Magnesium in Chronic Kidney Disease: Should We Care?

Esther R. van de Wal-Visscher  Jeroen P. Kooman  Frank M. van der Sande

Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Center, Maastricht, The Netherlands

Abstract

**Background:** Magnesium (Mg) is an essential cation for multiple processes in the body. The kidney plays a major role in regulating the Mg balance. In a healthy individual, total-body Mg content is kept constant by interactions among intestine, bones and the kidneys. **Summary:** In case of chronic kidney disease (CKD), renal regulatory mechanisms may be insufficient to balance intestinal Mg absorption. Usually Mg remains normal; however, when glomerular filtration rate declines, changes in serum Mg are observed. Patients with end-stage renal disease on dialysis are largely dependent on the dialysate Mg concentration for maintaining serum Mg and Mg homeostasis. A low Mg is associated with several complications such as hypertension, and vascular calcification, and also associated with an increased risk for both cardiovascular disease (CVD) and non-CVD mortality. Severe hypermagnesaemia is known to cause cardiac conduction defects, neuromuscular effects and muscle weakness; a slightly elevated Mg has been suggested to be beneficial in patients with end-stage renal disease. **Key Messages:** The role of both low and high Mg, in general, but especially in relation to CKD and dialysis patients is discussed.

**Keywords**
Magnesium · Chronic kidney disease · (Patho)physiology · Haemodialysis · Outcome

Introduction

Magnesium (Mg) is the fourth most abundant cation in the body and the second most important intracellular cation.

In recent years, Mg has gained much importance with the growing awareness that Mg is required as a cofactor in multiple enzymatic reactions and that it plays an important role in neuromuscular processes [1]. Mg also has a role in mineral bone metabolism, adenosine triphosphate metabolism, neurotransmitter release and in the regulation of vascular tone, heart rhythm and platelet-activated thrombosis [2].

In patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), changes in Mg homeostasis may occur. An understanding of the physiology in Mg handling is therefore of relevance for those taking care of patients with CKD and ESRD. A growing body of
literature associates both, hypomagnesaemia as well as hypermagnesaemia, with important clinical endpoints such as an increased risk of cardiovascular disease (CVD), arrhythmias and mortality.

Regulation of Mg Levels
Daily requirement for Mg in adults is estimated to be 8–16 mmol (200–400 mg), values close to the recommended daily allowance (420 mg/day for adult males and 320 mg/day for adult females) [3–5]. Mg is widely distributed in most human foods such as meat, green vegetables and cereals, except fat.

In an adult body, total Mg is approximately 25 g compared with 1,000 g of calcium [1, 6].

Approximately one-third of the total Mg in the body is present in the intracellular space, a small amount (2%) in the extracellular space, the remainder (56%) in bone. Less than 1% of the total body Mg is present in the intravascular compartment [7]. Normal serum Mg concentrations ranges from 0.7 to 1.1 mmol/L (1.4–2.0 mEq/L or 1.7–2.4 mg/dL), and can be categorized into 3 fractions: ionized (55–70%), protein-bound (20–30%) and complexed with anions such as phosphate, bicarbonate, citrate or sulphate (5–15%) [1, 8]. Ionized Mg and complexed Mg together form the ultrafilterable fraction of Mg, representing the portion of total plasma Mg that can be removed by the kidneys or dialysis [8, 9]. Serum Mg level may not be a good measure of the total amount of Mg in the body; nonetheless, most information comes from the determination of Mg in serum and red blood cells [10].

Mg balance depends on intestinal uptake, storage in bone and skeletal muscle, and renal excretion [1, 2, 8, 10, 11].

In the intestine, Mg is absorbed by a passive paracellular pathway, mainly in the distal jejunum and ileum, and by an active transcellular pathway in the ileum and colon [12]. The passive pathway is responsible for 80–90% of intestinal Mg absorption. Claudin-16 and -19 probably play a major role in this passive process [12]. Transient receptor potential melastatin 6 and 7 are the 2 transporters that are involved in the active pathway, which is responsible for the other 10–20% of intestinal Mg absorption. The active pathway is upregulated when Mg intake is low [8]. Absorption is further stimulated by vitamin D (1.25 [OH] 2D) and calcium, although high levels of calcium might decrease magnesium absorption [11, 13].

