

HYPOMAGNESEMIA

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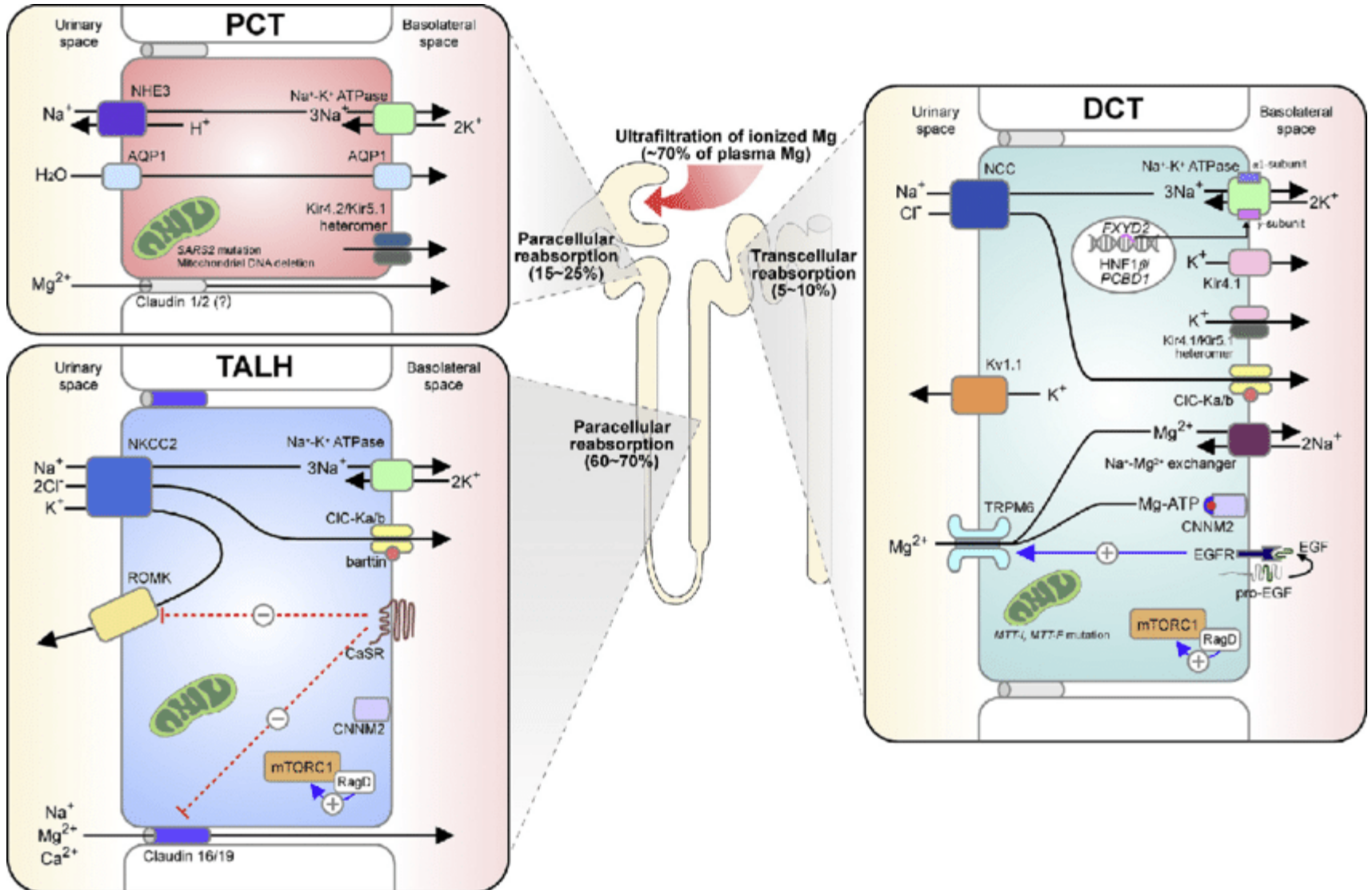
INTRODUCTION

