Abstract

Magnesium (Mg) is one of the most important cations in the organism, essential for regulating vascular tone, cardiac rhythm, and endothelial functions. In patients with advanced stage chronic kidney disease (CKD) Mg deficit was associated in various studies with vascular calcifications and increased cardiovascular morbidity and mortality. Patients with CKD frequently have hyperparathyroidism, parathormone (PTH) being an important risk factor for vascular calcifications. Increased serum Mg levels inhibit PTH secretion and stimulate left ventricular hypertrophy, while low serum Mg levels stimulate PTH secretion. Correcting Mg deficiency results in reduced cardiovascular mortality in these patients.

Keywords: magnesium, hypomagnesemia, chronic kidney disease, hemodialysis, peritoneal dialysis, parathormone.

Rezumat

Magneziul (Mg) este unul dintre cei mai importanți cationi din organism, esențial pentru reglarea tonusului vascular, a ritmului cardiac și a funcțiilor endoteliale. La pacienții cu boală renală cronică în stadiu avansat (ERC), deficitul de Mg a fost asociat în diferite studii cu calcificări vasculare și creșterea morbidității și mortalității cardiovasculare. Pacienții cu boală renală cronică prezintă frecvent hiperparatiroidism, parathormonul (PTH) fiind un factor de risc important pentru calcificările vasculare. Creșterea nivelului seric de Mg inhibă secreția de PTH și stimulează hipertrofia ventriculară stângă, în timp ce nivelurile scăzute de Mg din ser stimulează secreția de PTH. Corectarea deficitului de Mg are ca rezultat reducerea mortalității cardiovasculare la acești pacienți.

Cuvinte cheie: magneziu, hipomagneziemie, boală renală cronică hemodializă, dializă peritoneală, parathormon.

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INTRODUCTION

Magnesium (Mg) has an important role, albeit rather neglected, in most enzymatic processes in the organism¹. The variations in serum Mg level are relevant from both a therapeutic and a preventive perspective for disorders such as: cardiovascular diseases, preeclampsia, diabetes mellitus, osteoporosis, bronchial asthma, migraines. In osteoblasts and osteoclasts Mg regulates the formation apatite crystals and contribute to both bone mineralization and bone remodeling². The kidney has an essential role in maintaining magnesium balance by reabsorption and excretion, but its ability to perform these functions gradually diminishes with declining renal function³.

Cardiovascular diseases are the main cause of mortality in patients with chronic kidney disease (CKD). A significant proportion of the patients with CKD on renal replacement therapy (RRT) by dialysis have vascular, including coronary, calcifications⁴, which are intimately linked to the pathogenesis of cardiovascular diseases, that significantly increase the morbidity and mortality of patients with CKD^{4,5}. Low Mg serum level is associated with vascular calcifications and with the increased cardiovascular mortality in patients with advanced stage CKD^{6,7}.

Blood Mg level influences parathormone (PTH) secretion, which is an independent risk factor for vascular calcifications, left ventricular hypertrophy, and mortality of patients with advanced stage CKD².

EXPERIMENTAL (MATERIALS AND METHODS):

The present review has considered the studies in the literature addressing the correlation between magnesium homeostasis and the various disorders typical for patients with CKD. Magnesium is a relatively neglected element, whose variations have significant repercussions on cardiovascular morbidity and mortality in patients with CKD; therefore, correcting Mg serum level may be of both therapeutic and preventive value.

RESULTS AND DISCUSSIONS

The biological role of Mg

Magnesium (Mg) is one of the most important cations in the organism, involved in many enzymatic processes, in the electrolyte balance, and in the bone metabolism¹.

Mg plays a fundamental role in: energy metabolism; protein, fatty acids, and nucleic acid synthesis and in the synthesis and binding of hormonal receptors¹. Mg is also involved in bone mineralization, enzymes synthesis including adenylate-cyclase, regulating transmembrane ion fluxes, muscle contraction, cardiac excitability and nervous transmission¹.

In the cardiovascular system, Mg plays an important role in regulating cardiac rhythm, vascular tone, and blood pressure. Mg is able to prevent both thrombosis and atherosclerosis¹. Mg supplementation may reduce mortality in patients with myocardial infarction, after myocardial reperfusion injury [8]. Mg deficiency was associated in various studies with vascular calcifications and with increased cardiovascular mortality in patients with end stage renal disease (ESRD)^{1,2}.

