

Hypomagnesemia Associated with Chronic Renal Diseases: A Review Article

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Abstract

Magnesium (Mg^{2+}) is an essential cation for multiple processes in the body. The kidney plays a major role in regulating the Mg^{2+} balance. In a healthy individual, total-body Mg^{2+} content is kept constant by interactions among intestine, bones and the kidneys. Hypomagnesaemia is involved in the pathophysiology of hypertension, vascular calcification and metabolic derangements including diabetes mellitus and dyslipidemia, which are all risk factors for cardiovascular disease; the leading cause of mortality and morbidity in all stages of chronic kidney disease (CKD) including end-stage renal disease (ESRD). Magnesium is the second-most abundant intracellular cation after potassium and, overall, the fourth-most abundant cation after sodium, potassium, and calcium, and plays important roles in a number of biological processes in the human body such as protein synthesis, muscle and nerve transmission, neuromuscular conduction, and signal transduction. In case of chronic renal diseases, renal regulatory mechanisms may be insufficient to balance intestinal Mg^{2+} absorption. Usually Mg^{2+} remains normal; however, when glomerular filtration rate declines, changes in serum Mg^{2+} are observed.

Keywords: Chronic renal diseases, Hypomagnesemia.

Chronic Renal Disease:

Introduction

Although health care advancements have increased the average life expectancy, they have also provided the surprising result that chronic diseases are still a widespread condition. Half of all US residents are reported to have a chronic health condition. A major member of the family of these chronic diseases is chronic kidney disease (CKD) (1).

CKD is associated with impaired quality of life and substantially reduced life expectancy at all ages. It is also associated with excess risk for cardiovascular disease and other conditions such as diabetes, infection, and cancer (2).

ESRD is the most severe form of CKD and is fatal if not treated by renal replacement therapy (RRT), which can be dialysis or kidney transplantation. The prevalence and associated burden of CKD is rising worldwide with the fastest growth occurring in low-income and middle-income countries (3).

The most frequent causes of CKD are diabetic nephropathy, hypertension, glomerulonephritis, interstitial nephritis, pyelonephritis, polycystic kidney disease, obstructive nephropathy. CKD can also be the final result of untreated acute kidney injury (AKI) caused by infections, medicines, toxic substances, heavy metals including lead, cadmium, mercury and chromium (4).

Definition of CKD

Over the past decade, CKD has become an area of intensive clinical and epidemiological research. Historically, the CKD research literature has struggled to create consensus on definitions of CKD (4). This situation appeared to be resolved when the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) created guidelines providing a clear definition and classification system for CKD. These guidelines define CKD as the presence of kidney damage or glomerular filtration rate (GFR) of $< 60 \text{ mL/min/1.73m}^2$ for (≥ 3 months).

Kidney damage can be any of the following:

- Albuminuri.
 - Urinary sediment abnormalities.
 - Pathological abnormalities.
 - Structural abnormalities.
 - Electrolytes abnormalities due to tubular disorder.
 - History of kidney transplantation.
- (5).

Criteria for CKD**A) Duration ≥ 3 Months**

Kidney disorders can be chronic or acute. Clearly but theoretically, the span of > 3 months (> 90 days) is characterized as delineating "chronic renal disease. The reason for distinguishing chronicity is to differentiate CKD from acute kidney diseases (such as acute glomerulonephritis), which can involve several procedures and have distinct etiologies and outcomes. (2).

B) Decreased GFR

There are several functions in the kidney, including excretory, endocrine and metabolic features. The GFR is one part of the excretory system but is widely considered as the best overall kidney function index since it is normally decreased after significant structural damage and decreases in most other kidney functions in tandem with the GFR in CKD.

Levey and Coresh choose a threshold of $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$ (GFR categories G3a-G5) for ≥ 3 months to indicate CKD (6).

C) Markers of kidney injury**Albuminuria,**

Albuminuria is a kidney injury marker [increased glomerular permeability] and higher albuminuria levels are highly predictive of outcomes at individual and population levels at all levels of GFR (7).

The normal urine ACR (albumin-to-creatinine ratio) in young adults is $< 10 \text{ mg/g}$, on the other hand:

- Urine $\text{ACR} < 30 \text{ mg/g}$ (**category A1**) is normal or mild increased.
- Urine $\text{ACR} 30\text{-}300 \text{ mg/g}$ (**category A2**) generally corresponds to "micro albuminuria" now referred to as "moderately increased".
- Urine $\text{ACR} > 300 \text{ mg/g}$ (**category A3**) generally corresponds to "macro albuminuria" now termed "severely increased".

