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NEPHROLOGY - REVIEW

Magnesium metabolism in health and disease

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Abstract Magnesium (Mg) is the main intracellular divalent cation, and under basal conditions the small intestine absorbs 30–50% of its intake. Normal serum Mg ranges between 1.7–2.3 mg/dl (0.75–0.95 mmol/l), at any age. Even though eighty percent of serum Mg is filtered at the glomerulus, only 3% of it is finally excreted in the urine. Altered magnesium balance can be found in diabetes mellitus, chronic renal failure, nephrolithiasis, osteoporosis, aplastic osteopathy, and heart and vascular disease. Three physiopathologic mechanisms can induce Mg deficiency: reduced intestinal absorption, increased urinary losses, or intracellular shift of this cation. Intravenous or oral Mg repletion is the main treatment, and potassium-sparing diuretics may also induce renal Mg saving. Because the kidney has a very large capacity for Mg excretion, hypermagnesemia usually occurs in the setting of renal insufficiency and excessive Mg intake. Body excretion of Mg can be enhanced by use of saline diuresis, furosemide, or dialysis depending on the clinical situation.

Keywords Magnesium metabolism · Hypermagnesemia · Hypomagnesemia

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Magnesium: absorption and body distribution

Normal magnesium (Mg) body content is around 22.6 g and 50–60% of it is located in the bone [1, 2]. Magnesium is the main intracellular divalent cation, 99% of it being in the intracellular space [3].

The recommended Mg dietary content for adults is approximately 420 mg/day in men and 320 mg/day in women. However, the usual dietary Mg intake falls below this recommendation in a large proportion of the population [4].

Under basal conditions the small intestine absorbs 30–50% of Mg intake, although this percentage diminishes with increasing amount of magnesium intake, senescence, and chronic renal disease. Magnesium absorptive process is, in part, under the influence of active vitamin D [5–7].

Normal serum Mg ranges between 1.7–2.2 mg/dl, or 0.75–0.95 mmol/l, or 1.5–1.9 mEq/l at any age (1 mmol = 2 mEq = 24 mg Mg), and approximately 20% of this cation is bound to albumin in the intravascular compartment [1, 3]. Serum Mg concentration correlates poorly with its body content, because patients with Mg deficiency may have normal serum Mg levels [6]. The most reliable clinical method of evaluating its body content is the Mg tolerance test. This test is based on the observation that Mg-deficient patients tend to retain a greater proportion of a Mg load and, consequently, excrete less Mg in urine than normal individuals do. A reduction in Mg excretion in this setting means that

Mg has been incorporated into the cells because of its need. This test is not valid in patients suffering from renal insufficiency or renal Mg wasting states (e.g. diuretics) [8].

Magnesium is essential for several enzymatic functions (especially those related to carbohydrate metabolism), DNA transcription and replication, mNRA translation, and bioelectric-activity, ionic pumps, and calcium-channel function. Because of its properties, Mg is usually used as a therapeutic agent in clinical entities such as asthma, pre-eclampsia, and coronary arteriopathy [1, 9].

Renal handling of Mg

Even though eighty percent of serum Mg is filtered at the glomerulus, only 3% of it is finally excreted in the urine [6]. Renal excretion is determined largely by the rate of filtration and its tubular reabsorption, while tubular secretion does not seem to play a significant role in its renal handling [10]. Between 10 and 15% of filtered Mg is reabsorbed in the proximal convoluted tubules [11], while 60–70% is passively reabsorbed in the thick ascending loop of Henle. This reabsorption takes place via paracellular channels, because of a lumen-positive transepithelial gradient generated by the luminal NaK2Cl cotransporter and potassium recycling into the lumen [8, 12, 13]. In addition, on the basilar pole of this segment there is a calcium (Ca) receptor sensitive to increased plasma Ca or Mg concentration. This receptor activates the arachidonic acid cascade to inhibit the apical NaK2Cl cotransporter and the potassium channel. In this setting, the positive potential of the lumen is reduced leading to augmentation of Ca and Mg urinary losses. Conversely, during hypocalcemia and hypomagnesemia the basilar Ca receptor is not stimulated and, as a consequence, the luminal positive potential of this segment is preserved leading to an increase in Ca and Mg reabsorption [8, 14]. In the distal convoluted tubules, Mg reabsorption is still significant and represents the fine regulation of its excretion [13].

