Hypomagnesemia

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Distribution of Magnesium

- Magnesium is the fourth most common element on earth and has atomic number 12
- The total mass of magnesium in a 70 kg man is about 30 g.
- It acts as a coenzyme for more than 600 enzymatic reactions, including DNA repair mechanisms, nerve impulse propagation, bone formation and many more.

Physiologic Role of Magnesium

- Cofactor for adenosine triphosphate (ATP)
- Maintenance of the genome (replication, transcription, translation, and DNA repair)
- Key role in stabilizing the structure of nucleic acids and proteins
- Modulation of ion channels and transporters can affect the whole-body flux of electrolytes (ROMK)
- Significant function in the formation, turnover, and maintenance of the skeleton by regulating parathyroid hormone secretion and by its indirect effect on vitamin D metabolism

Distribution of Magnesium

- Up to two-thirds of the total body magnesium is present in bone, with most of the rest found in muscle and soft tissue. Less than 1% of the total body magnesium is present in blood, with the larger portion in erythrocytes.

- Of the fraction in plasma, about 32% is protein bound (25% is bound to albumin, and 8% is bound to globulin). Most of the magnesium in the body (99%) resides in the intracellular compartment

Magnesium Handling in the Gastrointestinal Tract

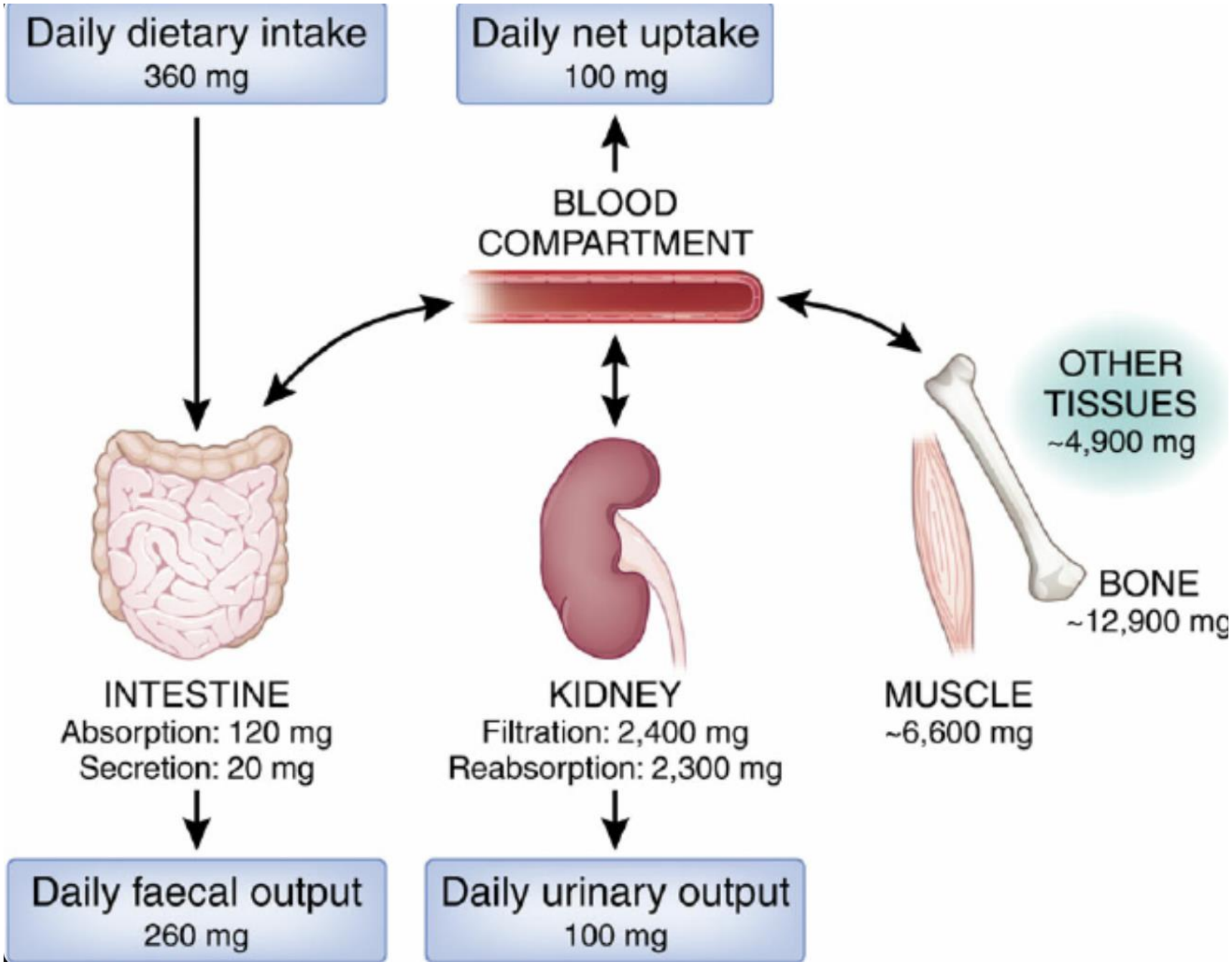
- The minimal daily requirement of magnesium ranges from 165 mg to 240 mg.
- The Institute of Medicine recommended daily allowance is 310-320 mg for women and 400-420 mg for men.
- In a regular diet, just under 50% of dietary magnesium is absorbed.
- Magnesium absorption occurs largely in the distal small intestine, with some absorption in the colon as well.