Urine $\text{ACR} > 3500 \text{ mg/g}$ usually be accompanied by symptoms and signs of nephrotic syndrome (e.g., low serum albumin level, proteinuria, edema, and high serum cholesterol) (8).

Table (1): Criteria for CKD(9).

Markers of kidney injury (one or more)	Albuminuria (AER >30 mg/24 hours; ACR >30 mg/g) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m ² (GFR categories G3a–G5)

Abbreviations: **CKD**, chronic kidney disease; **GFR**, glomerular filtration rate; **AER**, albumin excretion rate; **ACR**, albumin-to-creatinine ratio.

Urinary sediment abnormalities

Urinalysis is a simple and useful test that is often characterized as a "liquid kidney biopsy" to diagnose kidney diseases. In a variety of kidney and urinary tract disorders, developed elements such as cells, casts, crystals, and microorganisms may appear in the urine sediment, but renal tubular cells, casts of red blood cells (RBC), casts of white blood cells (WBC), coarse granular casts, wide casts, and large numbers of dysmorphic RBCs are pathognomonic of kidney harm (10).

Electrolyte and other abnormalities due to tubular disorders

Abnormalities of electrolytes and other solutes may result from disorders of renal tubular reabsorption and secretion, e.g., nephrogenic diabetes insipidus, renal tubular acidosis and Fanconi syndrome (11).

Pathologic abnormalities directly observed in kidney tissue obtained by biopsy

Evidence of renal parenchyma defects in kidney biopsies, irrespective of eGFR or other kidney damage markers, must be recognised as an important parameter in determining kidney damage. The pathological classification of renal parenchymal diseases illustrates the localization of the disease to glomeruli, vessels, interstitial tubules, or cysts (12).

Magnesium and Hypomagnesaemia

Magnesium (Mg²⁺) is an essential cation for multiple processes in the body. The kidney plays a major role in regulating the Mg²⁺ balance. In a healthy individual, total-body Mg²⁺ content is kept constant by interactions among intestine, bones and the kidneys (12).

(Mg²⁺) is fundamental for many physiological functions. The equilibrium between complexed and free ionized forms is critical to homeostasis via regulation and control of metabolic processes. Magnesium serves an essential role as cofactor in more than 300 enzymatic reactions regulating a myriad of cellular processes throughout the body (12).

Mg²⁺ is strongly chelated to adenosine triphosphate (ATP) forming a complex required for many rate-limiting enzymes especially kinases that are involved in phosphorylation reactions that transfer a phosphoryl group from ATP to an acceptor molecule (13).

It also plays an important role in the carbohydrate metabolism where it regulates rate-limiting enzymes involved in glycolysis, glucose homeostasis, and insulin action including both insulin receptor

responses (tyrosine kinases) and the insulin-signaling cascade (13).

Additionally, it has a stabilizing role for proteins, nucleic acids, and biological membranes. It takes part in intracellular signaling by regulating ion channels and transportation (Vaduganathan et al., 2013).

In case of chronic kidney disease (CKD), renal regulatory mechanisms may be insufficient to balance intestinal Mg^{2+} absorption. Usually Mg^{2+} remains normal; however, when glomerular filtration rate declines, changes in serum Mg^{2+} are observed (Frank et al., 2018).

Body content and distribution of magnesium

In human beings, 2% of the total body Mg^{2+} is in the extracellular fluid, whereas the remaining 98% is intracellular. Approximately 67% of body Mg^{2+} is stored with calcium and phosphorus in bones, 20% in muscles, and 11% in soft tissues other than muscles. Like calcium, extracellular Mg^{2+} is present in 3 forms: Ionized or free form (55%) thought to constitute the biologically active fraction, Protein-bound form (20%–30%) and Complexed form (15%–25%) as shown in the figure (5) (Bateman, 2017).

The normal plasma level of magnesium is 1.7–2.6 mg/dl.