Among the main stimuli that increase the urinary Mg excretion are: high natriuresis, osmotic load, and metabolic acidosis. Among those that reduce it are: metabolic alkalosis, parathyroid hormone, and, possibly, calcitonin [8, 10].

Renal handling of Mg in the elderly

The ageing process does not modify the fractional excretion of magnesium (FEMg) in healthy individuals, but if these people undergo a volume overload their FEMg increases to a point that significantly lowers their serum Mg level.

Because it has been shown that sodium reabsorption is reduced in the thick ascending loop of Henle in healthy old people [15], and this tubular segment is the main one implicated in Mg reabsorption, it could be hypothesized that this phenomenon could explain the increased fractional excretion of magnesium that elderly people have when they are volume expanded [16].

Changes in Mg metabolism

These consist of an increase or reduction in serum Mg content and the alterations that these changes bring to body Mg homeostasis.

Magnesium deficiency: causes, symptoms and treatment

Three physiopathologic mechanisms can induce Mg deficiency: reduced Mg intestinal absorption (e.g. malabsorption), increased urinary Mg losses (e.g. diuretics), or intracellular shift of Mg (e.g. hungry bone syndrome) [6, 17].

Even though, during nutritional deficiency states, the intestine is able to increase its absorptive capability by as much as 40% compared with normal [10], malnutrition can lead to Mg deficit, especially in the setting of chronic alcoholism [6, 18]. Enteric diseases which induce malabsorption (e.g. inflammatory bowel disease) may also cause Mg deficiency related to the digestive tract.

Renal Mg wasting may appear in the setting of volume expansion, osmotic diuresis (e.g.: glucosuria, post-obstructive diuresis), treatment with diuretics (loop diuretics and thiazide but not potassium-sparing ones), phosphorus depletion, tubular damage induced by drugs (cisplatin, amphotericine, aminoglycosides), or renal diseases (interstitial nephritis, Fanconi syndrome, Gitelman syndrome, etc) [5, 6, 19, 20]. Calcineurin inhibitors (cyclosporine and tacrolimus) also increase renal loss of magnesium and the

subsequent hypomagnesemia enhances CNIs nephrotoxicity [21].

A high serum ionized calcium level is another mechanism of Mg urinary wasting, because of direct stimulation of the basilar calcium sensor of the loop of Henle, mentioned above [2].

Low serum Mg secondary to its shift into the intracellular compartment only acquires clinical significance in refeeding or hungry bone syndromes.

Hypomagnesemia can, by itself, induce hypokalemia (often refractory to potassium repletion until Mg deficit is corrected), neuromuscular irritability, tetany, seizures, depression, carbohydrate intolerance, hypocalcemia, digoxin cardiotoxicity, and tachyarrhythmias resistant to standard therapy, and they respond only to Mg repletion. For this reason, in clinical conditions such as pre-eclampsia, acute myocardial infarction, tachycardia torsade de pointes, etc., intravenous Mg treatment is advocated [2, 3, 17].

Acute intravenous magnesium infusion can induce a reduction of its absorption in the thick ascending loop of Henle, and, consequently, a considerable amount of the administered Mg will be excreted in the urine. For this reason oral administration in asymptomatic patients is the preferred method of administration for Mg reposition [3].

In an emergency situation Mg should be administered intravenously over a 2–4 min period [8]. Because the added extracellular Mg equilibrates slowly with the intracellular compartment and renal excretion of extracellular Mg exhibits a threshold effect, approximately 50% of intravenously administered Mg is lost into urine [18]. In patients suffering from renal insufficiency, the rate of Mg repletion should be reduced and the patient should be carefully monitored frequently for signs and serum levels of hypermagnesemia; serum Mg should also be measured frequently [18, 19]. Additionally, intravenous administration of large amounts of $MgSO_4$ may result in an acute decrease in serum ionized calcium because calcium complexes with sulfate leading to an increase in its urinary excretion. Thus, administration of $MgSO_4$ to a hypocalcemic patient may precipitate tetany [19, 22, 23]. Oral Mg administration is used for repletion of mild cases of magnesium deficit, and this must take into account that it could cause diarrhea [3]. Potassium-sparing diuretics, that block the distal tubular epithelial sodium channel, may also induce renal Mg saving. It is proposed that, because these drugs reduce luminal sodium uptake and inhibit the development of a negative luminal transepithelial potential difference, they may favor passive reabsorption of Mg in the late distal or collecting tubules [2, 24–26].

