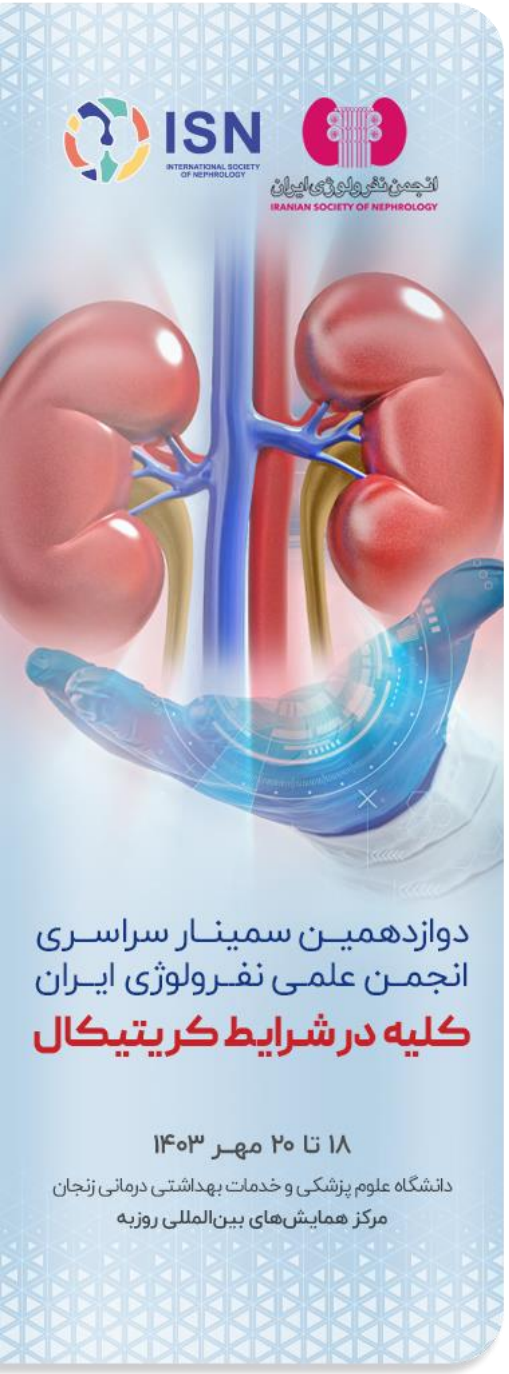
به‌نام خدای بخشاینده مهربان

In the name of Allah, the Beneficent, the Merciful.



مرکز تحقیقات نفرولوژی

Hypomagnesemia in critically ill patients

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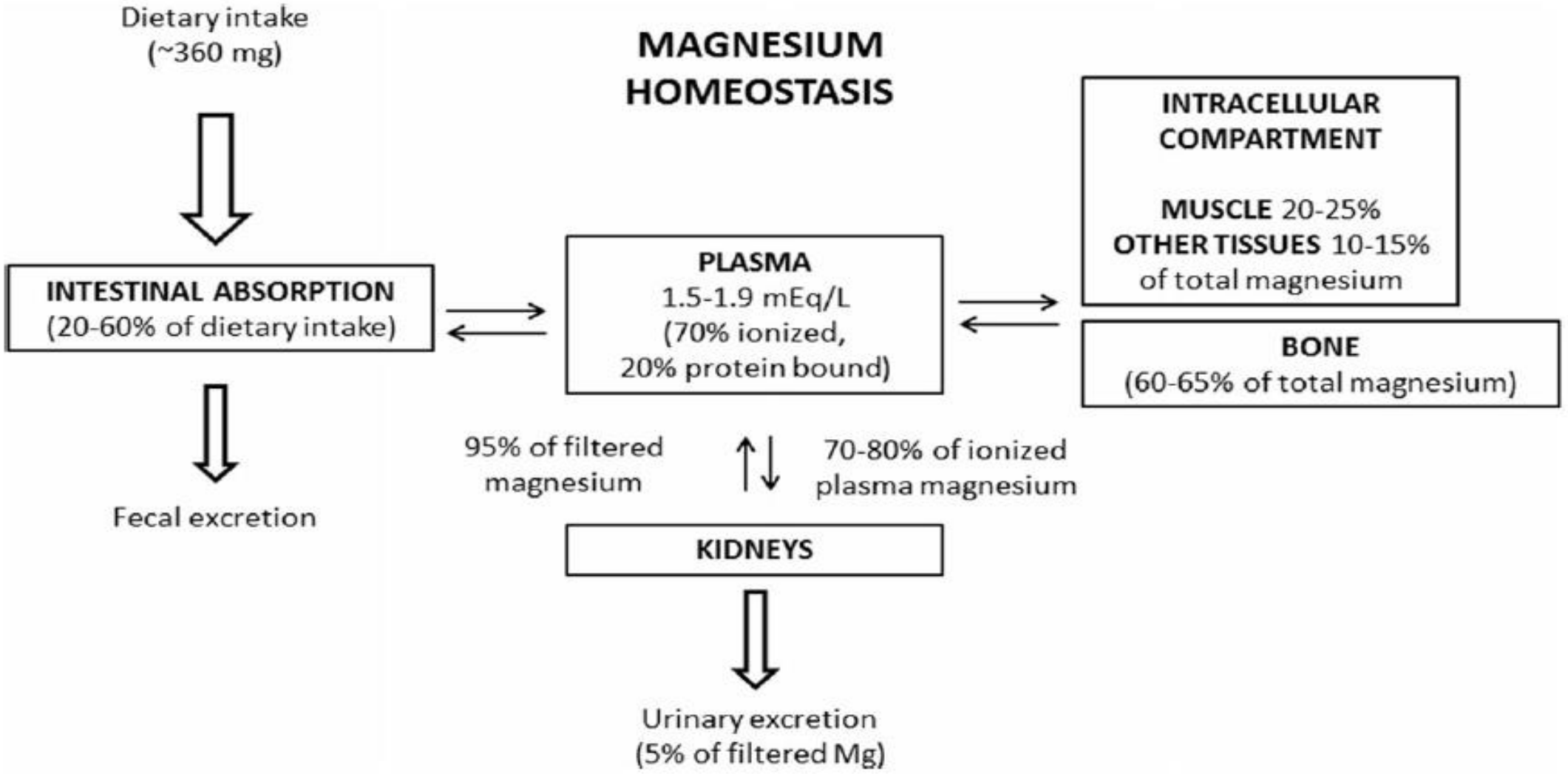
Autumn, 2024