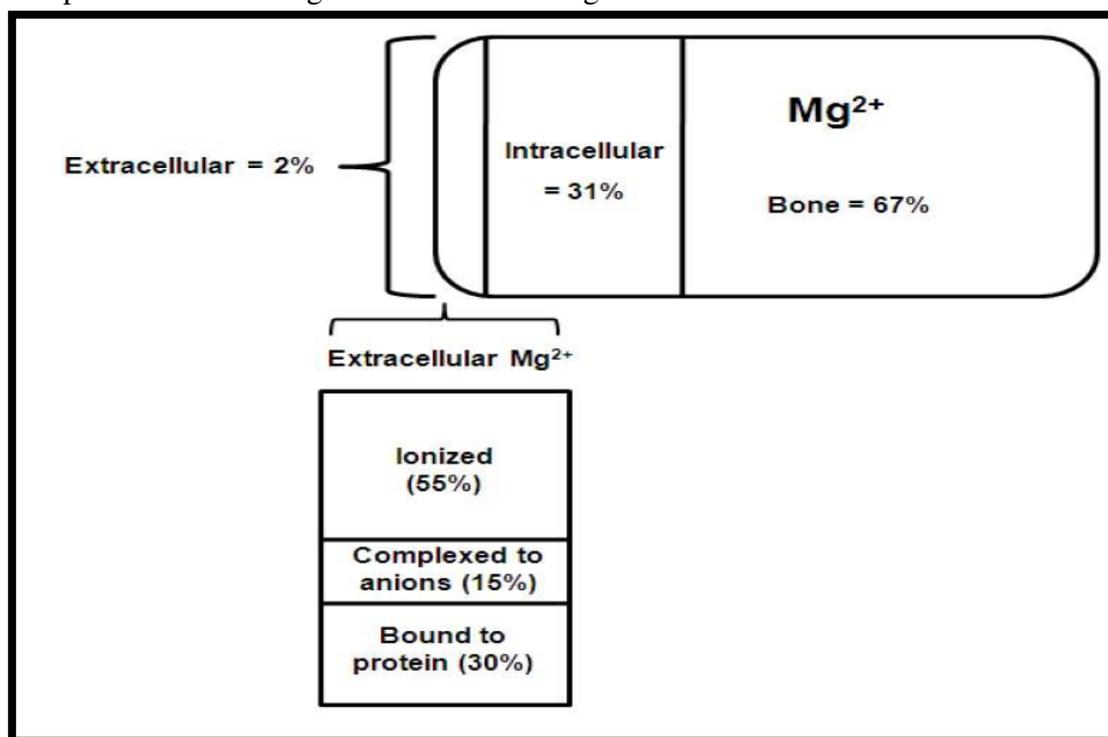


Fig. (1): Distribution of chemical forms of magnesium in body (Bateman, 2017).

Intestinal absorption of magnesium

Intestinal Mg^{2+} absorption occurs predominantly in the small intestine via a paracellular pathway, and smaller amounts are absorbed in the colon, mainly via a transcellular pathway. In humans, Mg^{2+} absorption starts approximately 1 h after oral intake, reaches a plateau after 2–2.5 h up to 4–5 h and then declines. With a daily intake of 370 mg, the absorption rate of Mg^{2+} in the intestine ranges from 30–50%. However, the efficiency of Mg^{2+} uptake is dependent on the ingested dose. For example, early studies with a low dietary Mg^{2+} intake showed that the relative absorption rate can reach 80%, whereas it is reduced to 20% with Mg^{2+} surfeits (14).

There are two different transport systems for magnesium:

Active transcellular transport at low concentrations.

Active transcellular uptake occurs by magnesium channel called TRPM 6 (The transient receptor potential cation channel subfamily Melastatin transporter 6), which is expressed along the brush border membrane of the small intestine. This is where magnesium-amino acid complexes can be absorbed intact as shown in figure (6) (15).

Passive paracellular pathway at high intestinal concentrations.

The passive paracellular pathway is responsible for 80-90% of magnesium uptake in the intestinal tract. Passive pathways work more effectively in an acidic (lower pH) environment, which is why magnesium absorption is optimal on an empty stomach and away from other minerals, drugs, fibers, and alkalizing agents (figure 7) (16).