Magnesium excess: causes, symptoms and treatment

The kidney has a very large capacity for Mg excretion, and when the renal threshold is exceeded most of the excess filtered Mg is excreted into the urine. Thus, hypermagnesemia generally occurs in renal insufficiency and excessive Mg intake settings. In chronic renal failure, the remaining nephrons adapt to the decreased filtered load of Mg by markedly increasing its fractional excretion. Thus, serum Mg levels are usually well maintained until glomerular filtration falls below 20 ml/min. However, in advanced renal insufficiency, significant hypermagnesemia is rare unless the patient receives exogenous Mg in the form of antacids or cathartics [6]. In addition, hypermagnesemia can be found in patients who are on lithium therapy, or suffering from hypothyroidism or Addison disease [8, 27].

Symptoms of Mg toxicity usually begin after its serum concentration exceeds 4–6 mg/dl. (1.74–2.61 mmo/l) They consist of hypotension, nausea, vomiting, facial flushing, urinary retention, ileus, depression and lethargy. They may progress to flaccid skeletal muscular paralysis, hyporeflexia, bradyarrhythmias, respiratory depression, and cardiac arrest [28]. Mild hypermagnesemia in individuals with good renal function may require cessation of Mg supply only, for example the magnesium pills or intravenous infusion they are receiving. In severe toxicity, temporary antagonism of its effects may be achieved by administration of intravenous calcium [8]. Renal excretion of Mg can be enhanced by using saline diuresis, furosemide, or dialysis, depending on the clinical situation [28].

Magnesium in particular situations

Diabetes mellitus

It has long been known that there is Mg deficit and increased renal Mg excretion in diabetes mellitus

patients. As a consequence, the American Diabetologic Association suggests oral Mg administration to all diabetic patients with low serum magnesium.

In diabetes mellitus type I, it can be hypothesized that this deficit might be related to elevated serum leptin, an adipose regulatory peptide, in this population. Studies on animals suggest that leptin has receptors in the kidney where it acts principally by inhibiting tubular sodium reabsorption. It has also been reported that serum leptin correlates with urinary magnesium/creatinine concentration in patients suffering from type I diabetes with hyperglycemia. Hyperleptinemia could lead to hypomagnesemia by inducing increased diuresis and natriuresis [9, 29, 30].

Renal lithiasis

Magnesium also has an important role as a nephrolithiasis inhibitor, acting more effectively in combination with citrate. Magnesium citrate slows brushite crystal growth rate, nucleation rate, and supersaturation of urine. In addition, because Mg competes with calcium in binding oxalates, in both the gut and urine, the ratio of Mg/Ca in the urine is used as an estimate of stone risk. It has also been reported that Mg deficiency causes nephrocalcinosis and stone formation in rats [3, 31].

Bone disease

Epidemiologic studies have demonstrated a positive correlation between dietary Mg intake and bone density and/or an increased rate of bone loss with dietary Mg reduction. Studies in young rats demonstrated a profound effect of Mg depletion on bone, characterized by impaired bone growth, reduced osteoblast number, increased osteoclast number, and loss of trabecular bone with stimulation of cytokine activity (TNFα, IL1, etc.) in bone. In most species, including humans, Mg deficiency results in impaired parathyroid hormone (PTH) secretion and/or PTH end organ resistance. Serum $1,25(OH)_2D$ levels are also low in Mg-deficient humans and rats [4, 9, 32].

In end-stage renal disease patients, bone mineralization and microhardness decreased with increasing bone Mg content and intact PTH level [33–35]. Magnesium may be involved in the suppression of PTH secretion, lowering bone turnover, thus leading to an aplastic bone disorder [33, 34]. At physiological calcium and Mg concentrations, these divalent cations were relatively equipotent at inhibiting PTH secretion. However, at low serum calcium concentration a threefold greater Mg concentration is required for similar PTH inhibition; then a suppressive effect of hypermagnesemia on PTH secretion would be completely and rapidly offset by the stimulation produced by hypocalcemia [36].