Magnesium in the body

- Magnesium in the body Mg2+ shows chemical similarities with calcium ($Ca^{2}+$) and zinc ($Zn^{2}+$).
- Consequently, their transport in the body is often facilitated via the same divalent cation transporters, channels and pathways .
- However, Mg2+ is considerably larger in its hydrated states. Mg2+ binds water (H2O) tighter than Ca2+.
- Therefore, it is possible for Mg2+ transporters to also transport the smaller hydrated Ca2+ but it is not possible for the Ca2+ transporters to transport the larger hydrated Mg2+ .

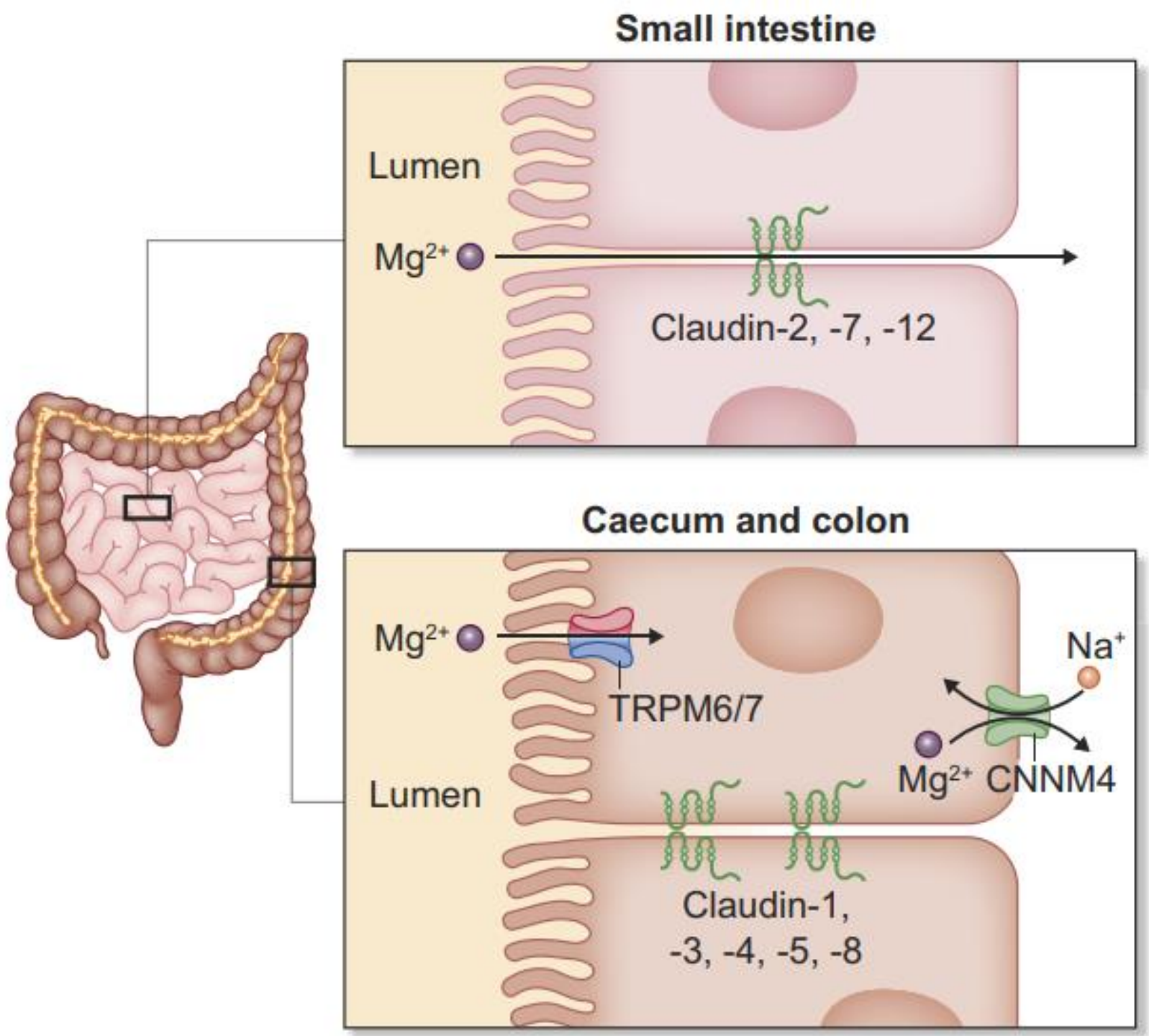
Hypomagnesemia

- **Inadequate Intake**: Malnutrition or Starvation- Alcohol Use
- **Malabsorption**: Gastrointestinal Disorders - Proton Pump Inhibitors
- **Excessive Renal Loss**: Diuretics - Endocrine Disorders - Genetic Disorders
- **Gastrointestinal Losses**: Diarrhea and Vomiting - Short Bowel Syndrome
- **Increased Requirements**: Pregnancy and Lactation
- Other Factors: Chronic Diseases - Medications