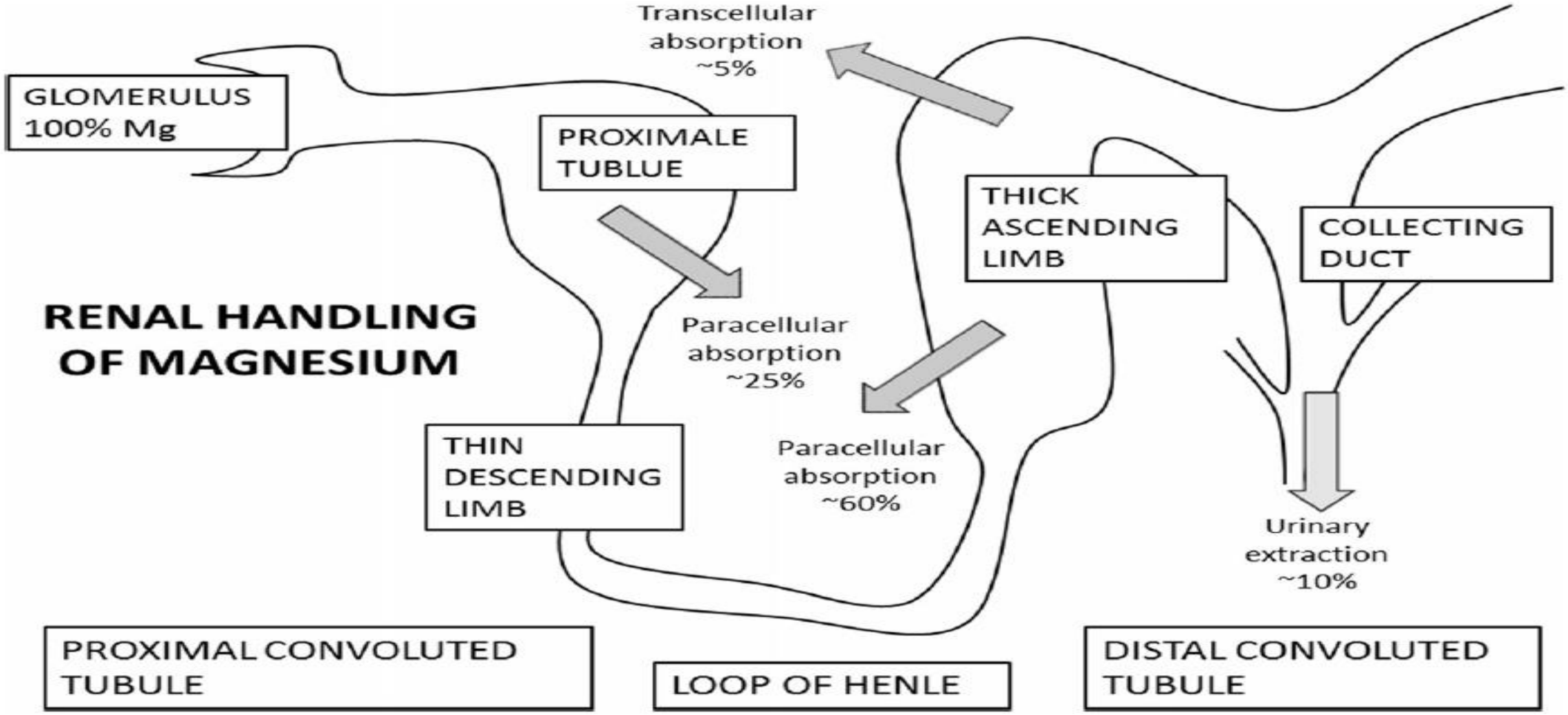
Outlines

- Introduction
- Causes ofhypomagnesemia
- Consequences of hypomagnesemia
- Treatment

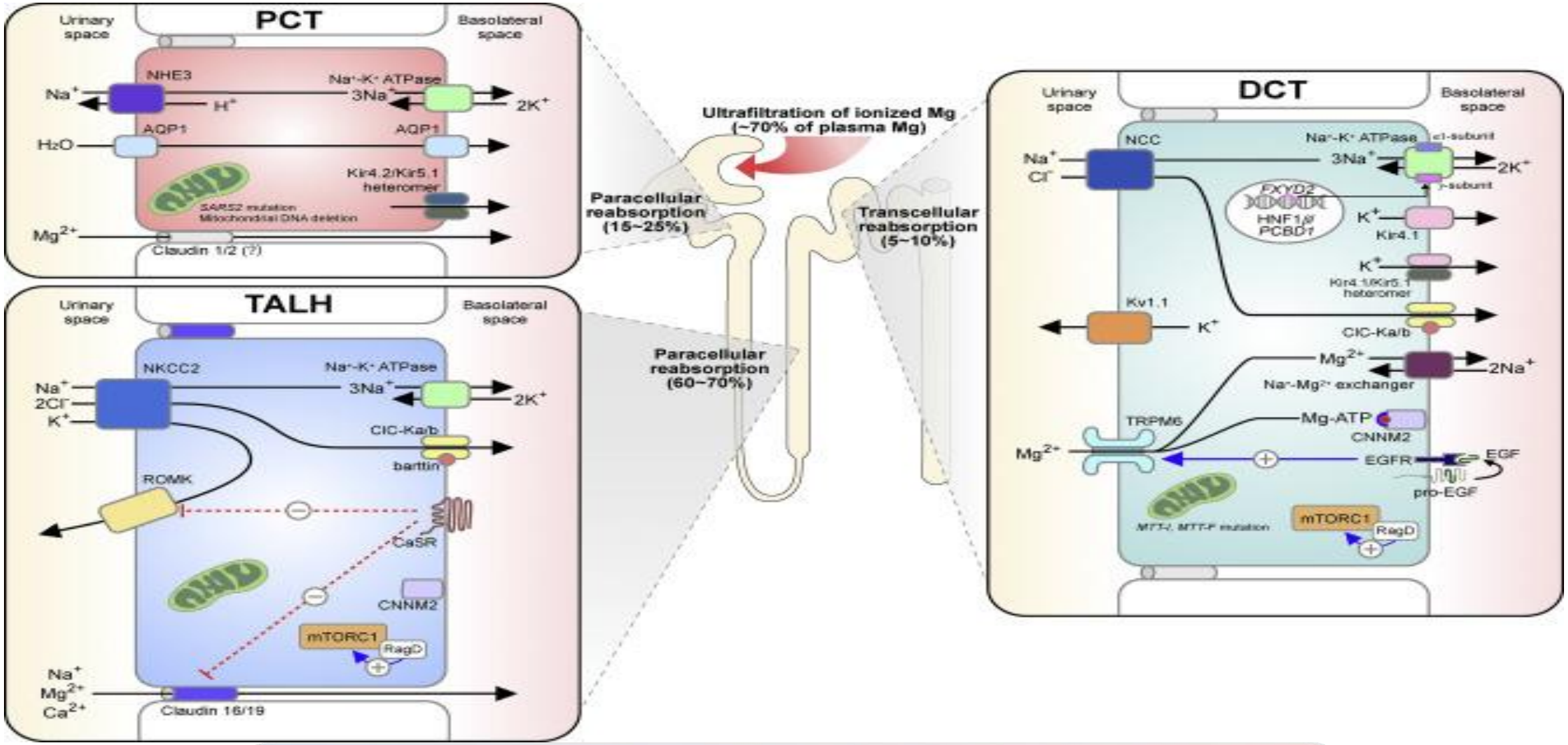
Mg homeostasis



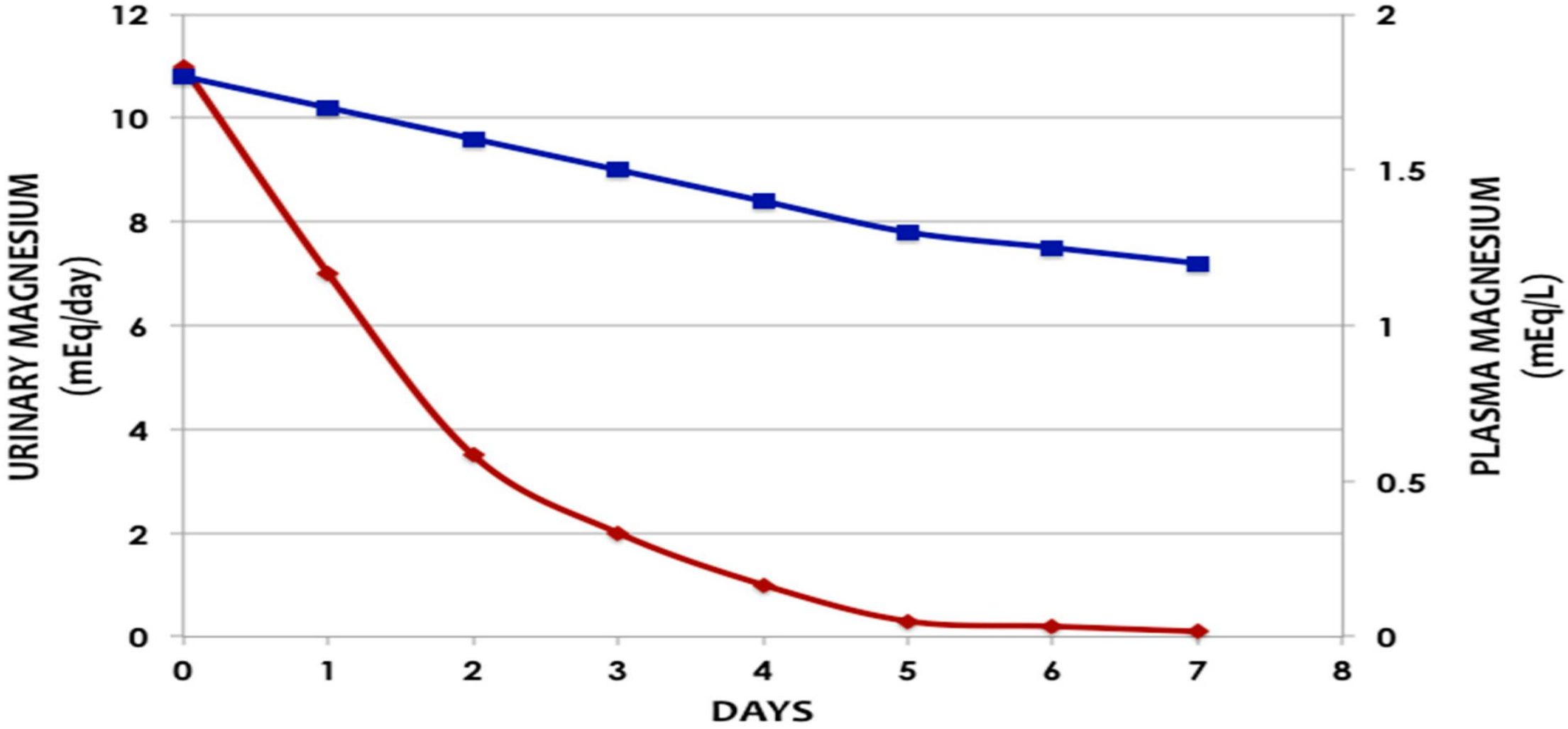
Renal Mg handling



Mg reabsorption in TAL and DCT



Mg homeostasis and the role of kidney



Defining magnesium status

- serum concentration of Mg
  - normal serum levels in patient with intracellularly Mg depleted
  - intracellular stores are recruited to keep the serum levels within its range