Mg may also prevent insulin resistance and osteoporosis¹.

Mg deficiency acts as a proinflammatory factor and dampens specific immune response^{9,10}.

Homeostasis Mg

Mg is distributed unevenly among the various tissues: most of the Mg (56%) is in the bones, which are the main Mg store of the organism; approximately one third is in the intracellular space, respective 27% in the muscles and 19% in soft tissues, and only 2% in extracellular space^{11,12}.

In humans, less than 1% of the total Mg in the organism is in the intravascular space, either in plasma or in the red blood cells¹³. Blood Mg, which accounts for about 0,3% of the total Mg pool in the organism, may be in one of three forms: ionized (55-70%), protein (especially albumin) bound (20-30%) or anionic complexes, in combination with: phosphate, citrate, bicarbonate or sulfate (5-15%)¹³. Ionized Mg and Mg in the anionic complexes constitute the fraction of plasma Mg that may be eliminated by renal excretion in the urine or by dialysis^{14,15}.

Mg balance in the organism depends on dietary intake, intestinal absorption, amount of Mg deposited in muscles and bones, and renal excretion^{3,14,16,17,18}.

About 30-40% of the ingested Mg is absorbed in the gut, mainly in the distal jejunum and ileum by passive paracellular transport¹² and in the ileum and colon by active transcellular transport¹⁹. In order to maintain Mg balance supplementary dietary intake is necessary, the recommended daily dose in adults being 420 mg daily in males and 320 mg daily in females. With reduced dietary magnesium intake, intestinal absorption

may increase to up to 80%^{20,21}. About 10% of the daily Mg intake is provided by drinking water²².

Mg balance is regulated mainly by the kidneys, kidney filtration and reabsorption being essential for maintaining a steady blood Mg level between 0,75-0,9 mmol/l (i.e. 7-2.4 mg/dl) in healthy adults. The amount of Mg filtered daily in the glomeruli is 2400 mg, 95% of which is reabsorbed in Henle loop (65%) or in distal tubules (30%). Only 100 mg of Mg are excreted daily in the urine²².

Vitamin D, PTH, and estrogen hormones play an important role in Mg homeostasis²⁰.

Hemolysis increases serum Mg concentration, as red blood cells contain a relatively high amount of Mg²⁰.

Disorders of magnesium balance

Hypomagnesemia is defined by a Mg serum level < 1.5 mg/dl.

Hypomagnesemia may have several causes, mainly insufficient intake (inadequate diet, rich in processed food; prolonged nasogastric tube feeding; poor intestinal absorption due to diarrhea, pancreatic failure, alcoholism, inflammatory bowel diseases) and excessive renal losses (renal tubular dysfunctions, diabetes mellitus, acute tubular necrosis, hyperfiltration, diuretics, increased post-obstructive diuresis, after renal transplantation, Bartter and Gitelman syndromes, hyperaldosteronism, hypercalciuria, diabetic ketoacidosis)²².

Hypomagnesemia may be induced by several drugs (aminoglycosides, amphotericin B, cisplatin, cyclosporin, loop and thiazide diuretics, proton pump inhibitors) or may be the result of genetic disorders, namely autosomal dominant familial hypomagnesemia with hypercalciuria and nephrocalcinosis, with secondary hypocalcemia or associated with convulsions and mental retardation²².

Mg deficiency is difficult to pin down by measuring Mg serum level due to the low Mg serum concentration. One may resort to more elaborate investigations such as: red blood cells Mg assessment, ionized serum test, MRI spectroscopy, but these are uncommon in clinical practice, most laboratories measuring only total Mg serum level. Consequently, the diagnosis of Mg deficiency relies on identifying the clinical symptoms of hypomagnesemia, which occur when serum Mg level drops to 1.2 mg/dl: anxiety, panic attacks, irritability, insomnia, attention and concentration deficit, apathy, headache, migraines, bronchial asthma attacks, appetite loss, nausea, vomiting, constipation, weakness, tremor, convulsions, muscle cramps and spasms.