Daily dietary intake
360 mg
Daily net uptake
100 mg
BLOOD
COMPARTMENT
OTHER
TISSUES
~4,900 mg
BONE
~12,900 mg
INTESTINE
Absorption: 120 mg
Secretion: 20 mg
KIDNEY
Filtration: 2,400 mg
Reabsorption: 2,300 mg
MUSCLE
~6,600 mg
Daily faecal output
260 mg
Daily urinary output
100 mg

Magnesium Handling in the Gastrointestinal Tract

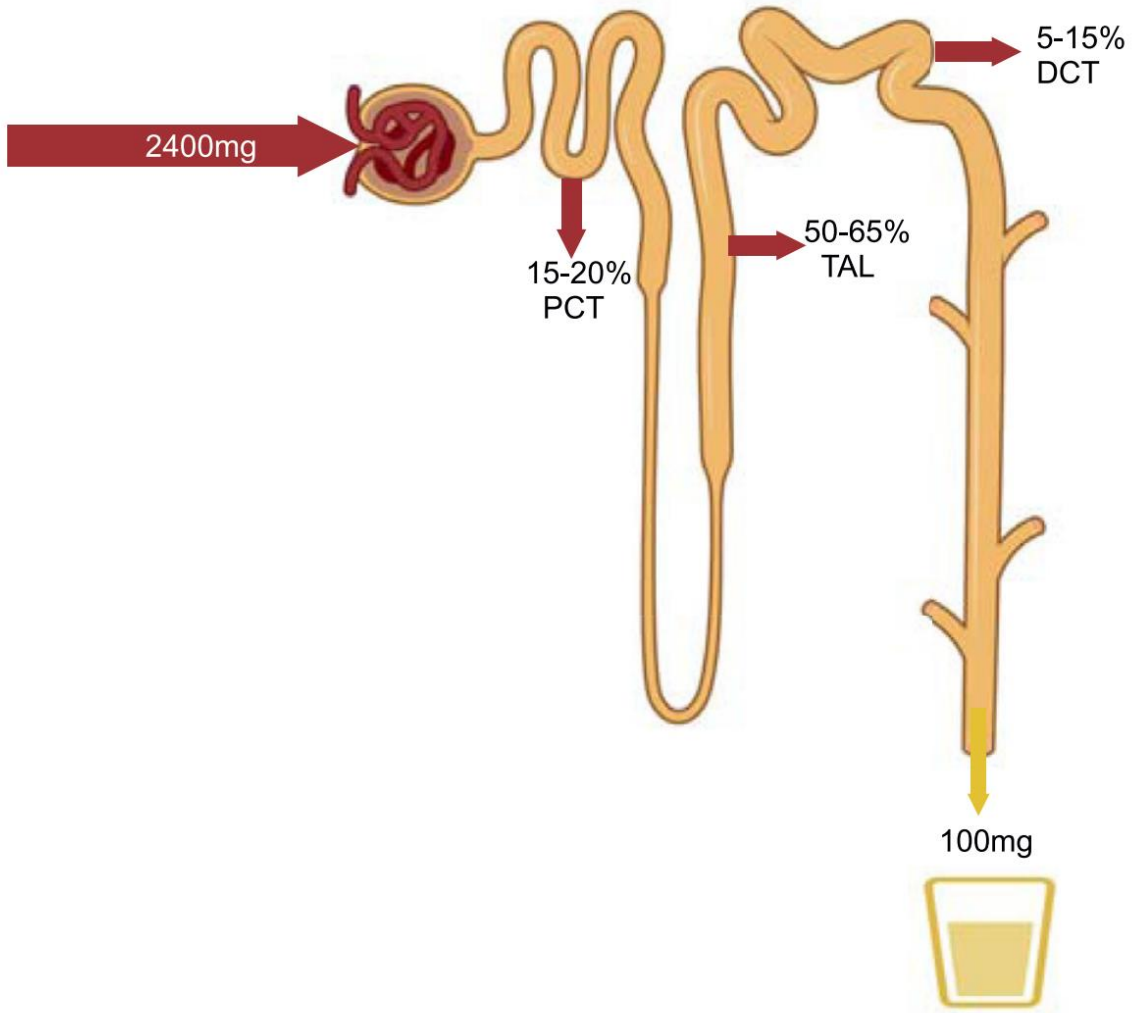
- **Primary Site**: Magnesium is predominantly (80-90%) absorbed in the small intestine, particularly in the jejunum and ileum, with some absorption occurring in the colon.
- In steady state, 2% of the absorbed magnesium may be secreted as part of pancreatic, biliary, and intestinal secretions. In renal failure, gut excretion of magnesium increases.