Hypomagnesemia versus Mg Depletion

- Mg tolerance test
  - reduced urinary excretion (less than 80%) of an infused magnesium load (2.4 mg/kg given over the initial four hours)
  - Patients with malnutrition, cirrhosis, diarrhea, or long-term diuretic use typically have a positive test,

- intracellular levels of Mg in RBC,…

Causes of hypomagnesemia in critically ill patients

- GI disorders

- Renal Loss

Gastrointestinal causes

- Both upper and lower intestinal tract fluid contain Mg.

- loss of GI fluids:
  - vomiting
  - nasogastric suction
  - Diarrhea
  - enteritis, inflammatory bowel disease
  - intestinal and biliary fistulas
  - intestinal surgery resections
  - pancreatitis

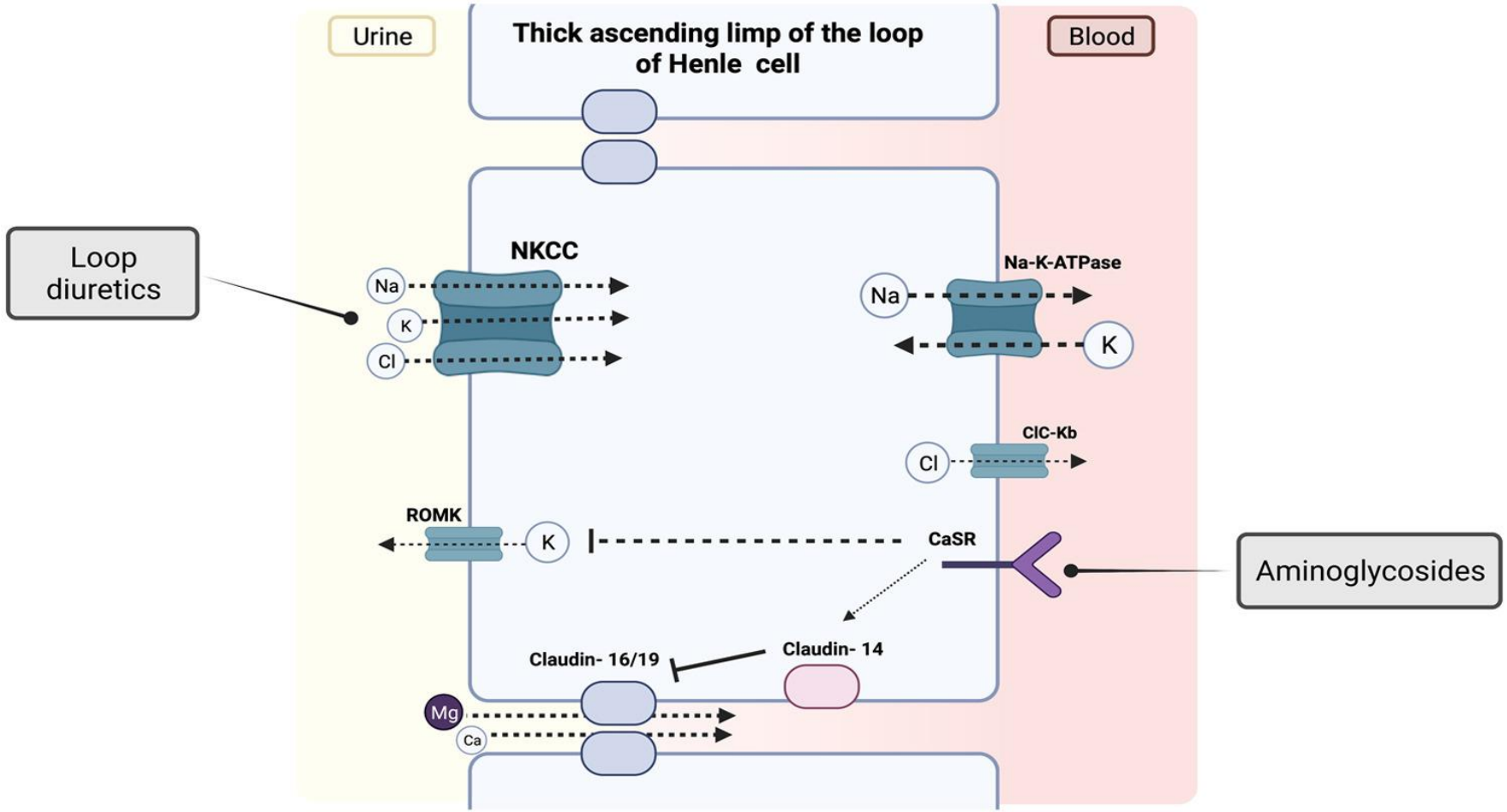
Renal Causes

- Chronic parenteral fluid therapy
- Osmotic diuresis (glucose, mannitol, urea)
- Hypercalcemia
- Alcohol
- Drugs
- Metabolic acidosis (starvation, ketoacidosis, alcoholism)
- Renal diseases
  - Chronic pyelonephritis, interstitial nephritis, and glomerulonephritis
  - Diuretic phase of acute tubular necrosis
  - Postobstructive nephropathy
  - Renal tubular acidosis
  - Post-renal transplantation
  - Primary renal hypomagnesemia