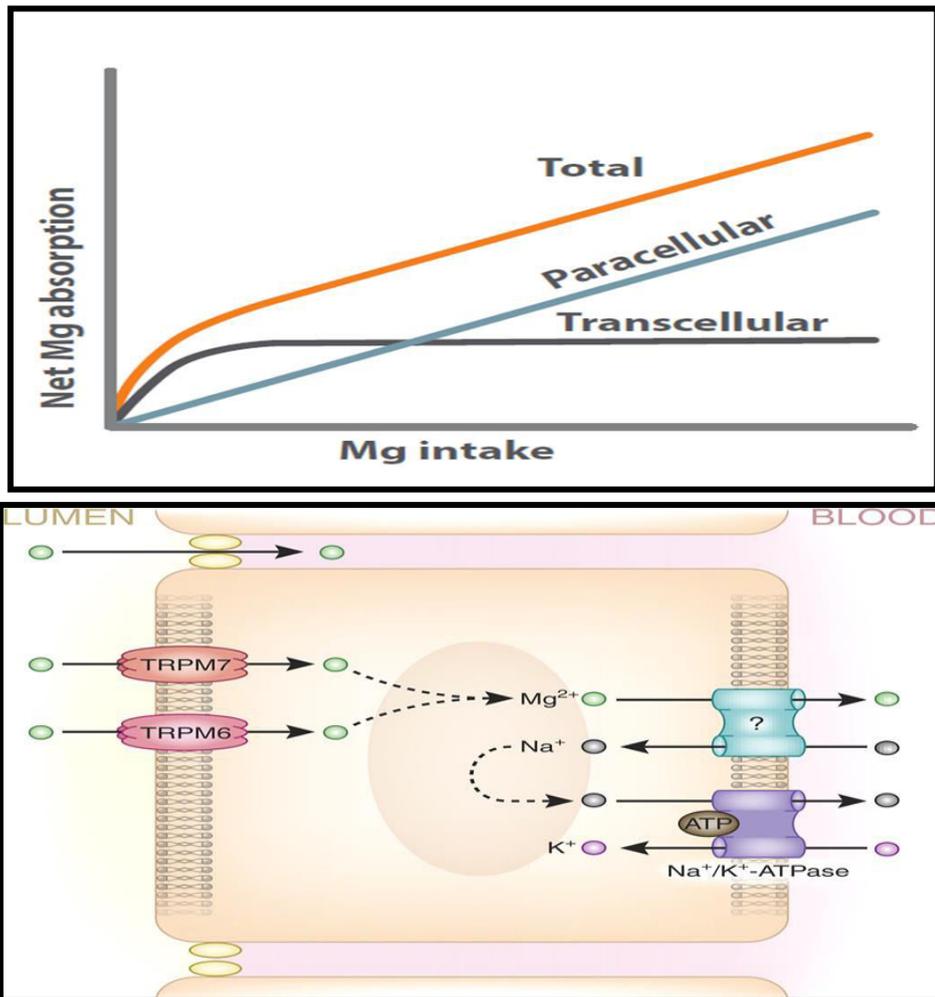


Fig. (2): Intestinal absorption of magnesium (16).

Renal reabsorption of magnesium

After glomerular filtration, the non-protein-bound fraction of Mg^{2+} is reabsorbed along the nephron before it is finally lost within the urine. Under normal conditions, more than 95% of filtered Mg^{2+} in the pro-urine is reabsorbed along the tubular system by several coordinated transport processes. The major sites of renal Mg^{2+} reabsorption are, the thick ascending loop of Henle (TALH, 65–70%), the proximal convoluted tubule (PCT, 10–20%), and the distal convoluted tubule (DCT, 10%), (figure 8) (16).