Small intestine
Lumen
Mg2+
Claudin-2, -7, -12
Caecum and colon
Mg2+
TRPM6/7
Na+
Mg2+
CNNM4
Lumen
Claudin-1,
-3, -4, -5, -8

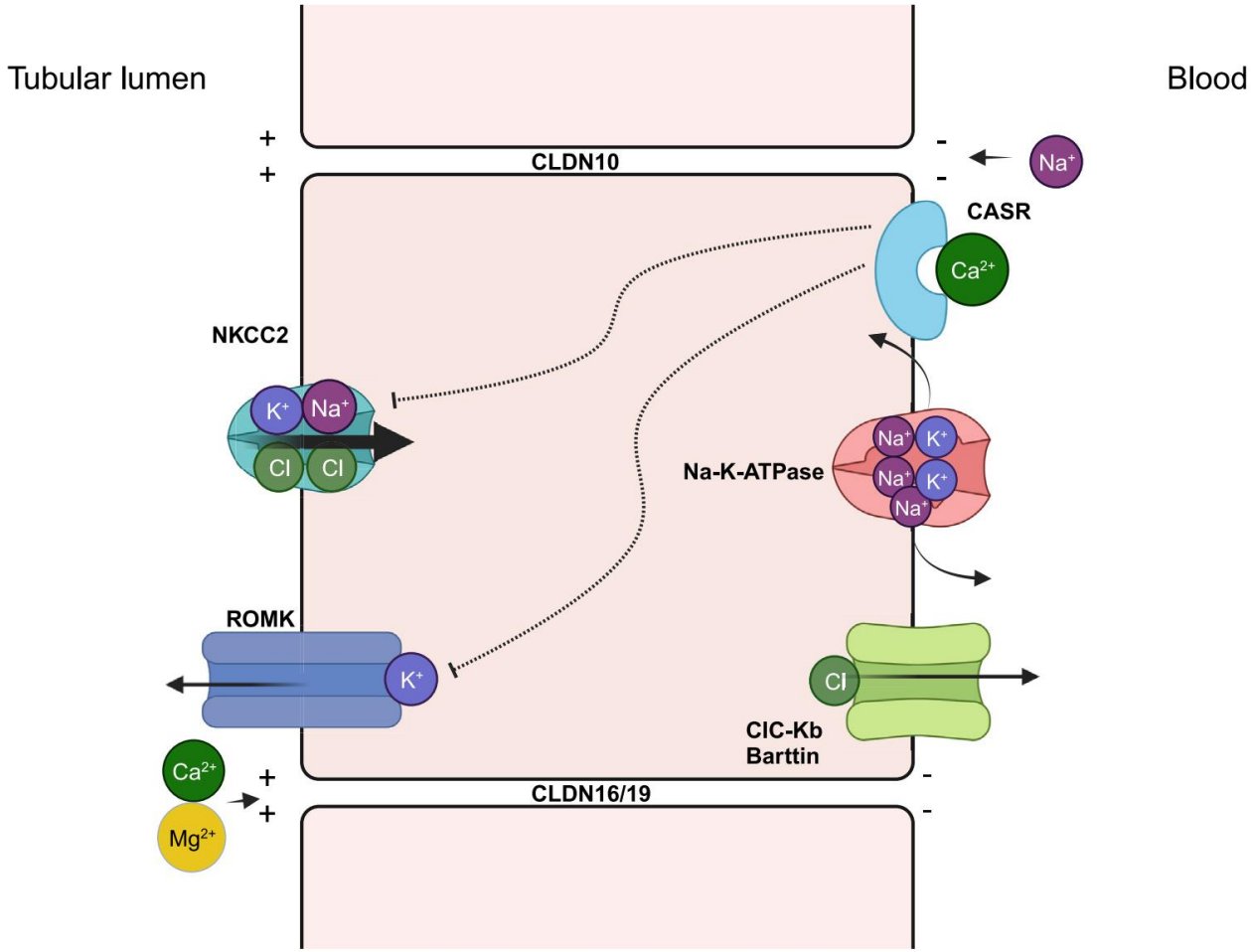
Magnesium reabsorption along the renal tubule

- **Primary Site**: The kidneys play a crucial role in magnesium excretion. About 2400 mg of magnesium is filtered daily through the glomeruli, with approximately 95% reabsorbed back into circulation.
- **Reabsorption Sites**:
- **Thick Ascending Limb of Henle**: This segment accounts for 60-70% of magnesium reabsorption through passive mechanisms.
- **Distal Convoluted Tubule**: Here, a smaller percentage (5-10%) is actively reabsorbed, fine-tuning magnesium levels based on the body's needs.
- **Excretion Rate**: Under normal conditions, only about 3-5% of filtered magnesium is excreted in urine, which can vary significantly depending on dietary intake and physiological needs