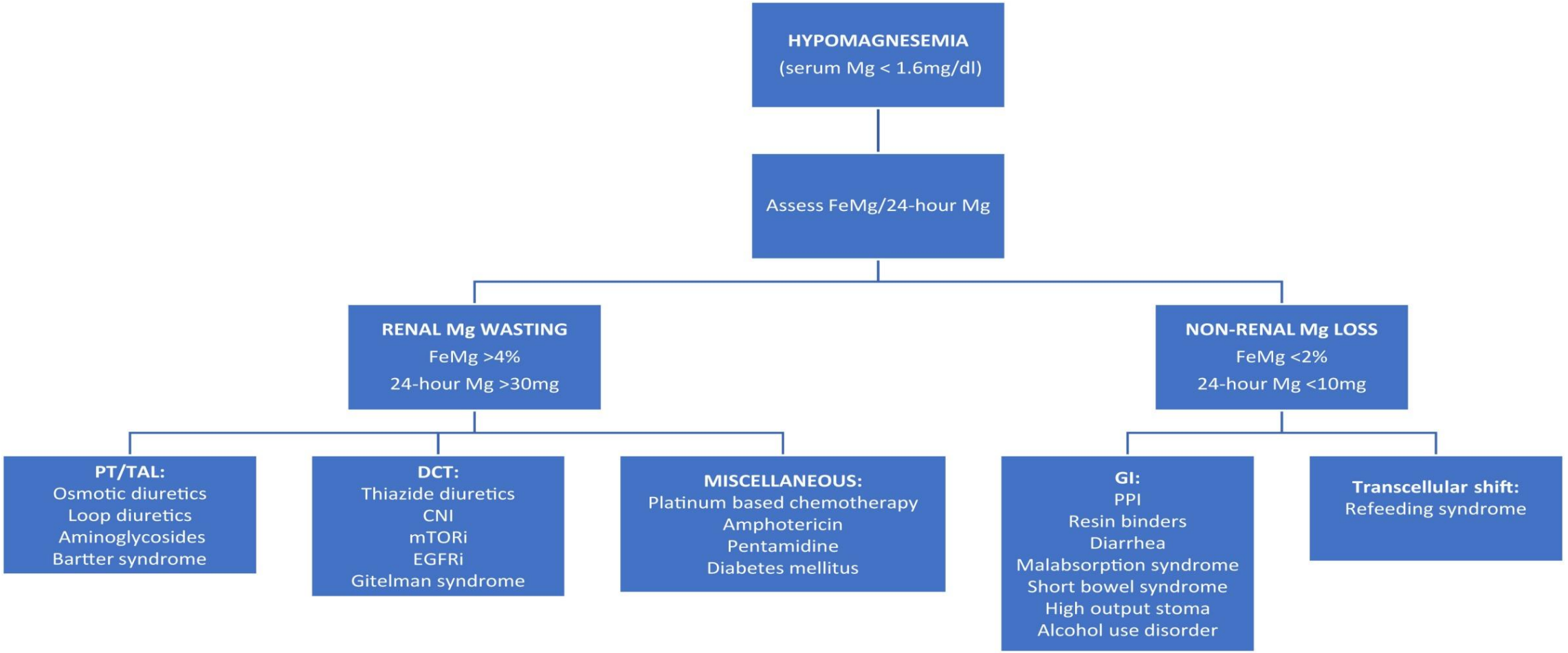
Drugs associated with Mg deficiency

Drugs	Mechanisms causing Mg deficiency
	Renal loss
Diuretics	
Loop	Increased renal Mg excretion by affecting the transepithelial voltage and inhibiting passive absorption.
Thiazides	Enhance Mg entry into the cells in the distal convoluted tubule.
Antimicrobial	
Amphotericin B Aminoglycosides Capreomycin Pentamidine	Renal urinary Mg wasting caused by nephrotoxins may be part of tubular necrosis and acute renal failure. Notably, impairment in Mg reabsorption in the loop of Henle and distal tubules may occur before the onset and may persist after the resolution of renal damage.
Chemotherapy	
Cisplatin	Renal urinary Mg wasting caused by nephrotoxins may be part of tubular necrosis and acute renal failure. Cisplatin treatment is also associated with lowered intestinal absorption
Immunosuppressive	
Calcineurin inhibitors	Urinary Mg wasting due to a downregulation of the Mg^{2+} transport proteins (TRPM6) in the loop of Henle and distal convoluted tubules.
Epidermal growth factor receptor inhibitors	
Cetuximab Panitumumab Matuzumab	Urinary Mg wasting due to a downregulation of the TRPM6 in the loop of Henle and distal convoluted tubules.
	Gastrointestinal loss
Proton-pump inhibitor	Impairing the intestinal Mg absorption by inhibiting Mg transporters (TRPM6 and TRPM7).
	Miscellaneous
Foscarnet	A general potent chelator of divalent cations which therefore has the potential to reduce ionized levels of Mg.
Cardiac glycosides	Mg deficiency is associated with cardiac glycosides. The exact mechanisms are not known.

Loop diuretics, AG, and hypomagnesemia



Approach to hypomagnesemia



Effects of moderate to severe Mg deficiency

- Biochemical
- Clinical
  - Neuromuscular
  - Cardiovascular
- Role of Mg in immunomodulation