Hypomagnesemia is frequent in intensive care patients, being especially common in the aftermath of surgical interventions²².

Hypermagnesemia is defined by serum Mg level above 2.2 mg/dl.

Hypermagnesemia is a rare occurrence, especially in in-patients, being more common in patients with CKD and in elderly patients. At Mg serum levels above 7.3 mg/dl deep tendon reflexes are abolished and at levels above 12 mg/dl potentially fatal cardiac arrhythmias may occur²³.

Common causes of hypermagnesemia: lithium therapy, hypothyroidism, familial hypocalciuric hypercalcemia, Addison disease, milk-alkali syndrome, Mg containing medication (antacids).

Hypermagnesemia decreases serum PTH level and enhances calcium solubility, resulting in decreased tisular calcifications²³.

Magnesium role in CKD

The prevalence of CKD in general population varies from country to country, but generally is on an ascending trend, mainly due to the high prevalence of diabetes mellitus complicated with diabetic nephropathy and renal vascular diseases (hypertensive nephrosclerosis and ischemic nephropathy). In patients with CKD, cardiovascular morbidity and mortality are significantly increased compared to general population²⁴.

The role of the kidney in Mg homeostasis, although vital in healthy individuals, diminishes with declining kidney function. In the kidney, 70-80% of plasma Mg is freely filtered in the glomeruli. Patients with CKD are vulnerable to a diet rich in Mg or to Mg containing medications including antacids or diuretics²².

Alterations in mineral metabolism may occur as early as stage 3 CKD (glomerular filtration rate GFR < 60 ml/min/1.73 m²), the kidney being unable to properly excrete phosphate anions, resulting in hyperphosphatemia and secondary hyperparathyroidism. Furthermore, renal vitamin D conversion decreases, with consequent hypocalcemia and increased PTH levels, leading to the bone mineral disorders associated with CKD²⁵. Vitamin D also influences Mg intestinal absorption, but Mg may also be absorbed by vitamin D independent mechanisms.

In the kidney, hypomagnesemia stimulates, while hypermagnesemia inhibits tubular Mg reabsorption. In the early stages of CKD (GFR >30 ml/min/1.73 m²), Mg excretion increases with decreasing GFR, thereby preventing hypermagnesemia, while a slight decrease

in Mg serum level induces a rapid drop in urinary Mg excretion²¹. In stage 4 CKD, as GFR falls below 30 ml/min/1.73 m² and with significant decline in renal function, hypermagnesemia is more common, especially in patients with ESRD, in which GFR < 10-15 ml/min/1.73 m²³.

In various observational studies, hypomagnesemia was considered a predictive factor for CKD progression by only partially understood mechanisms, probably related to its role in endothelial dysfunction, inflammation, vascular calcifications, thrombotic processes, diabetes mellitus, and insulin resistance²⁶.

Secondary hyperparathyroidism is an unavoidable complication of advanced stage CKD, calcium being the main activator of PTH secretion by means of Ca-sensing receptor (CaSR), but the PTH secretion is influenced also by the plasma Mg, by incompletely deciphered mechanisms³. The relation between PTH and Mg is complex and similar to homeostasis Ca: high blood Mg levels suppress PTH secretion by activating CaSR, in parathyroid glands. PTH is an important independent risk factor for vascular calcifications, left ventricular hypertrophy, and mortality in patients on RRT¹— thus, the PTH lowering effect of hypermagnesemia may explain its ability to decrease cardiovascular morbidity and mortality in these patients. By contrast, low serum Mg level stimulate PTH secretion.

On the other hand, PTH stimulates Mg reabsorption in distal tubule and increases Mg release from the bones²².

In patients on RRT by dialysis, the quantity of total and ionized Mg in the serum is slightly increased, depending on the residual renal function, on diet, but also on the removal by dialysis. Moreover, a negative Mg balance may be the result of diuretic treatment in the early stages of CKD or of decreased intestinal Mg absorption secondary to acidosis. In patients on RRT, bone Mg increases to up to 66%, both in the cortical and trabecular bone, indicating an increase in total Mg in the organism in these patients¹.