The kidney is a key regulator of Mg balance; 70% of the circulating Mg is filtered by the glomerulus, which accounts for 2,400 mg. Approximately 90–95% of filtered Mg is reabsorbed. Unlike other ions, only small amounts of Mg (10–25%) are reabsorbed in the proximal tubule, with 70% reabsorbed through the paracellular pathway in the loop of Henle. The fine-tuning of Mg regulation occurs in the distal convoluted segment through an active process mediated by transient receptor potential melastatin ion channels [14].

In case of a decline in Mg intake, Mg absorption in the intestine can be increased from 40 to 80% by both passive and active transport mechanisms. The urinary fractional excretion of Mg can be decreased to 0.5% [15, 16]. When oral Mg intake stays low, bones will slowly release Mg to the plasma. In case of high intake of Mg, healthy kidneys can increase urinary Mg excretion in order to maintain plasma Mg concentration within the normal range. Unlike other ions, there is limited hormonal regulation of Mg balance. Active vitamin D can increase intestinal Mg absorption. Epidermal growth factor and oestrogens increase distal tubule Mg reabsorption, although the clinical significance of this is unclear [10, 17].

Effects of CKD and ESRD on Magnesium Levels

The kidney is crucial in the maintenance of normal serum Mg concentrations. The ability of excretion deteriorates when renal function declines [2]. In CKD stage 1–3, an increase in fractional Mg excretion compensates for the loss of renal function, and as a consequence, Mg levels are regulated within the normal range [18]. In advanced CKD stage 4–5, compensatory mechanisms become inadequate and the fraction of filtered Mg excreted increases as a result of the impaired tubular reabsorption. This becomes even more marked when the glomerular filtration rate falls below 10 mL/min. So, the compensatory rise in fractional Mg excretion is insufficient to prevent an increase in serum Mg concentration. In dialysis patients, losing the regulatory role of the kidneys can have significant effects on magnesium balance. In patients with ESRD, with a glomerular filtration rate less than 10 mL/min, it might appear that hypermagnesaemia is the only possible outcome in such patients [13, 19, 20].

However, both CKD and ESRD patients on dialysis have usually normal serum levels of Mg and sometimes even low serum Mg concentration (hypomagnesaemia) [21, 22]. This is due to the complex intake of Mg, other dietary intake, drugs, and dialysate Mg concentration on Mg balance and thus total-body Mg. Hypomagnesaemia might be a side effect of a number of different medications, such as thiazide diuretics, proton-pump inhibitors (PPI), cisplatin, aminoglycoside antibiotics and calcineurin in-
Magnesium in CKD

Mg possesses an anti-atherosclerotic effect, which is mediated partly via its anti-inflammatory and antioxidant properties; conversely, by inhibiting endothelial proliferation, upregulating plasminogen activator inhibitor-1 and vascular cell adhesion molecule-1, Mg deficiency promotes endothelial dysfunction [20, 43–46]. The Atherosclerosis Risk in Communities (ARIC) study, showed in a large cohort in patients with a normal kidney function, a 1.6 times greater risk of developing CKD and a 2.4 times greater risk of developing ESRD when serum magnesium <0.7 mmol/L, not confounded by other risk factors, thereby focusing on the effect of endothelial damage [47].

A deficiency in Mg promotes hydroxyapatite formation and calcification of vascular smooth muscle cells [48–50]. On the other hand, chronic hypermagnesaemia in dialysis patients plays an important role in the genesis of adynamic bone disease, although the exact mechanisms are not yet clear.

Finally, Mg deficiency is closely related to insulin resistance and metabolic syndrome [51]. Mg is an essential cofactor for multiple enzymes involved in glucose metabolism. It was reported that increased Mg intake was significantly associated with a lower incidence of type 2 DM [52–54].

By Which Mechanisms Could Mg Be Protective?