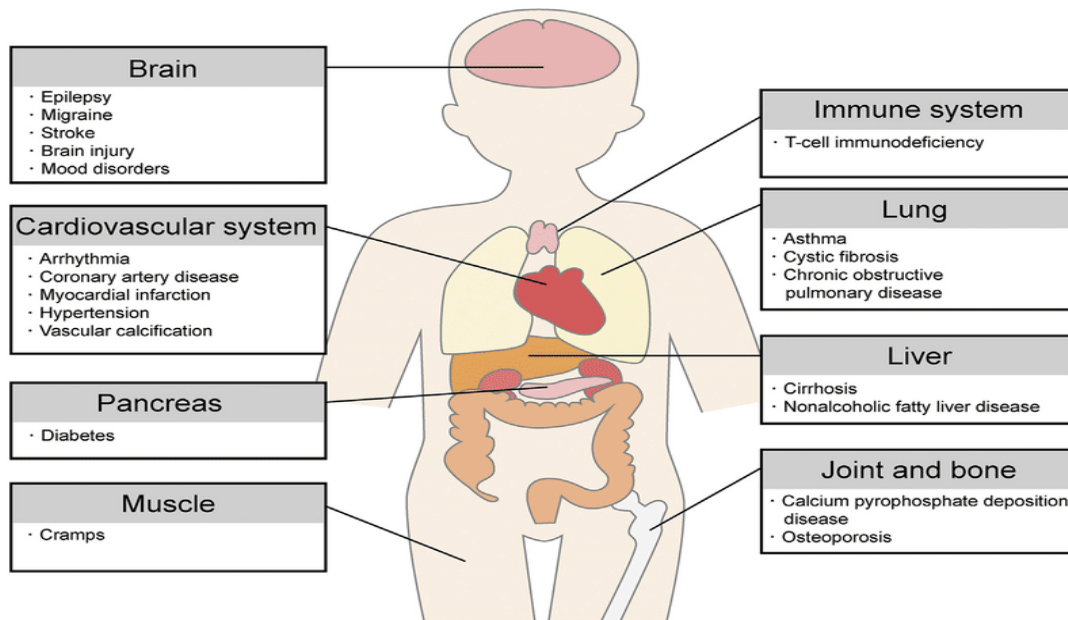
- Magnesium is the **second** most abundant cation in ICF.
- Normal plasma magnesium concentration is **1.7 to 2.1 mg/dl**.
- Less than **1%** of total body Mg is in plasma.
- Protein-bound (30%), complexed with anions (15%), and free or ionized (around 55%).
- **Cofactor** for about 600 enzymes .Activation of ATP , DNA repair, nucleic acid stabilisation.
- Magnesium gating in the distal nephron is important for **potassium homeostasis**.
- Role in regulating parathyroid hormone secretion by its indirect effect on **vitamin D metabolism**.

MAGNESIUM TRANSPORT

- Magnesium **reabsorption** happens in proximal convoluted tubule, cortical thick ascending limb of Henle's loop, and distal convoluted tubule.
- Around **25%** of filtered Mg $2p$ is reabsorbed passively via **paracellular pathway** (probable claudin 1 and 2) in **proximal convoluted tubule**.
- The positive luminal voltage generated by apical **NKCC2 and ROMK** provides the driving force for paracellular reabsorption of **70% filtered Mg $2p$ in thick ascending limb of Henle's loop**.
- The Mg $2p$ is reabsorbed actively through **TRPM6 in DCT**.
- The Mg $2p$ **efflux** is conducted in Na p -Mg $2p$ exchanger and possibly also in CNNM2.