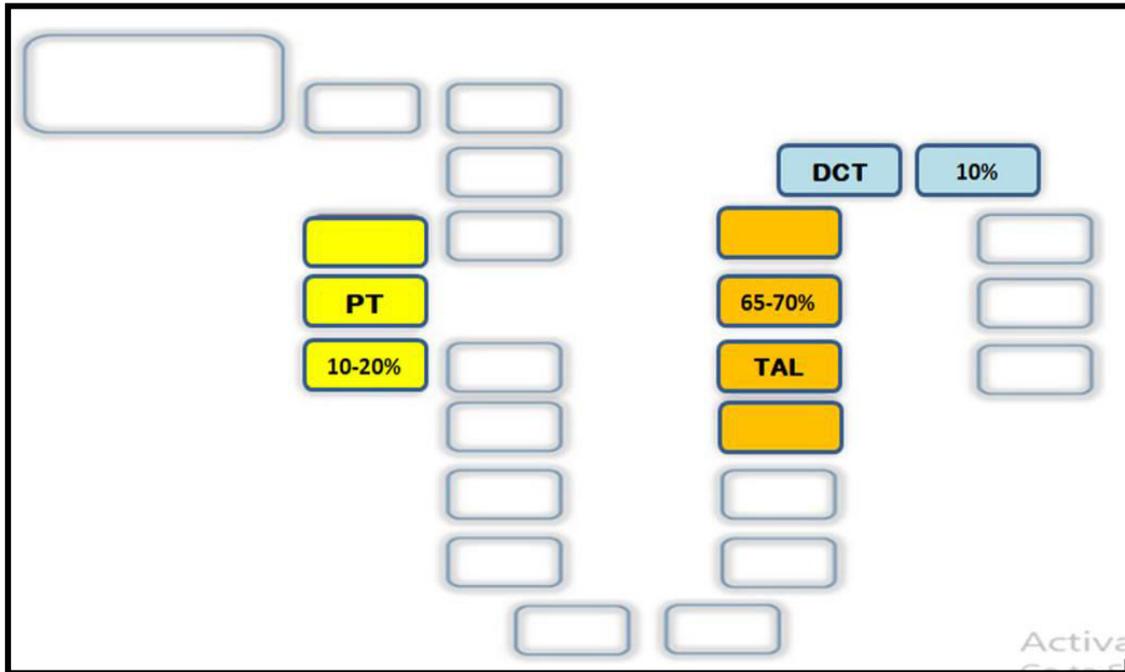


Fig. (3): Mg²⁺ reabsorption along the nephron (16).

In the PCT, magnesium undergoes reabsorption through a paracellular pathway driven by a trans epithelial electrochemical gradient (17).

In the TALH, Mg²⁺ transport primarily occurs through the paracellular shunt pathway, driven by a highly positive lumen potential. The lumen potential produced is a result of active sodium transport by Na⁺-K⁺-2Cl⁻ cotransporter (NKCC2) at the apical membrane and consequent apical back flux of potassium via renal outer medullary potassium channel (ROMK) and basolateral chloride reabsorption via Chloride channel Kb (Clc-Kb) (17). Paracellular Mg²⁺ permeability is increased by claudin-16 and claudin-19 and decreased by claudin-14. Major pathways in the regulation of TAL Mg²⁺ transport occur through activation of basolateral receptors Calcium-sensing receptors (CaSR); a member of the family of G-protein-coupled receptors or parathyroid hormone 1 receptor PTH1R (17).

Claudin-147 expression is decreased by activation of PTH1R and increased by activation of CaSR (17).

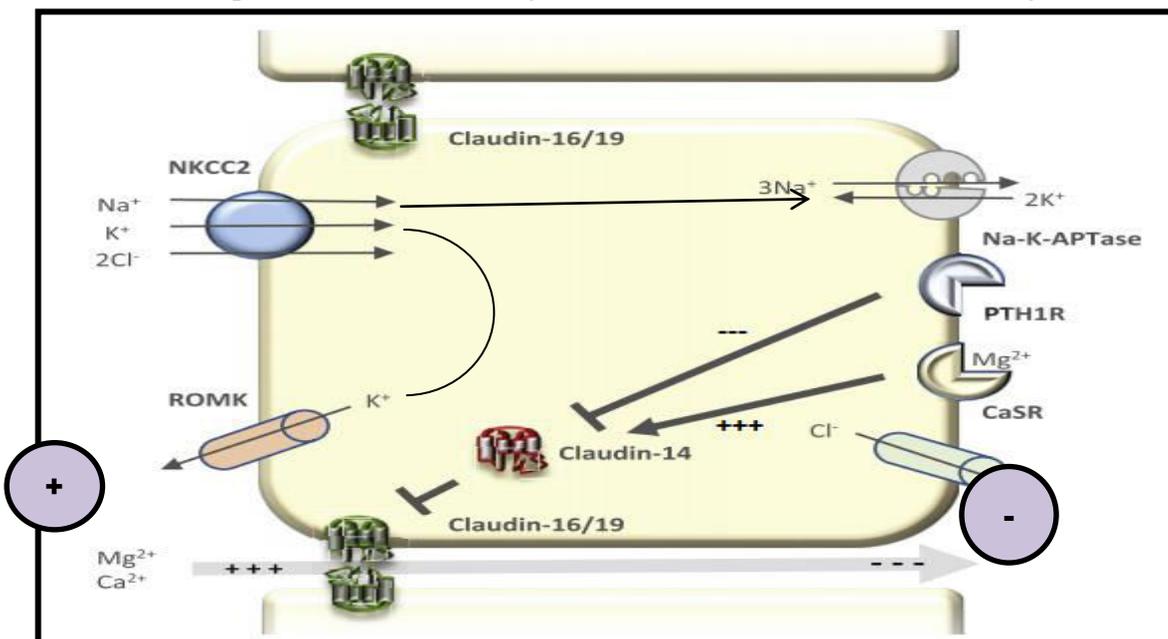


Fig. (4): Magnesium transport in the thick ascending limb of the loop of Henle (TALH) (18).