Mg plays an important role in multiple processes as transport functions, signal transduction, enzyme activities, energy metabolism, nucleic acid and protein synthesis, as well as neuromuscular, vascular processes and bone metabolism [1, 2, 11].

There are several mechanisms that may explain the increased CVD risk of patients with hypomagnesaemia [37]. Mg possesses an anti-atherosclerotic effect, which is associated with hypokalaemia, which causes cardiac arrhythmias; supplementation of these 2 elements should have an antiarrhythmic effect [29, 30]. Mild hypomagnesaemia predisposes to cardiac arrhythmias at the time of an acute ischemic event. Furthermore, Mg deficiency may lead to anorexia, vomiting, lethargy and weakness, and in cases of severe deficiency, paraesthesia and mental confusion [11]. In the most severe cases, these are usually associated with hypokalaemia and hypocalcaemia [31–34]. Outcome studies in the general population have indicated potential associations between low serum Mg levels and atherosclerosis, hypertension, diabetes, and left ventricular hypertrophy, as well as both CVD mortality and all-cause mortality [13, 35–37]. In several studies, higher mortality rates were also observed in maintenance HD patients with low serum Mg levels [38–40]. Current literature suggests that Mg may have a protective effect on the CV system [41]. In a more recent observational study in a large group of US HD patients, the authors showed that higher serum Mg levels were associated with lower mortality risk [42].

Mg and Outcome in CKD and ESRD

Hypomagnesaemia as well as severe hypermagnesaemia may present with various clinical symptoms.

In the absence of any kidney disease, severe hypermagnesaemia is very rare. Hypermagnesaemia may present with malaise, articulation disorders, ataxia, nausea and vomiting [1, 23]. Severe hypermagnesaemia is known to cause cardiac conduction defects, and neuromuscular effects and muscle weakness [28]. In the presence of other electrolyte disorders, these symptoms can accelerate. These findings are seldom observed, unless plasma Mg concentration is higher than 1.7–2.1 mmol/L (4–5 mg/dL).

Hypomagnesaemia seems to play a role in the pathogenesis of ischemic heart disease, because of the change in the lipoprotein composition [21]. Hypomagnesaemia is associated with hypokalaemia, which causes cardiac arrhythmias; supplementation of these 2 elements should have an antiarrhythmic effect [29, 30]. Mild hypomagnesaemia predisposes to cardiac arrhythmias at the time of an acute ischemic event. Furthermore, Mg deficiency may lead to anorexia, vomiting, lethargy and weakness, and in

hibitors [23]. Patients with CKD normally have severely depressed intestinal Mg absorption compared to healthy individuals, probably due to a deficiency of active vitamin D [24]. PPI are known to impair the adaptive increase in active intestinal Mg absorption in the face of Mg depletion, and may therefore predispose to hypomagnesaemia in both CKD and ESRD patients [21]. On the other hand, sevelamer hydrochloride used as a phosphate-binding drug in both CKD and ESRD is associated with an increase in Mg concentration [25]. The increased intake of certain dietary fibres may enhance mineral and thus Mg absorption [26]. Use of low-Mg dialysate (0.25 mmol/L or 0.5 mEq/L) is a risk factor for hypomagnesaemia in patients on both haemodialysis (HD) and peritoneal dialysis [21, 22]. So, even in minimal renal Mg excretion, total-body Mg content can be below, normal, or high in dialysis patients.

Other renal causes of hypomagnesaemia are congenital or acquired tubular defect due to mutated magnesiumotropic proteins, post obstructive diuresis, post-acute tubular necrosis, renal transplantation, and interstitial nephropathy. Examples are familial hypomagnesaemia with hypercalciuria and nephrocalcinosis, Bartter’s or Gitelman’s syndrome, and isolated autosomal-recessive hypomagnesaemia. Also, endocrine causes like hyperaldosteronism, syndrome of inappropriate antidiuretic hormone and diabetes mellitus cause hypomagnesaemia [8, 27].
Clinical Effects of Dialysate Magnesium Prescription

The ultrafilterable Mg (ionized plus complexed Mg) is the only portion of total plasma Mg that can be removed during a dialysis treatment. Albumin and several nonprotein anions bind to Mg. These plasma concentrations are variable. Therefore, the ultrafilterable Mg concentration may also vary but is usually around 70% of total plasma Mg concentration [55]. The concentration gradient of Mg, the difference between the ultrafilterable plasma Mg and dialysate Mg, is the primary determinant of Mg flux. Mg is removed from the patient if the plasma Mg concentration exceeds that of the dialysate Mg. Mg is added to the patient if Mg is lower than that of the dialysate. A small amount of Mg is also removed by ultrafiltration [55].