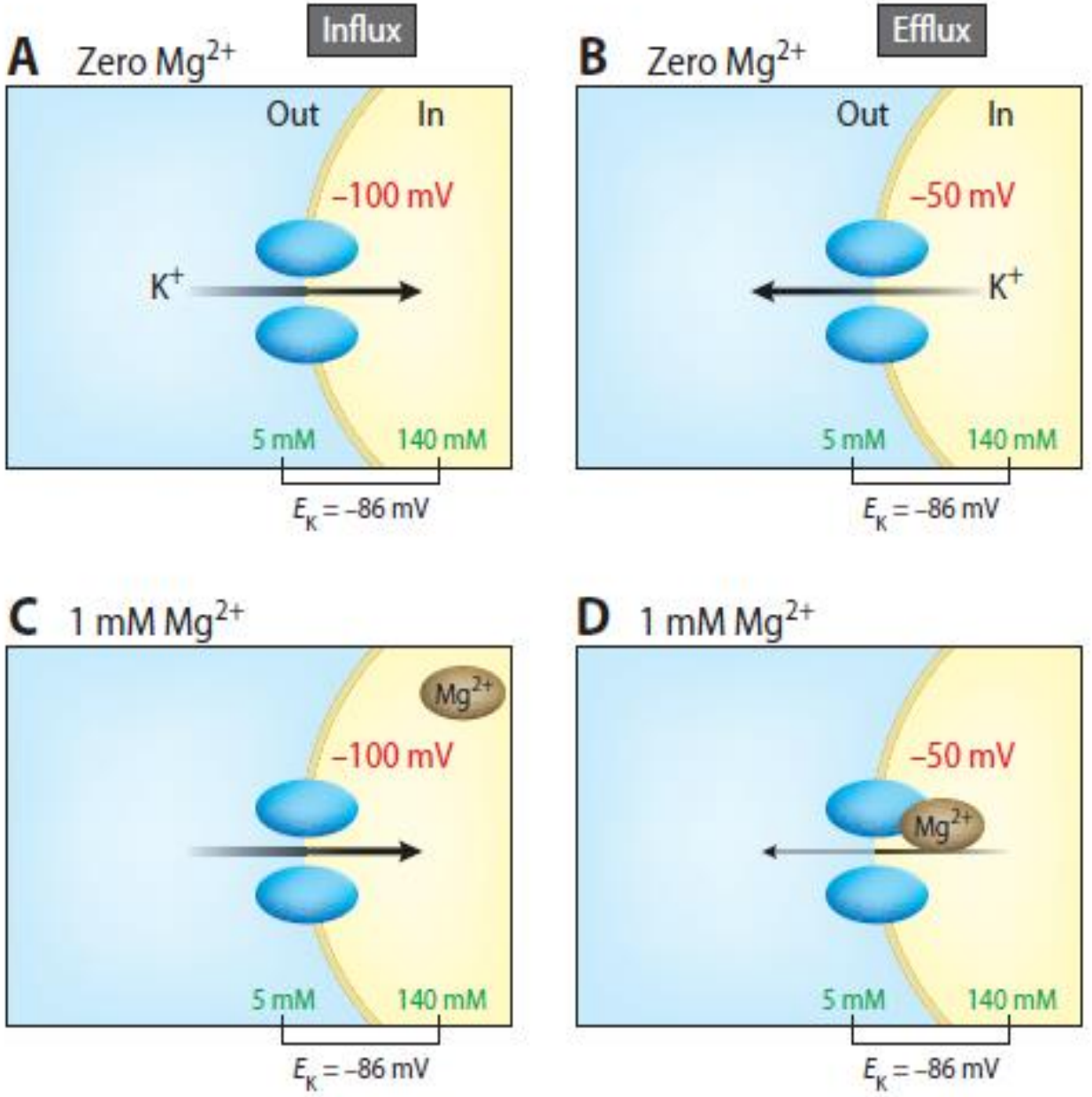
Biochemical effects of Mg deficiency

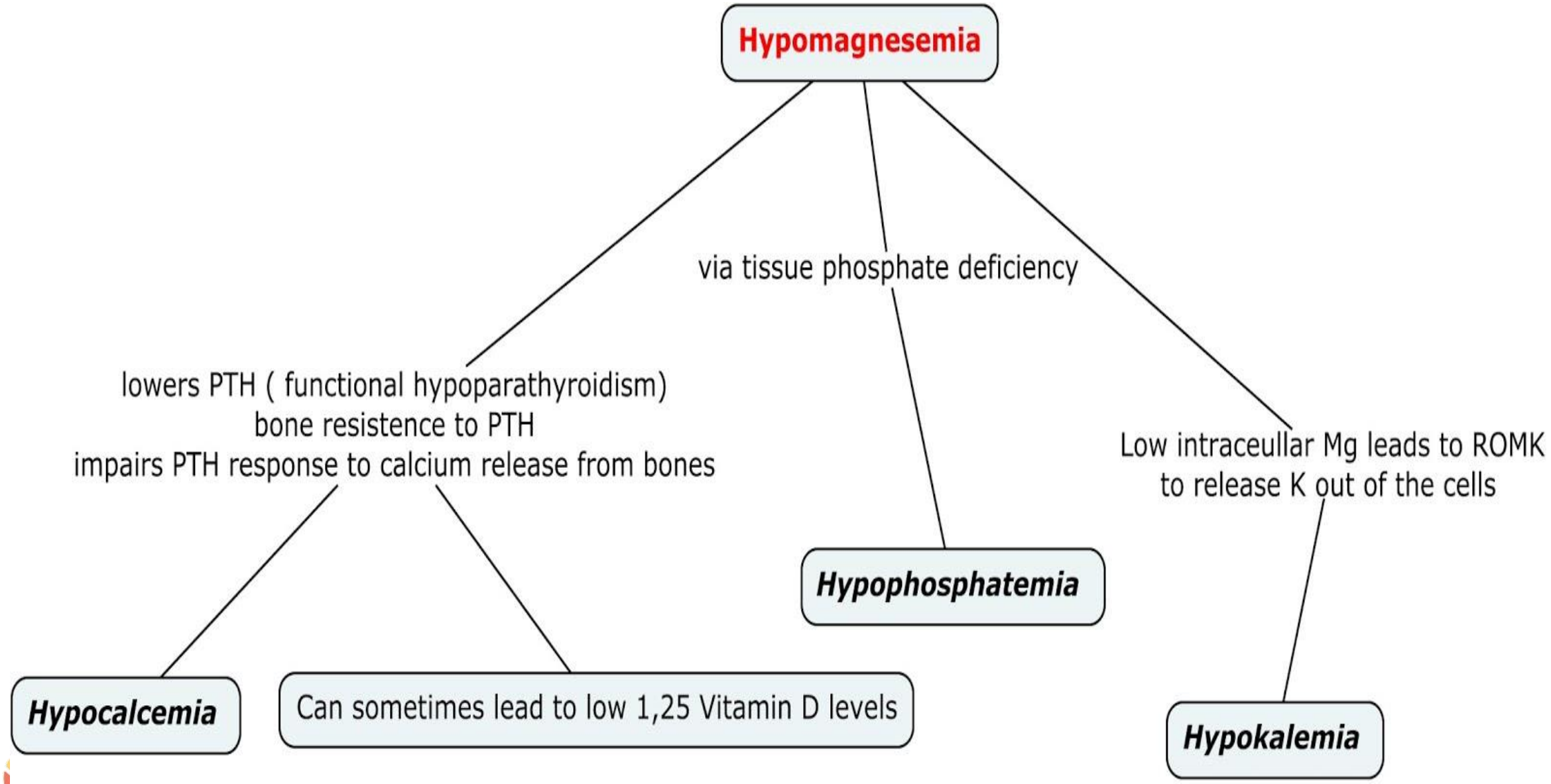
- Hypokalemia
  - Renal K wasting
  - Decreased intracellular K

- Hypocalcemia
  - Impaired parathyroid hormone secretion
  - Renal and skeletal resistance to parathyroid hormone
  - Resistance to vitamin D

Hypokalemia in Magnesium Deficiency

- Mg regulating activity of the ROMK
- high intracellular Mg blocks ROMK channel pore
- Mg prevents potassium efflux




Hypomagnesemia
via tissue phosphate deficiency
lowers PTH (functional hypoparathyroidism)
bone resistence to PTH
impairs PTH response to calcium release from bones
Low intraceullar Mg leads to ROMK
to release K out of the cells
Hypophosphatemia
Hypocalcemia
Can sometimes lead to low 1,25 Vitamin D levels
Hypokalemia

Clinical manifestations of hypomagnesemia

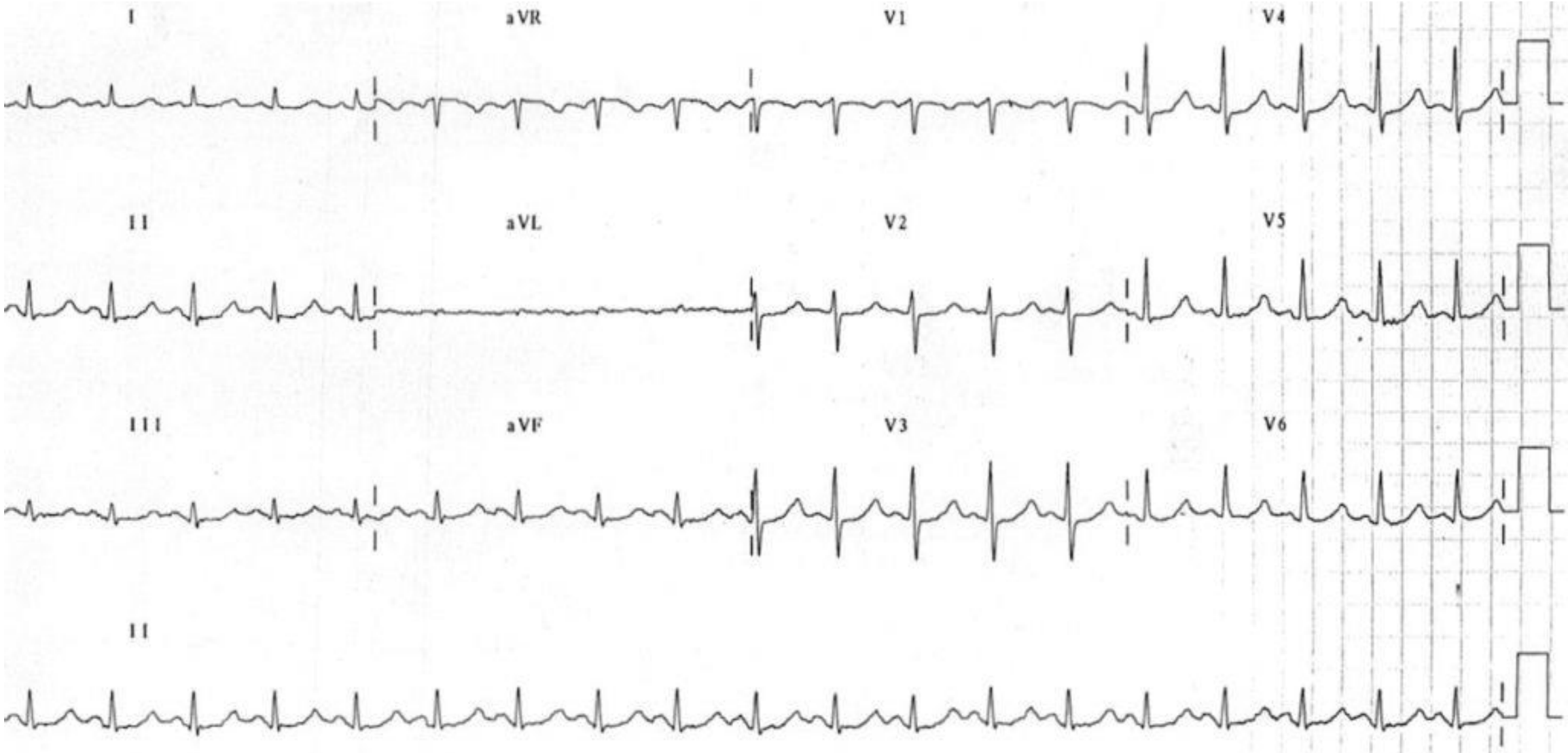
- Cardiovascular
- Neuromuscular

Cardiovascular

- Mg levels influence myocardial excitability.