Dialysis

An increase in dialysate magnesium concentration for two months resulted in a decrease in serum calcium, phosphorus, and PTH levels, whereas a decrease in dialysate magnesium was associated with an increase in serum PTH level [36].

In dialysis patients, the dialytic procedure assumes the primary role of magnesium removal, therefore the serum magnesium concentration parallels the dialysate magnesium content, which is 0.5–1.5 mEq/l in peritoneal and hemodialysis dialysates whereas it is 0.75–3 mEq/l in hemofiltration substitution solutions [37, 38].

Hypermagnesemia is common when a standard dialysate magnesium content of 1.2 mg/dl is used in these patients, even though their muscle magnesium content is normal. Moreover, a reduction in the level of magnesium in the dialysis fluid leads to a decrease in the serum magnesium level, but zero magnesium dialysate can induce severe leg cramps in dialysis patients [7].

In peritoneal dialysis, when 0.75 mmol/l of magnesium and 1.5% glucose solution is used in chronic ambulatory peritoneal dialysis, slight magnesium uptake from the dialysis solution usually occurs by diffusive gradient. However, a negative dialytic balance with the same solution when ultrafiltration is increased by a 4.25% dextrose solution, because convective removal counteracts diffusive uptake, yielding negative magnesium mass transport in most patients [38].

Magnesium can also have a role as a phosphate binder in dialysis patients, and concomitantly represents a way of avoiding use of calcium for this purpose. Although calcium has a higher affinity for phosphorus than magnesium on a milligram per milligram basis, the poorer gastrointestinal absorption of magnesium relative to calcium leaves more elemental magnesium available for phosphorus binding. Serum Mg levels should be measured to avoid potential toxicity secondary to hypermagnesemia [7].

Heart and vascular disease

Hypomagnesemia is an essential feature of heart failure associated with complex ventricular arrhythmias which, consequently, can be alleviated/abolished by magnesium supplementation, because of enhanced automaticity or triggered activity. Factors known to contribute to magnesium depletion in this population include reduced dietary intake (anorexia), exaggerated urinary excretion generated by diuretics, and/or activation of the neurohormonal and renin-angiotensin-aldosterone system that leads to stimulation of aldosterone and antidiuretic hormone secretion, which inhibits tubular magnesium reabsorption and thus exaggerates urinary magnesium loss [39].

In addition to cardiac arrhythmias, magnesium deficiency may generate impairment of myocardial metabolism, further reduction in cardiac contractility, and coronary and systemic arterial constriction in hemodialysis patients.

Magnesium depletion contributes to an increase in catecholamine secretion. In patients suffering from arterial hypertension, catecholamines have been demonstrated to regulate intracellular magnesium loss in lymphocytes, thus creating a loop in which magnesium deficiency induces catecholamine secretion while elevated catecholamines stimulate further magnesium loss. Both mechanisms contribute to vasoconstriction and further hypertension. Magnesium has been demonstrated to inhibit catecholamine release by a mechanism involving blockade of voltage-gated calcium channels, thus breaking the deleterious loop and lowering systemic blood pressure. Another potential cardiovascular protective action of magnesium was attributed to LDL-cholesterol oxidation and oxidative stress reduction [40, 41].

In addition, a number of small retrospective studies suggest that dialysis patients with high serum Mg levels may be protected from vascular calcification. Prevention of crystal growth may be a possible mechanism for its protective effect [7].

Conclusion

Normal magnesium body content is the result of a good nutrition status, normal intestinal and renal function, and a balanced intra–extra cellular magnesium ratio.

Altered magnesium balance can be found in diabetes mellitus, chronic renal failure, nephrolithiasis, osteoporosis, aplastic osteopathy, and heart and vascular disease.

Its deficit can be treated by using magnesium supplements or potassium-sparing agents, whereas its excess in the body can be solved by hydration, furosemide administration, or dialysis treatment, depending on the circumstances.

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