Use of low dialysate Mg has been shown to be a risk factor for hypomagnesaemia in patients both on HD and peritoneal dialysis [21, 22]. In the past, dialysate Mg concentrations of 1.5 mEq/L were used, and more recently, the standard of care in the United States is 0.75–1.0 mEq/L. When a 1.5 mEq/L dialysate Mg is prescribed, most patients will have normal or a slightly higher serum Mg [56, 57]. When using a 1.0 mEq/L dialysate Mg concentration, a small number of patients will have pre-dialysis hypomagnesaemia [58, 59]. Moreover, hypomagnesaemia is even more common (5–33%) when a 0.5 mEq/L dialysate Mg is used. Use of a too low dialysate Mg may have hemodynamic effects during HD as has been shown in several studies. When using a dialysate Mg of 1.5 mEq/L, episodes of hypotension during HD were less common when compared with a 0.5 mEq/L.

A high plasma Mg is less common [56, 58]. However, the results of studies are inconsistent and suggest other factors that influence the Mg concentrations, such as malnutrition and medication (PPI, sevelamer, magnesium containing phosphate-binders) use [20].

One should keep in mind that dialysis prescriptions by themselves, may affect Mg flux across the dialyzer and in consequence the plasma Mg concentration. For instance, dialysate bicarbonate concentration (pH) will have an effect on the number of anionic sites on albumin and may increase or decrease the Mg binding to albumin in plasma, and therefore, the plasma ionized Mg fraction. Variations in ionized Mg concentration of 0.29 mg/dL per pH unit have been shown. Also use of dialysate-citrate might affect Mg concentration because citrate may form a complex with Mg, which is dialyzable and increase intradialylytic Mg removal. Changes in dialysate glucose or administering glucose in the dialysate will stimulate insulin, which may increase the cellular Mg uptake into insulin-sensitive tissues.

Another clinical effect of an increase in dialysate Mg concentrations was a decrease in serum calcium, phosphate and parathyroid hormone levels [60–62]. Hypomagnesaemia is common in HD patients when a dialysate Mg concentration of 1.0 mEq/L is used. This may have also unwanted haemodynamic effects. A study showed that when using dialysate calcium of 2.5 mEq/L in combination with Mg of 0.5 mEq/L, a significant drop in mean arterial pressure occurred as a result of low cardiac contractility without compensation by an increase in total peripheral resistance [63].

Treatment

Mg deficiency should be supplemented by the administration of Mg salts. Mg could be used as a phosphate binder [20]. The advantage of Mg-containing phosphate binders is the lack of aluminium content; however, there are mild gastrointestinal symptoms, and higher oral doses of Mg are in general not well tolerated and could induce diarrhea [64].

In a recently published review, the authors recommend that Mg should be measured regularly and adjust dialysate Mg accordingly in order to maintain plasma Mg within the normal range [55]. In general, dialysate Mg concentration should be kept at 1.0 mEq/L. Only in a minority of cases, the dialysate prescription of Mg at 1.25–1.5 mEq/L could be used as needed. We stress that a dialysate Mg in concentrations lower than 0.5 mmol/L should not be used.

Summary

Mg is an important but an under-investigated cation. It plays an important role in multiple processes and as coenzyme in a variety of processes. The kidneys are elementary in maintaining Mg concentrations. In CKD and ESRD, the ability of the kidneys to regulate Mg levels properly disappears. Low levels of Mg are associated with CVD. It is therefore advised to measure Mg more frequently. Knowing the results of Mg, a tailor made dialysate Mg should be implemented in daily clinical practices.

Disclosure Statement

There is nothing to disclose.