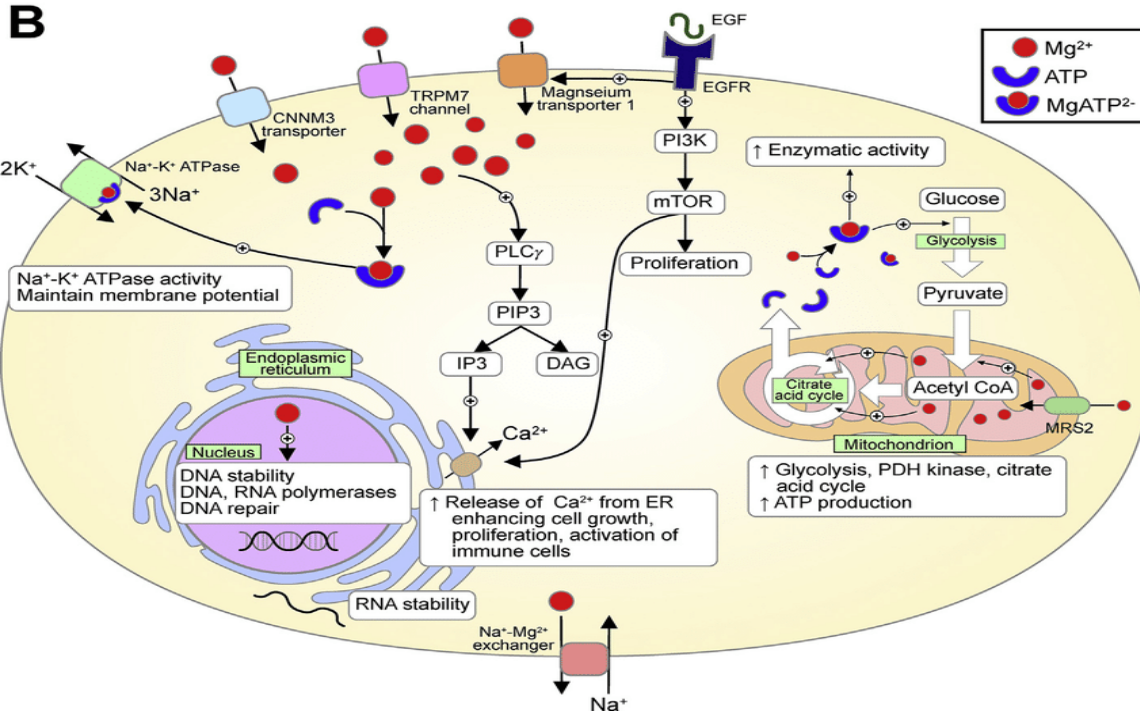
MAGNESIUM HANDLING PCT /DCT/TALH



A

Pathophysiology of hypomagnesemia.

(A) Clinical manifestations and organ-specific consequences of hypomagnesemia.

B

(B) Cellular physiology of Mg²⁺. Several transporters are responsible for the cellular Mg²⁺ homeostasis.

Mg²⁺ stabilizes the structures of DNA and RNA, DNA and RNA polymerases, and their repair in the nucleus.

Additionally, Mg²⁺ also regulates the cell growth and proliferation. In cytosol, Mg²⁺ is involved in many enzymatic reactions and regulates the glycolysis and ATP synthesis.

APPROACH

Hypomagnesemia

Urine Mg^{2+} excretion
(FEMg or Daily Mg^{2+} excretion)

Low

High

Non-Renal Mg^{2+} wasting

Renal Mg^{2+} wasting

Decreased Gastrointestinal absorption

- Low dietary Mg^{2+} intake
- Prolonged nasogastric decompression
- Diarrhea
- Enteric fistula
- Steatorrhea
- Short-gut syndrome
- Alcoholism
- Proton pump inhibitor

Sequestration or Intracellular Shifting

- Acute pancreatitis
- Hungry bone syndrome
- Refeeding syndrome
- Foscanet
- Massive blood transfusion
- Third trimester pregnancy
- Lactation
- Excess parenteral nutrition
- Cardiopulmonary bypass

Increased Glomerular Filtration

- Hyperfiltration
- Volume expansion
- Diabetes mellitus
- Post-obstruction polyuria
- Increased ionized Mg^{2+}
- Reduced serum anions: Phosphate, citrate, oxalate
- Chronic metabolic acidosis

Defects in Proximal Convoluted Tubule

- Mitochondrial diseases^{*}
- HUPRA syndrome^{**}
- Kearns–Sayre syndrome
- Hypokalemic tubulopathy, salt wasting, disturbed acid-base homeostasis and deafness
- Renal fanconi syndrome
- Drugs: Cisplatin, gentamicin, pentamidine