Magnesium and peritoneal dialysis

In patients with CKD on RRT by peritoneal dialysis (PD), Mg dialysate concentration is a major determinant of Mg homeostasis. A magnesium concentration of 0.75 mmol/l in the PD solution results in moderate hypermagnesemia¹. The intake of Mg containing medicines (laxatives, antacids) may also contribute to the high serum Mg level in these patients¹.

A study performed by *Navarro and colab.* on 51 de

patients on PD for at least 6 months, showed that patients with low PTH serum levels had serum Mg level significantly higher than patients with high PTH serum levels, pointing out an inverse correlation between PTH and serum Mg²⁷.

Saba and colab. reported similar results in 26 patients on PD in which three different Mg concentrations in PD solution were employed: 0.75; 0.5; 0.25 mmol/l. Serum PTH level was lower in patients using solutions with higher Mg concentration; the authors concluded that dialysis solutions high in Mg may prevent secondary hyperparathyroidism and, consequently, vascular calcifications and cardiovascular death²⁸.

Mg in hemodialysis

In patients on hemodialysis, serum Mg concentration is direct proportional with Mg content of the dialysate. Generally, Mg concentration in the dialysis fluid is 0.75 mmol/l. In several studies in which a dialysate low in Mg (0.6 mg/dl), patients had a Mg serum level between 1.7-2.5 mg/dl.

Low Mg concentration in the dialysate was associated with higher PTH serum level, which is recognized as an independent risk factor for vascular calcifications, left ventricular hypertrophy and mortality cardiovascular in patients on hemodialysis. Mg deficiency was correlated with vascular and mitral calcifications in patients on hemodialysis, frequent in these patients, associated with hyperparathyroidism, increased calcium phosphate product, duration of dialysis, and age¹.

On the other hand, by the effect on the vascular smooth muscle and by intradialytic variations, hypomagnesemia was associated with intradialytic hypotension and with ventricular arrhythmias, significantly contributing to the increased cardiovascular morbidity and mortality in patients on hemodialysis¹.

In a study performed on 47 patients on hemodialysis, *Turgut and colab.* have demonstrated an inverse correlation between Mg serum level and carotid intima-media thickness measured by carotid Doppler echography, proving the beneficial effect of Mg supplementary oral intake for 2 months on PTH serum level and on intima-media thickness²⁹.

Valvular calcifications occur with increased frequency in dialysis patients and are associated with an increased prevalence of arrhythmias and conduction defects, with left ventricular diastolic dysfunction, and with dilatated cardiomyopathy. In about 30% of dialysis patients various arrhythmias were identified by ambulatory ECG monitoring, some of them severe, their

prevalence increasing with age, left ventricular hypertrophy, preexistent cardiac disease, and the coexistence of electrolyte disorders that may alter cardiac conduction (K, Ca, Mg)²⁵.

The protective ability of Mg against mitral calcifications in hemodialysis patients was demonstrated by *Tzanakis and colab* in a study on 56 patients, those with and without valvular calcifications (as detected by echocardiography) having similar serum levels of calcium, phosphates, calcium phosphate product, and PTH, and only differed by Mg serum level. A Mg serum level below 3 mg/dl was associated with a twofold increase in mitral annulus calcifications compared to a Mg serum level above 3 mg/dl^{1,30}.

Mg in patients with renal transplant

Immunosuppressant medication employed after renal transplantations, especially treatment regimens including calcineurin inhibitors (cyclosporin, tacrolimus) induce hypomagnesemia by inhibiting Mg reabsorption in the renal tubules. Some studies³¹ have demonstrated that low serum Mg levels were associated with an increased rate of functional decline of the transplanted kidney and of graft rejection. Furthermore, oral Mg supplementation in patients after renal transplantation has been shown to prevent cyclosporin nephrotoxicity¹.

CONCLUSIONS

Many studies have demonstrated a protective role of Mg in preventing calcifications, atherosclerosis, cardiac arrhythmias, and cardiac disease in patients with CKD. In dialysis patients, serum Mg level is correlated with PTH level; moderate chronic hypermagnesemia is associated with low PTH levels and effectively prevents vascular and valvular calcifications, arrhythmias, and chronic myocardial ischemia. Correcting Mg deficiency results in decreased cardiovascular mortality, generally increased in patients on chronic dialysis.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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