Abbreviations: NKCC2, Na⁺-K⁺-2Cl⁻ cotransporter; ROMK, renal outer medullary potassium channel; Clc-Kb, Chloride channel Kb; CaSR, calcium "sensing" receptor; PTH1R, parathyroid hormone 1 receptor.

In the DCT, magnesium transport is an active transcellular process. Polarization of the apical membrane by the voltage-gated potassium channel (Kv1.1) provides the driving force for magnesium to enter the cell via the magnesium channel TRPM6. The molecular mediator of magnesium extrusion at the basolateral membrane remains unknown, but it is thought to be by a channel regulated by cyclin M2 gene (CNNM2). Epidermal growth factor receptor (EGFR) activation also leads to increased active TRPM6 at the apical membrane (18).

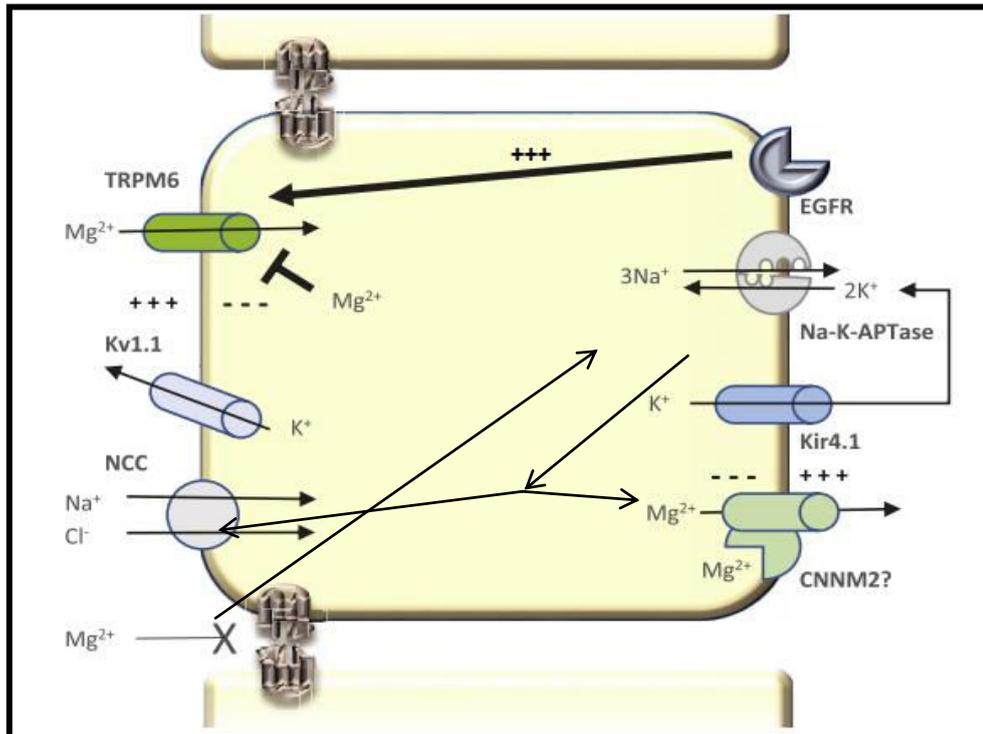


Fig. (5); Magnesium transport in the distal convoluted tubule (DCT) (18).

Abbreviations: EGFR, epidermal growth factor receptor; TRPM6, The transient receptor potential cation channel subfamily Melastatin transporter 6; NCC, sodium chloride cotransporter; Kv1.1, voltage-gated potassium channel; CNNM2, cyclin M2 gene; Kir4.1, inward rectifier K⁺ Channel.

A variety of factors influence the renal handling of Mg²⁺. For example, expansion of the extracellular fluid volume increases the excretion of calcium, sodium, and magnesium. Magnesium reabsorption in the loop of Henle is reduced, probably due to increased delivery of sodium and water to the TAL and a decrease in the potential difference that is the driving force for magnesium reabsorption (Dreuke et al., 2007).

Hypomagnesaemia

Causes of Hypomagnesaemia

A) Gastrointestinal causes:

Gastrointestinal causes include inadequate dietary intake of magnesium, reduced gastrointestinal absorption or increased gastrointestinal loss due to rapid gastrointestinal transit. Poor dietary intake of magnesium has become an increasingly important factor; as many people consume a diet that is low in magnesium content with refined foods, such as white bread or polished rice, remove the parts of plant foods that are rich in magnesium (19).