Defects in Thick-ascending Loop of Henle

- Bartter syndrome
- Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
- Kidney tubulopathy and cardiomyopathy syndrome
- Drugs: Aminoglycoside, loop diuretics, calcineurin inhibitors

Defects in Distal Convoluted Tubule

- Hypomagnesemia with secondary hypocalcemia
- Isolated-recessive hypomagnesemia
- Gitelman syndrome
- NISBD2^{*}
- KCS2 syndrome[†]
- EAST syndrome^{**}
- *HNF1B* nephropathy
- Episodic ataxia, type I
- Isolated-dominant hypomagnesemia
- HPABH4D^{**}
- HSMR syndrome 1^{††}
- HSMR syndrome 2^{††}
- Mitochondrial diseases[†]
- Gitelman syndrome phenocopy
- Hypokalemic tubulopathy, salt wasting, disturbed acid-base homeostasis and deafness
- Drugs: Thiazide, Cetuximab

^{*}Mitochondrial hypomagnesemia may have characteristics of proximal, loop of Henle, and distal tubulopathy

^{**}Neonatal inflammatory skin and bowel disease, type 2

^{††}Hyperphenylalaninemia, tetrahydrobiopterin-deficient, type D

[†]Kenny-Caffey syndrome, type 2

^{†††}Hypomagnesemia, seizure, and intellectual disability syndrome

^{††††}Epilepsy, ataxia, sensorineural deafness, and tubulopathy syndrome

^{†††††}Hyperuricemia, pulmonary hypertension, and renal failure syndrome

TREATMENT

MAGNESIUM

Goal serum magnesium concentration 2.0 – 2.4 mg/dL

Intravenous Treatment of Hypomagnesemia

Serum magnesium concentration	Intravenous magnesium sulfate dose [†]	Oral magnesium oxide dose	Recheck serum magnesium concentration
1.6 – 1.9 mg/dL	2 g	800 mg	4 to 6 hours after dose if symptomatic otherwise with next AM lab draw
1.0 – 1.5 mg/dL	4 g	Not recommended	4 to 6 hours after dose if symptomatic otherwise with next AM lab draw
< 1.0 mg/dL	6 g and notify MD	Not recommended	4 to 6 hours after dose if symptomatic otherwise with next AM lab draw
Rate of intravenous infusion of magnesium	Recommend infusing 1 g magnesium sulfate/hour (~8 mEq magnesium/hour), up to maximum of 2 g magnesium sulfate/hour (doses of up to 32 mEq magnesium can be given over 4 – 5 minutes in severe symptomatic hypomagnesemia (urgent or emergent situation))		

† 1 g magnesium sulfate = 8.1 mEq magnesium

****Consider adding scheduled oral magnesium oxide as indicated****

Reduce the IV Mg dose **by 50 %** and closely monitoring Mg in CKD patients with eGFR less than 30 ml/min/1.73 m².

Table 5. Different magnesium formulations.

Magnesium Supplement	Elemental Magnesium (Percent)	Bioavailability (as Fractional Absorption of the Administered Dose)	Bioavailability (Relative Comparison)	Tolerability (Diarrhea)
Magnesium Oxide	60	4%	Extremely low	++
Magnesium Carbonate	45	*	Extremely low	*
Magnesium Hydroxide	42	4%	*	++
Magnesium Citrate	16	12%	Good	++
Magnesium Lactate	12	12%	Excellent	+
Magnesium Chloride	12	12%	Good	+
Magnesium Aspartate	10	*	*	*
Magnesium Sulfate	10	4%	*	++
Magnesium Gluconate	5	*	Good	±

Data obtained from Guerrero et al [46], Firoz M [47], Ranade [48], Epocrates [49], The Schrier Atlas of Diseases of the Kidney [50]. * Data could not be obtained. ++ Indicates higher incidence of diarrhea, + indicates lesser incidence of diarrhea. ± Indicates equivocal incidence of diarrhea.

Typical daily dose in a patient with normal kidney - **240 to 1000 mg** of elemental Mg in divided doses.

Patients with hypomagnesemia due to renal magnesium wasting may benefit from the addition of a potassium-sparing diuretic such as **amiloride or triamterene**.