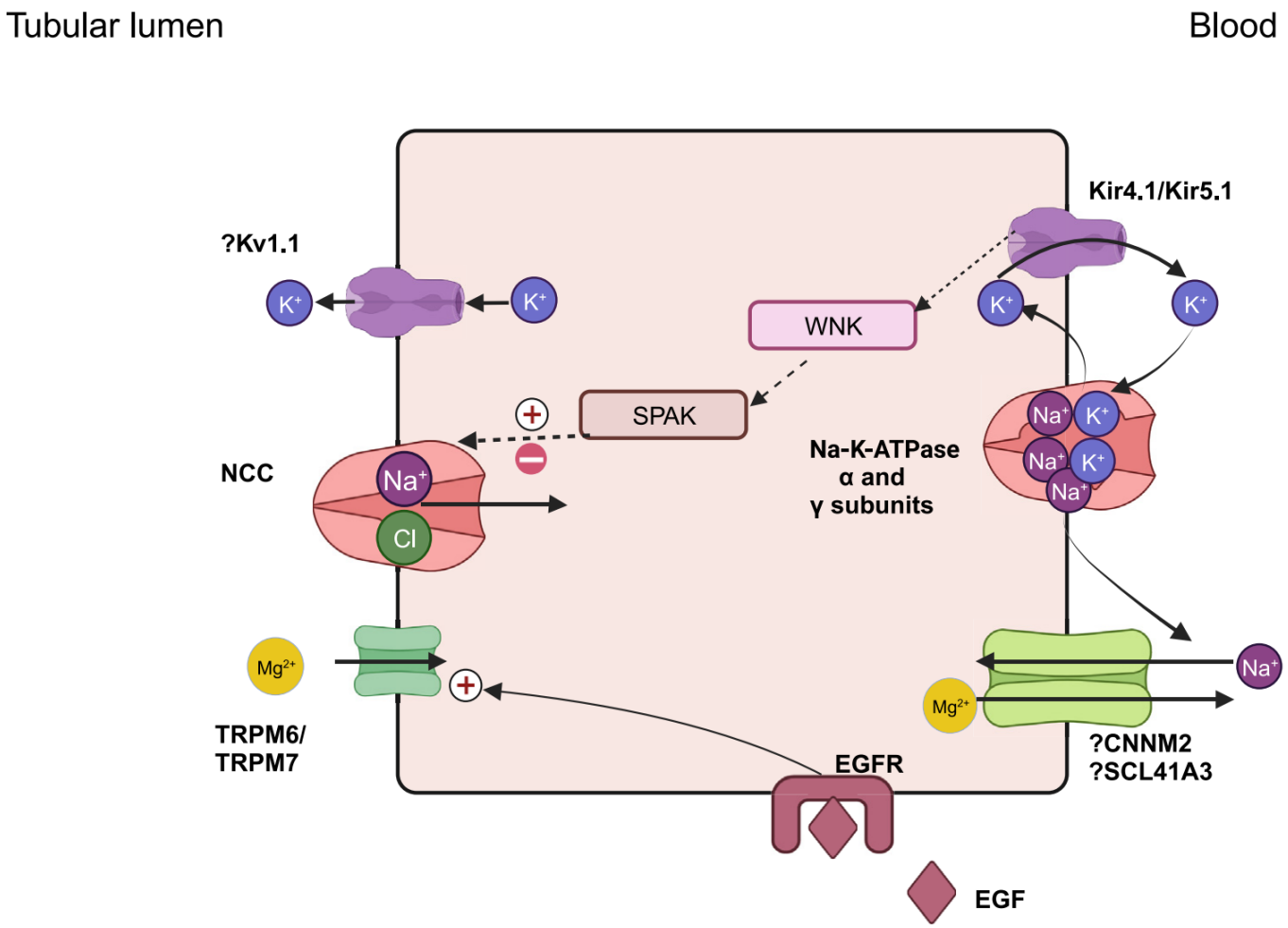
Magnesium reabsorption along the renal tubule



Magnesium transport in TAL via paracellular pathway mediated by claudin-16/19



Transcellular Magnesium transport in DCT via TRPM6/TRPM7



Magnesium storage and homeostasis in the body

- Ionized Mg2+ is considered the **biologically active** form of Mg2+,taking part in enzymatic reactions and physiological processes.

- However, in the clinic total serum Mg2+ is assessed as measure of Mg2+ levels, while assessment of whole-body Mg2+ in the form of ionized Mg2+ would offer a better representation of the overall Mg2+ status.