B) Renal causes:

Changes in the glomerular filtration rate (GFR) influence tubular magnesium reabsorption. When the GFR decreases, the filtered load of magnesium in chronic kidney failure is also reduced and fractional reabsorption is also reduced, such that the plasma magnesium value remains normal until the patient reaches end-stage renal disease (ESRD) (Dreuke et al., 2007). Hypomagnesaemia is occasionally observed in chronic renal failure due to an obligatory renal Mg^{2+} loss. It is also seen during the diuretic phase of acute renal failure (Yu, 1999).

C) Metabolic causes:

- Hypercalcemia inhibits magnesium reabsorption through activation of the CaSR resulting in enhancement in the formation of arachidonic acid - derived 20- hydroxyecosatetraenoic acid (20-HETE), which reversibly inhibits apical potassium channels (ROMK2 channels) (Wang et al., 1996).

Secretion of potassium into the lumen via these channels has 2 functions:

It provides potassium for sodium chloride reabsorption by the Na-K-2Cl cotransporter (NKCC2), and it makes the lumen electropositive, which permits passive calcium and magnesium reabsorption (20).

Thus, inhibition of ROMK2 channels in the TAL will reduce active sodium transport and passive calcium and magnesium reabsorption.

Activating mutations of the CaSR results in autosomal-dominant hypocalcemia with hypercalciuria (ADHH), a condition characterized by hypocalcemia, hypercalciuria, and hypomagnesemia and by low, but detectable, levels of PTH (Okazaki et al., 1999).

- Phosphate depletion can also increase urinary magnesium excretion, through a mechanism that is not clear (21).
- Chronic metabolic acidosis results in renal magnesium wasting, whereas chronic metabolic alkalosis is known to exert the reverse effect. Chronic metabolic acidosis decreases renal TRPM6 expression in the DCT, increases magnesium excretion, and decreases serum magnesium concentration, whereas chronic metabolic alkalosis results in the exact opposite effects (Nijenhuis et al., 2006).
- Hypokalemia is common in patients with hypomagnesemia, occurring in 40-60% of cases. This is partly due to underlying disorders that cause magnesium and potassium losses, including diuretic therapy and diarrhea (Perez Gonzalez et al., 2009).

The mechanism for hypomagnesemia-induced hypokalemia relates to the intrinsic biophysical properties of renal outer medullary K (ROMK) channels mediating K^+ secretion in the TAL and the distal nephron. ROMK channels represent the first (Kir1.1) of 7 subfamilies making up the 2-transmembrane segment inward-rectifier potassium channel family. The channels are designated as inward rectifiers because they have a greater inward conductance of potassium ions than they do an outward conductance of them at negative membrane potentials (if external and internal K^+ concentrations are equivalent) (20). Evidence also suggests that this wasting may be due to a hypomagnesemia-induced decline in adenosine triphosphate (ATP) and the subsequent removal of ATP inhibition of the ROMK channels responsible for secretion in the TAL and collecting duct. (20).

The classic sign of severe hypomagnesemia (< 1.2 mg/dL) is hypocalcemia. The mechanism is multifactorial. Parathyroid gland function is abnormal, largely because of impaired release of PTH. Impaired magnesium-dependent adenylyl cyclase generation of cyclic adenosine monophosphate

(cAMP) mediates the decreased release of PTH (22).

D) Drugs:

Loop diuretics (including furosemide, bumetanide, and ethacrynic acid) produce large increases in magnesium excretion through inhibition of the Na-K-Cl cotransporter in the TAL (23).

Long-term thiazide diuretic therapy also may cause magnesium deficiency, through enhanced magnesium excretion and, specifically, reduced renal expression levels of the epithelial magnesium channel TRPM6 and inhibition of thiazide sensitive NaCl cotransporter leading to inhibition of NaCl entry into the cell (24).

Long term uses of proton-pump inhibitors (PPIs) such as omeprazole impair the intestinal Mg absorption by inhibiting Mg transporters (TRPM6 and TRPM7) (25).

Renal magnesium wasting is common in patients treated with cyclosporine and tacrolimus, presumably because of reduced magnesium reabsorption associated with down regulation of TRPM6 (Chang et al., 2007).