- ECG changes
  - QT prolongation, QRS Widening and peaking of T waves in moderate Mg deficiency
  - PR interval prolongation, progressive widening of the QRS complex, and diminution of T wave in severe Mg depletion

- dysrhythmias
  - AF (after cardiac surgery)
  - PVC, Polymorphic VT, VF in severe deficiency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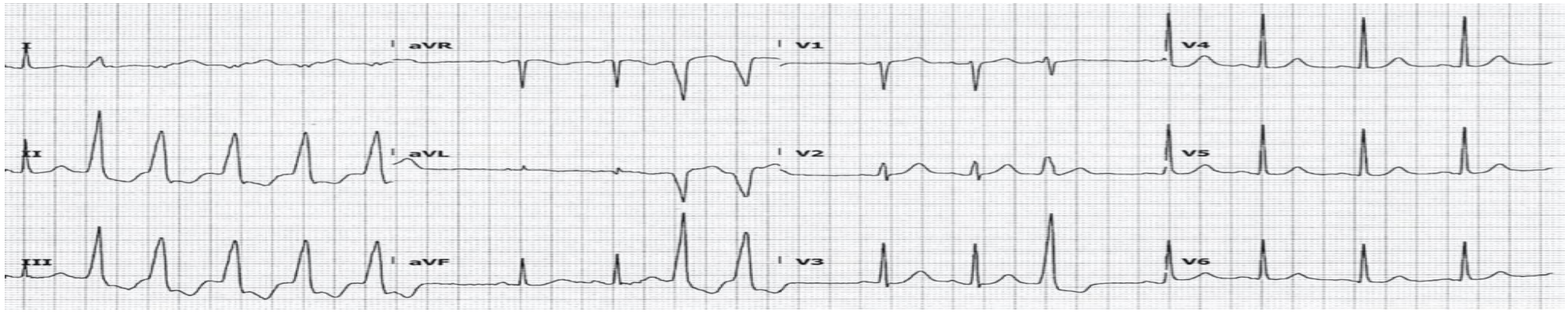
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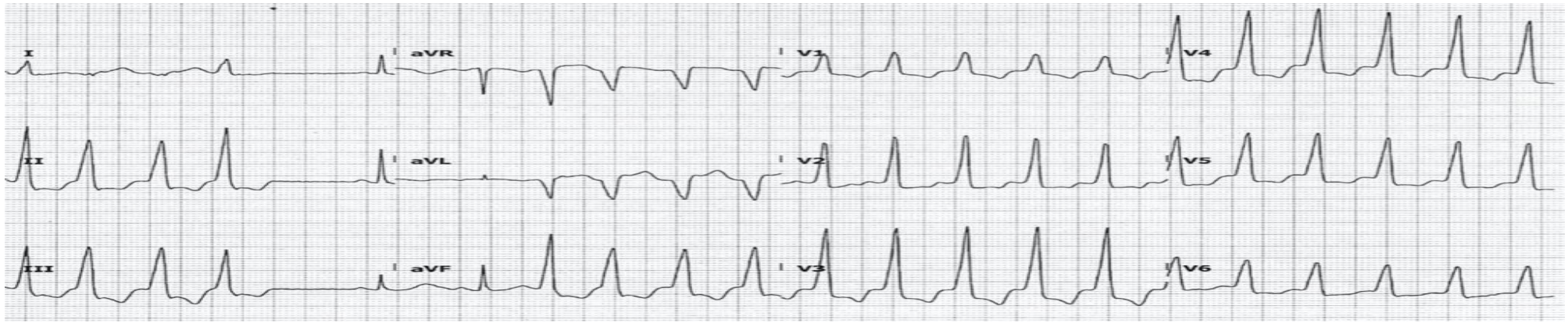
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Neuromuscular Manifestation

- Neuromuscular hyperexitability
  - often the first clinical manifestation
  - Concomitant Mg and calcium deficiency enhance neurological symptoms
    - tetanus with positive Chvostek and Trousseau signs
    - muscle spasms
    - Cramps

- decrease of extracellular Mg^{2+}
  - influx of calcium in presynaptic nerves
  - Release of a greater amount of neurotransmitters

Vertical nystagmus is a rare but a diagnostically and useful sign of severe hypomagnesaemia.

Magnesium and the Immune System

- Mg deficiency:
  - activation of innate immune system
    - PMN activation, increased phagocytosis, ROS production
  - impairment of adaptive immune system
    - Role of Mg in development and proliferation of lymphocytes
    - Mg^{2+} transporter TRPM7 is important for T-cell development
    - Extracellular Mg regulate CD8+ T-cells, via co-stimulatory molecule LFA-1 mediated pathway

Moderate magnesium deficiency contributes significantly to chronic low-grade inflammation.

Mg and Sepsis

- Hypomagnesemia: elevated levels of IL6 and TNF-α
- Mg administration protects from LPS-induced lethal septic shock
- Magnesium and thiamine are crucial cofactors in Krebs cycle:
  - Role of Mg in increasing the rate of lactate clearance
- Hypomagnesemia
  - increased risk of infections
  - worsened sepsis progression
  - decreased survival rates in critically ill patients.

Mg and Respiratory Diseases

- Asthma attack
  - bronchodilation
  - reduce inflammation

- COVID-19
  - correlation between severe COVID-19 symptoms and low serum of Mg
  - Mg, vitamin C, and vitamin D supplementation in COVID-19 patients was associated with significant reduction in oxygen supplementation

Mg and Kidney Injury

- Magnesium enhances kidney blood flow:
  - endothelium-dependent release of NO
  - counteracting the vasoconstriction induced by catecholamines

- Mg favoring vasodilation

- Hypomagnesemia may increase the risk of AKI by disrupting kidneys' vascular autoregulation

Clinical and Experimental Nephrology (2022) 26:997–1004
https://doi.org/10.1007/s10157-022-02245-6

ORIGINAL ARTICLE

Association of magnesium abnormalities at intensive care unit admission with kidney outcomes and mortality: a prospective cohort study

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Abstract

Background Magnesium abnormalities have been associated with adverse kidney outcomes and mortality in critically ill patients, however, this association remains inconsistent. This study aimed to investigate the association of magnesium abnormalities at intensive care unit (ICU) admission with kidney outcomes (i.e., acute kidney injury (AKI) and kidney function recovery) and mortality risk in a large cohort of critically ill patients.

Methods A prospective cohort study was conducted by collecting data from three ICUs in Brazil. The ICU admission serum magnesium level was used to define hypomagnesemia (< 1.60 mg/dL) and hypermagnesemia (> 2.40 mg/dL). The Kidney Disease Improving Global Outcomes AKI Guideline was used to define AKI based on serum creatinine levels. Kidney function recovery was defined as full recovery, partial recovery, and non-recovery at ICU discharge. Mortality was screened up to 28 days during ICU stay.

Results A total of 7,042 patients was analyzed, hypomagnesemia was found in 18.4% ($n = 1,299$) and hypermagnesemia in 4.4% ($n = 311$). Patients with hypomagnesemia were 25% more likely to develop AKI after adjustment for confounding variables (OR = 1.25; 95% CI 1.08–1.46). No significant association was found for hypermagnesemia and AKI (OR = 1.18; 95% CI 0.89–1.57). Kidney function recovery was similar among groups but hypermagnesemia had lower non-recovery rates. Both hypomagnesemia and hypermagnesemia were associated with 65 and 52% higher mortality risk after adjustments for confounders, respectively (HR = 1.65; 95% CI 1.32–2.06 and 1.52; 95% CI 1.01–2.29).

Conclusions Hypomagnesemia, but not hypermagnesemia, at ICU admission was associated with AKI development. On the other hand, both hypomagnesemia and hypermagnesemia were associated with higher mortality risks.

Fig. 2 Odds ratio for acute kidney injury in patients admitted with magnesium abnormalities at intensive care units