Consumption and supplementation of magnesium in health and disease

- The daily recommended dietary allowance for Mg^{2+} in adults is about 400 mg for males and 310 mg for females, which increases to 350 mg during pregnancy
- A trend towards the use of Mg^{2+} supplementation can be observed in recent years. Many claim that Mg^{2+} supplementation helps with sleep, muscle cramps and anxiety.
- Several meta-analyses and reviews conclude that there is not enough scientific evidence to prove that these claims are true in healthy individuals .

Consumption and supplementation of magnesium in health and disease

- However, Mg2+ supplementation can be of therapeutic use in patients suffering from hypomagnesemia .
- In **healthy individuals**, increased ingestion of Mg2+ poses little risk. In the case of increased ingestion, the intestinal absorption is decreased, while the renal excretion rate can increase up to 100% to balance Mg2+ levels. Still, it should be noted that extremely high doses of Mg2+ supplementation can lead to symptoms such as **diarrhea**, **nausea** and **abdominal cramping**, but will resolve once the Mg2+ has been digested

MAGNESIUM PATHOPHYSIOLOGY

- Mg2+ deficiency (serum Mg2+ <0.7mm/l)
- Asymptomatic
- Fatigue
- Muscle cramps
- Arrythmias
- Developmental delay
- Seizures

Hypomagnesemia

→ Serum level < 1.7 mg/dL

Neuromuscular manifestations

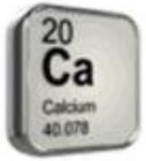
- Tremor, tetany, seizures
- Weakness
- Apathy
- Delirium
- Coma

Cardiovascular manifestations

- Prolonged QTc
- Widening of QRS
- Atrial and ventricular dysrhythmias

Hypokalemia

- Renal potassium wasting



Abnormalities of calcium metabolism

- Hypocalcemia
- Hypoparathyroidism
- Parathyroid hormone resistance
- Decreased synthesis of calcitrol

MAGNESIUM PATHOPHYSIOLOGY

- Prevalence of hypomagnesemia ± 2.5% in the general population and about 12%–20% in hospitalized patients
- **Risk factors**:
- Age
- Gastrointestinal track diseases
- Type 2 diabetes
- Excessive alcohol consumption
- Pharmacological drugs

MAGNESIUM PATHOPHYSIOLOGY

- Hypomagnesemia often is accompanied by hypokalemia or hypocalcemia.
- Hypokalemia is caused by decreased inhibition of ROMK in the collecting duct in response to hypomagnesemia.
- ROMK is inhibited by Mg2 + , stimulating basolateral excretion of K+ .

- Low Mg2 + levels lead to decreased inhibition of ROMK, resulting in increased efflux of K+ into the pre urine resulting in hypokalemia and increased excretion of K+ .

MAGNESIUM PATHOPHYSIOLOGY

- Low Mg2 + levels lead to increases CaSR signaling in the parathyroid gland, resulting in decreased PTH secretion ultimately resulting in decreased Ca2 + levels via secondary mechanisms such as decreased vitamin D levels needed for Ca2 +absorption .
- However, the exact mechanism and regulation of Ca2 + levels in response to hypomagnesemia remain elusive

Alcohol-induced hypomagnesemia

- Hypomagnesemia is often seen in people with increased alcohol consumption.
- Next to the direct effect of alcohol on **urinary Mg2 + wasting**, secondary effects such as **vomiting** or **diarrhea** may further contribute to hypomagnesemia in alcohol-dependent patients.
- Furthermore, other comorbidities of alcohol abuse, such as acute pancreatitis and cirrhosis, have been shown to be associated with decreased serum Mg2 + levels.
- Mg2 + supplementation has been suggested to ease alcohol withdrawal, while it is remains inconclusive whether Mg2 +positively influences this process .
- A recent study demonstrated that 60% of patients with alcohol withdrawal syndrome have hypomagnesemia, which was associated with an increased 1-year mortality risk .

Diabetes-induced hypomagnesemia

- One of the most common causes of hypomagnesemia is type 2 diabetes mellitus (T2DM).
- The incidence rate of hypomagnesemia in diabetes patients ranges from 10% to 45% .
- T2DM patients often present with **hypermagnesuria**, indicating disturbed renal Mg^{2+} handling as the underlying cause of hypomagnesemia .

Diabetes-induced hypomagnesemia

- Clinical trials investigating the effect of Mg^{2+} supplementation show conflicting results. Some studies show a minor improvements of fasting plasma glucose levels and triglyceride levels in the blood, while other did not observe a beneficial effect of Mg^{2+} supplementation on these factors in T2DM patients .

- It has also been shown that Mg^{2+} can be bound to free fatty acids (FFA), which makes Mg^{2+} undetectable with tests used for normal magnesium assessment. This results in the question of whether Mg^{2+} levels are decreased in T2DM patients or if the Mg^{2+} present, is bound to FFA .