E) Endocrinal causes:

Diabetes mellitus (DM) both type I and type II, are said to be the commonest causes of magnesium deficiency, with 25-39% of patients being affected. Hypomagnesemia in patients with uncontrolled diabetes mellitus appears to be associated with increased urinary magnesium excretion and is reversed by correction of the hyperglycemia with insulin (23)

F) Genetic causes:

- Gitelman syndrome is the most frequent genetic cause of hypomagnesemia. It is an autosomal recessive disorder caused by mutations in Solute Carrier Family 12 Member 3 (SLC12A3), the gene encoding the Na⁺-Cl⁻ cotransporter (NCCT) that is expressed on the apical membrane of the DCT, this syndrome is characterized by; hypokalemia, hypomagnesemia, and hypocalciuria (Scholl et al., 2012).
- Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), an autosomal-recessive disorder, in which profound renal magnesium and calcium wasting occurs. The hypercalciuria often leads to nephrocalcinosis, resulting in progressive renal failure, it is caused by mutation in the claudin-16 gene (26).
- Autosomal-dominant hypocalcemia with hypercalciuria (ADHH) is another disorder of urinary magnesium wasting. Affected individuals present with hypocalcemia, hypercalciuria, and polyuria, and about 50% of these patients have hypomagnesemia. ADHH is produced by mutations of the CASR gene, the gene that encodes for (CaSR) located basolaterally in TAL and DCT, which is involved in renal calcium and magnesium reabsorption (Nijenhuis et al., 2005).

Manifestations of Hypomagnesaemia

Many patients with Hypomagnesemia remain asymptomatic. As Mg²⁺ deficiency is usually secondary to other disease processes or drugs, the features of the primary disease process may complicate or mask Mg²⁺ deficiency. Signs and symptoms of Mg²⁺ deficiency are usually not seen until serum magnesium decreases to 0.6 mmol/l (1.46 mg/dl) (Soar et al., 2010).

Clinical manifestations of magnesium deficiency are:

Biochemical manifestations of hypomagnesemia:

A) Hypokalemia

Hypokalemia is common in patients with Mg^{2+} deficiency and about half of the patients with clinically potassium deficiency also have Mg^{2+} depletion. This condition is believed to occur secondary to the decreased normal physiologic magnesium inhibition of the ROMK channels in the apical tubular membrane (27).

B) Hypocalcemia

Hypocalcemia is a well-known manifestation of Mg^{2+} deficiency and studies indicate that Mg^{2+} deficiency inhibit the release of PTH. Moreover, parenteral Mg^{2+} stimulates PTH secretion, and it is therefore suggested that reduced PTH secretion is a key contributor to hypocalcemia in Mg^{2+} deficiency (Griffin et al., 2013).

Clinical manifestations of hypomagnesemia:

A) Cardiovascular

Mg^{2+} has several effects on the cardiac conduction system. It is an essential cofactor of the Sodium-Potassium-ATPase (Na-K-ATPase) pump which controls the movement of sodium and potassium across cell membranes; Mg^{2+} levels therefore influence myocardial excitability. Low serum Mg has been correlated to increased risk of atrial fibrillation (AF) (Khan et al., 2013).

Hypomagnesemia is also associated in severe cases with widening of the QRS complex, peaking of T wave, prolongation of the PR interval, ventricular premature complexes, polymorphic ventricular tachycardia (Torsade de pointes), and ventricular fibrillation (De Vecchis et al., 2018).

B) Neuromuscular

Neuromuscular hyperexcitability is often the first clinical manifestation in patients with hypomagnesemia. Concomitant Mg^{2+} and calcium deficiency enhance neurological symptoms, but also patients with isolated Mg deficiency present neuromuscular hyperexcitability such as positive Chvostek and Trousseau signs, muscle spasms, and cramps which probably all are due to lowering of the threshold for nerve stimulation (28).

C) Asthma

Mg^{2+} is established treatment of resistant asthma attacks. Mg^{2+} increases the effect of salbutamol through inhibiting calcium influx by blocking the voltage-dependent calcium channels which then relaxes the smooth muscle. Mg^{2+} also has an immunoregulatory effect by reducing pro-inflammatory mediators and promoting synthesis of prostacyclin and nitric oxide which stimulates Broncho dilatation (Turner et al., 2017).

D) Preeclampsia

Mg^{2+} therapy has been used for decades as eclampsia prophylaxis. In 2002, the results from the “Magnesium Sulphate for Prevention of Eclampsia trial” were published. Ten thousand patients with preeclampsia were randomized to receive Mg^{2+} therapy or placebo. The Mg^{2+} therapy group showed significant fewer cases of eclampsia compared to the placebo group, maternal death was fewer among women who received Mg^{2+} therapy, and Mg^{2+} did not seem to give harmful side effects to either the mother or the fetus (Altman et al., 2002).

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