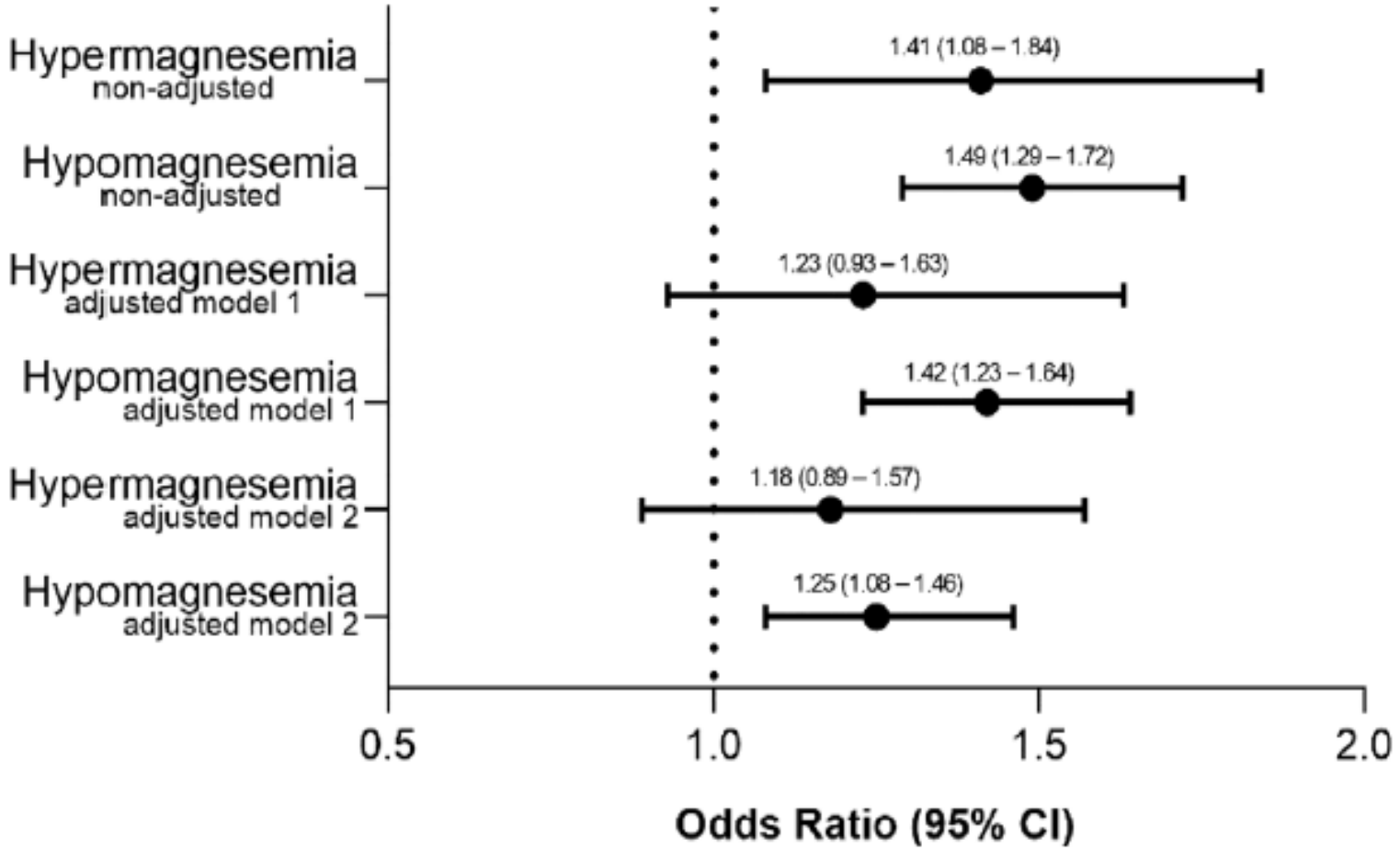
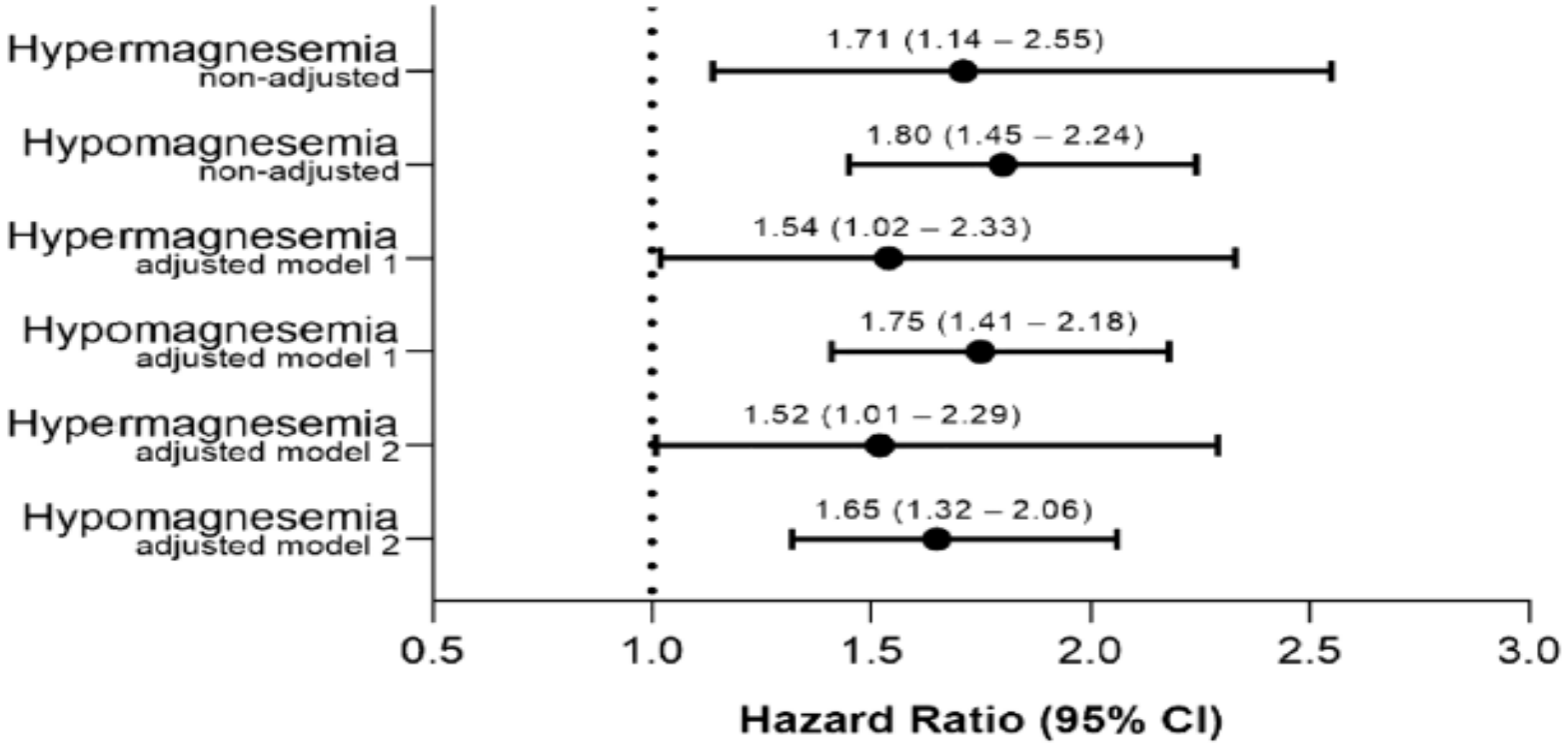


Fig. 4 Hazard ratio for all-cause mortality in patients admitted with magnesium abnormalities at intensive care units



Mg and Outcome in ICU

Volume 109, Issue 7
July 2016

JOURNAL ARTICLE

Hypomagnesemia and mortality in patients admitted to intensive care unit: a systematic review and meta-analysis

Sikarin Upala, Veeravich Jaruvongvanich, Karn Wijarnpreecha, Anawin Sanguankeo

QJM: An International Journal of Medicine, Volume 109, Issue 7, July 2016, Pages 453–459,
https://doi.org/10.1093/qjmed/hcw048
Published: 24 March 2016 **Article history**

Abstract

Background: Reports of mortality due to magnesium dysregulation in the critical care setting are controversial. We performed a systematic review and meta-analysis to evaluate the association between hypomagnesemia and mortality in patients admitted to the intensive care unit.

Methods: Eligible studies assessing the association between hypomagnesemia or hypermagnesemia and mortality in the critical care setting were comprehensively searched in MEDLINE and EMBASE from their inception to September 2015. Inclusion criteria were published observational studies in adults who were admitted to the intensive or critical care setting with initial serum magnesium measurement. We used the definition of abnormal magnesium level defined by each study. Primary outcome was all-cause mortality. We performed meta-analysis using random-effects model and calculated pooled effect estimate of outcome comparing between hypomagnesemia and normal magnesium category.

Results: From 30 full-text articles, 6 studies involving 1550 participants were included in the meta-analysis. There was a statistically significant higher risk of mortality in critically ill patients who had hypomagnesemia with RR of 1.90 (95% CI: 1.48–2.44, $P < 0.001$, $I^2 = 63.5\%$). Risk for needing mechanical ventilation was also higher in the hypomagnesemia group with RR of 1.65 (95% CI: 1.12–2.43, $P = 0.01$, $I^2 = 84\%$). Length of ICU stay was also higher in the hypomagnesemia group with mean difference of 4.1 days (95% CI: 1.16–7.04, $P = 0.01$).

Conclusion: The findings of this meta-analysis indicate hypomagnesemia is associated with higher mortality, the need of mechanical ventilation and also the length of ICU stay in patients admitted to ICU.