Diabetes-induced hypomagnesemia

- Another potential parameter in the inconclusive results could be the difficulty to obtain a substantial increase in serum Mg^{2+} levels via oral supplementation.
- If there is no substantial increase, then it is difficult to make conclusive statements about the effects of Mg^{2+} on T2DM. However, the relationship between T2DM and Mg^{2+} remains to be further investigated, and in particular aspects such as the influence of magnesium binding to FFA and increase in serum Mg^{2+} levels are of interest

Drug-induced hypomagnesemia

- **Protein pump inhibitors** (PPIs)
- Immunosuppressive drugs
- Diuretics
- PPIs inhibit the gastric H^+/K^+-ATPase and are commonly used in the general population (10%–20% in the Western world) .
- Prolonged PPI use has been associated with hypomagnesemia.
- Increased pH levels **decrease the solubility of Mg^{2+},** leading to reduced paracellular Mg^{2+} absorption in the small intestine.
- **TRPM6 activity** is decreased at higher pH levels and the colonic microbiome composition is disturbed, both of which may contribute to decreased Mg^{2+} uptake in the colon.

Drug-induced hypomagnesemia

- Several **immunosuppressive drugs** interfere with renal Mg^{2+} reabsorption.
- In particular, calcineurin inhibitors (CNIs) are strongly associated with severely decreased serum Mg^{2+} levels and are generally recognized as nephrotoxic .
- **Calcineurin inhibitors** (CNI) mediate hypomagnesemia through down-regulation of TRPM6 in the DCT
- Mammalian target of rapamycin (**mTOR**) inhibitors
- Tacrolimus > Cyclosporine > Sirolimus

Drug-induced hypomagnesemia

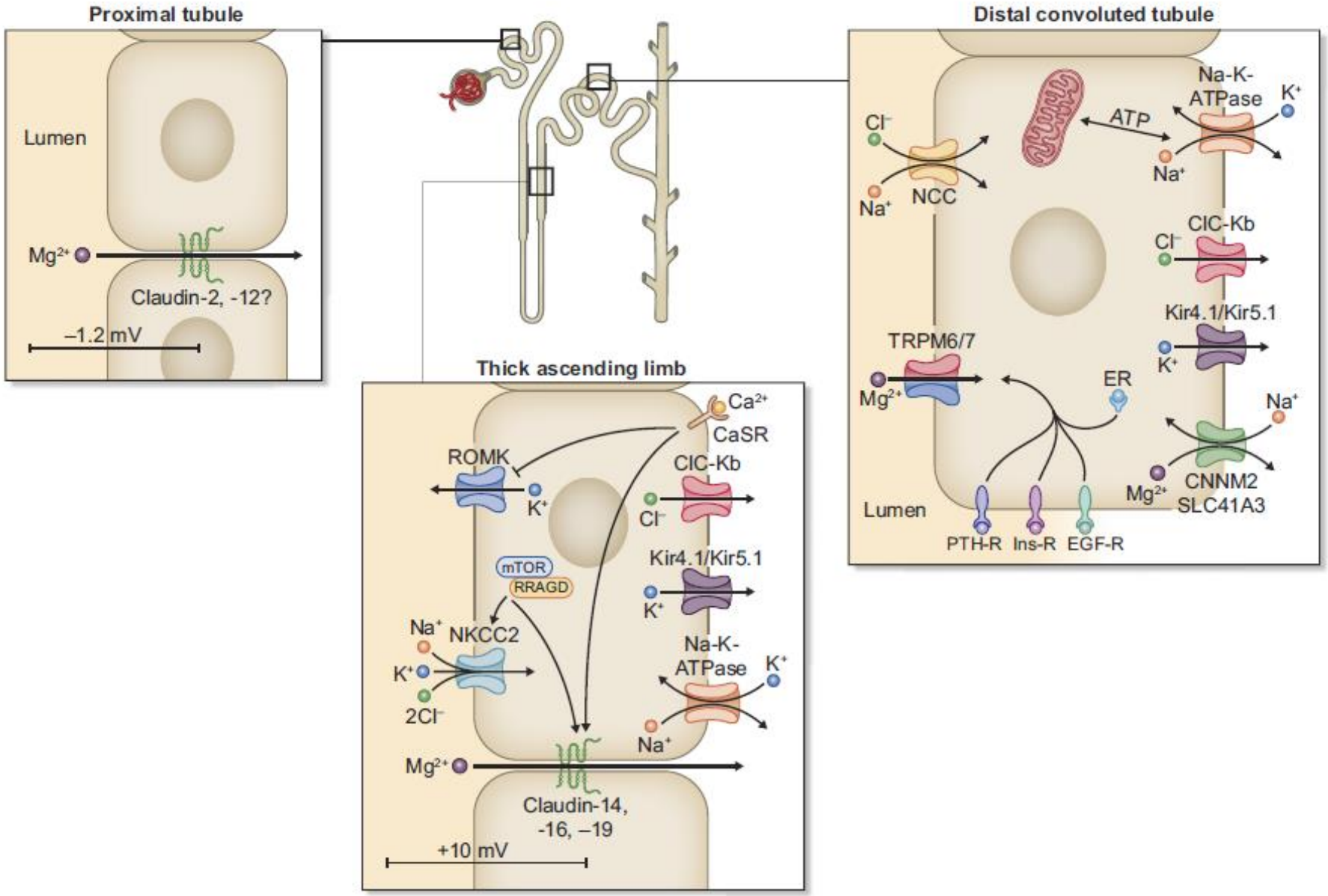
- **Platinum-based** chemotherapeutic agents, especially cisplatin, leaves most patients in negative magnesium balance.
- The mechanism is direct tubular toxicity and down-regulation of TRPM6 and NCC in the DCT. Hypomagnesemia can persist up to 6 years after discontinuation of therapy
- **Epidermal growth factor receptor** (EGFR) inhibitors such as cetuximab.