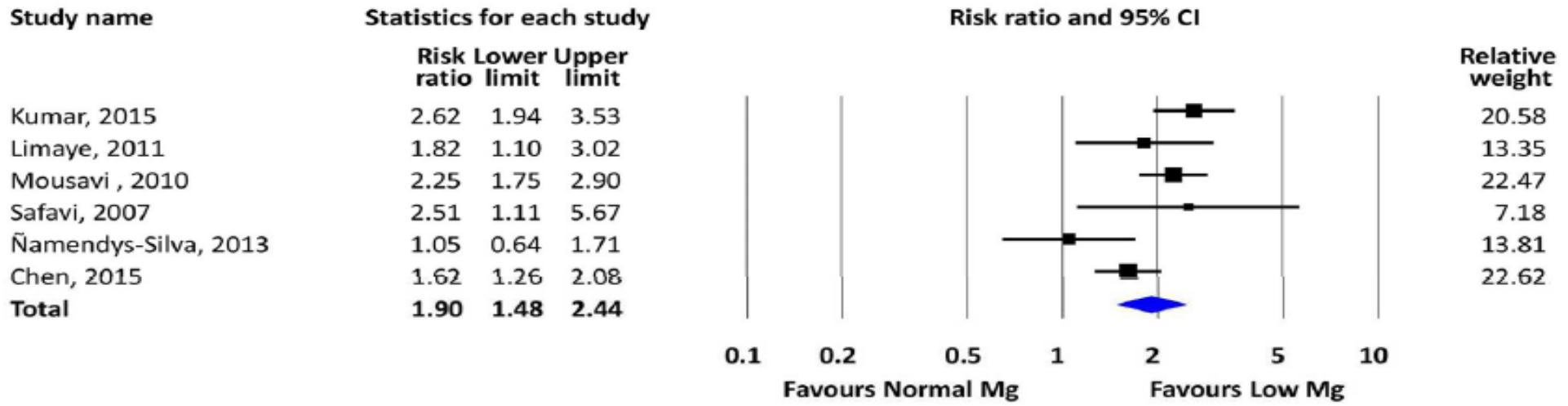


Figure 1: Forest plot of comparison in risk of mortality between hypomagnesemia and normomagnesemia

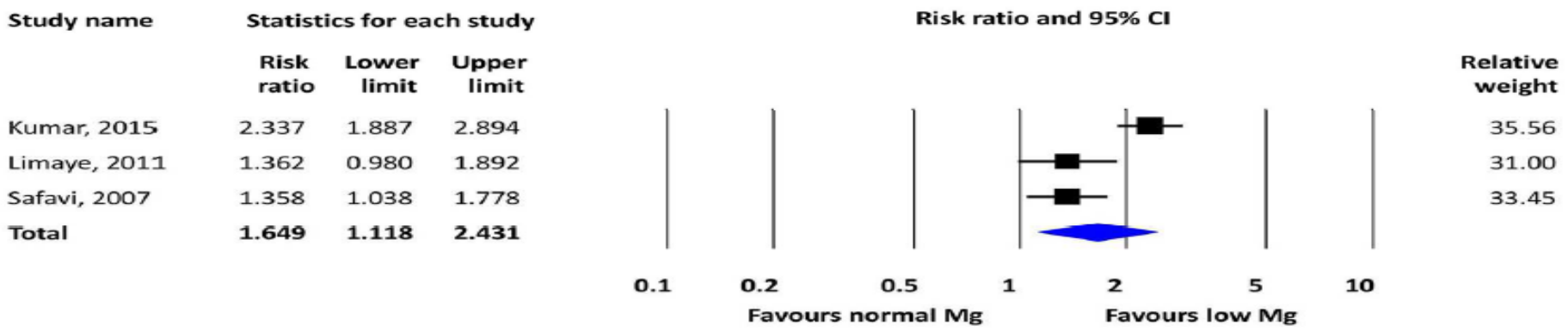


Figure 2: Forest plot of comparison in risk for needing of mechanical ventilation between hypomagnesemia and normomagnesemia

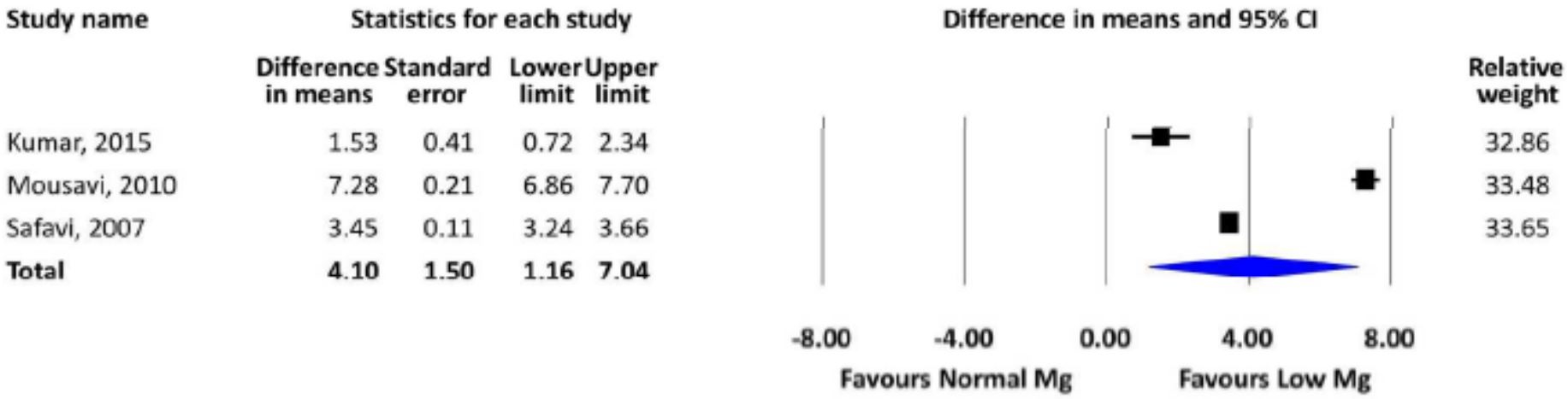


Figure 3: Forest plot of comparison length of ICU stay between hypomagnesemia and normomagnesemia

Hypomagnesemia Treatment

- Patients with severe symptoms: (Tetany, Arrhythmias, Seizure)
  - hemodynamically unstable patients

    1 to 2 grams of $MgSO_4$ over 2 to 15 minutes
  - hemodynamically stable patients
    - severe symptomatic hypomagnesemia: ($Mg<1mg/dL$)

      1 to 2 grams of $MgSO_4$ over 5 to 60 minutes followed by an infusion
  - Severe hypomagnesemia
    - Infusion: 4 to 8 grams of $MgSO_4$ over 12 to 24 hours

Treatment

Diagnose	Suggested Mg doses	Comments
Hemodynamically stable patients with severe symptomatic hypomagnesemia	1–2 g [8–16 mEq] (4–8 mmol) MgSO4 given initially over 5–60 min followed by an infusion 4–8 g [32–64 mEq] (16–32 mmol) given slowly over 12–24 h.	–
Torsades de pointes	2 g [16 mEq] (8 mmol) over 2–15 min followed by a continuous infusion.	The rate of Mg infusion depends on the clinical situation. Rapid infusion is associated with hypotension and asystole.
Preeclampsia	4 g [32 mEq] (16 mmol) over 10–15 min followed by 1 g [8 mEq] (8 mmol) every following hours.	Evidence is conflicting and no consensus about the optimal Mg regimen exists. Suggested loading doses vary from 4 to 6 g (32–48 mEq; 16–24 mmol) and maintenance doses of 1–3 g (8–24 mEq; 4–12 mmol)/h.

Hypomagnesemia Treatment

- stable hospitalized patients with plasma magnesium:
  - less than 1 mg/dL: 4 to 8 grams of MgSO4 over 12 to 24 hours
  - 1 to 1.5 mg/dL: 2 to 4 grams of MgSO4 over 12 to 24 hours
  - 1.6 to 1.9 mg/dL: 1 to 2 grams of MgSO4 over 12 to 24 hours

Mg Replacement

- rules of thumb
  - administration of 1 g (8 mEq) of intravenous Mg will increase serum Mg by 0.15 mEq/L (0.18mg/dL) within 18 to 30 h

- High levels of Mg (> 4–5 mmol/L)
  - muscle weakness
  - reduced respiration
  - cardiac arrest.

Role of Kidney

- Plasma Mg inhibits Mg reabsorption in TAL (major site of active magnesium transport)

- IV Mg infusion:
  - an abrupt but temporary elevation in the plasma Mg
  - Inhibition of stimulus to magnesium reabsorption in TAL

Up to 50 percent of the infused magnesium will be excreted in the urine

- Patients with kidney function impairment
  - Reduction in IV Mg dose by 50%
  - closely monitoring magnesium concentrations

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Thanks a lot for your attention