Drug-induced hypomagnesemia

- **Diuretics** :
- **Thiazide diuretics** are associated with a decrease in serum Mg^{2+} level of 5%–10%

- **Loop diuretics** negatively impact Mg^{2+} transport in the TAL by inhibition of NKCC2, disrupting the lumen-positive transmembrane potential usually driving reabsorption of Mg^{2+}.
- Paracellular Mg^{2+} transport is disrupted after administration of loop diuretics Hypomagnesemia is strongly dependent on the dose and duration of use .
- Thiazide diuretics block NCC, decreasing the intracellular sodium level in the DCT, which indirectly leads to inhibition of TRPM6/7 resulting in decreased Mg^{2+} uptake in the DCT. It has been observed *in vivo* that blocking of NCC leads to a decrease in DCT length as well as inhibition of TRPM6 via secondary mechanisms, resulting in impaired Mg^{2+} reabsorption .

Renal magnesium regulation



Drug-induced hypomagnesemia

- **Antibiotics** associated with hypomagnesemia include aminoglycosides, amphotericin B, foscarnet, and pentamidine.
- Aminoglycosides can **cause a Bartter-like presentation** with renal calcium, magnesium, and potassium wasting and metabolic alkalosis

Autoimmunity and hypomagnesemia

- Autoimmunity is a cause of hypomagnesemia.
- Autoantibodies as a new cause for renal Mg^{2+} wasting. However, the prevalence of autoimmunity as cause for acquired hypomagnesemia remains to be examined.

Genetic hypomagnesemia

- The genetic causes of hypomagnesemia can be grouped by their disease mechanisms. Mutations affecting the paracellular Mg^{2+} transport pathway in the TAL (*CLDN16, CLDN19, RRAGD, CASR*) results in the hypomagnesemia with hypercalciuria and nephrocalcinosis .
- In the DCT, mutations in *TRPM6* or *TRPM7* cause hypomagnesemia with secondary hypocalcemia.
- Additionally, patients with disturbed Na^{+} reabsorption in the DCT present with a **Gitelman-like syndrome**, characterized by hypokalemia, hypomagnesemia and metabolic alkalosis (*SLC12A3, CLCNKB, KCNJ10, KCNJ16, ATP1A1, FXYD2, HNF1B, PCBD1*).

Genetic hypomagnesemia

- In recent years, hypomagnesemia has also been described in patients with **mitochondrial disorders** (*MT-TI, MT-TF, SARS2* and others).
- Other causes of isolated hypomagnesemia include *KCNA1, EGF* and *CNNM2*. Although the mechanisms that explain the interplay between Na^{+} and Mg^{2+} reabsorption in the DCT are only partially understood, decreased DCT length seems to contribute to Mg^{2+} wasting in Gitelman-like syndromes.

Hypomagnesemia With Salt Wasting Gitelman Syndrome

- Gitelman syndrome is an autosomal recessive inherited condition due to mutations in SLC12A3 (which codes for NCC) and is the most common inherited cause of hypomagnesemia (1 in 40,000).
- Hypomagnesemia in Gitelman syndrome results from the down-regulation of TRPM6
- Hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis, and elevated plasma renin levels. low blood pressure, salt craving, paresthesia, and muscle cramps
- ventricular arrhythmias and seizures

Bartter Syndrome Type 3

- Bartter syndrome type 3 (BS3) is due to inactivating mutations in CLCNKB, which codes for the basolateral chloride channel ClC-Kb, in the TAL.
- ClCKb is also present in the DCT, and thus unsurprisingly BS3 exhibits phenotypic similarities to Gitelman syndrome

Autosomal Dominant Hypocalcemia

- Activating mutations affecting the basolateral CASR in the TAL.
- Higher set point for PTH release.
- Impaired paracellular reabsorption of calcium and magnesium, with hypomagnesemia occurring in more than 50% of patients.
- Tetany, spasms, and fasciculations to severe presentations including arrhythmias and seizures

Familial Hypomagnesemia With Hypercalciuria and Nephrocalcinosis (FHHNC)

- FHHNC is an autosomal recessive condition affecting the TAL due to inactivating mutations in CLDN16 and CLDN19
- Triad of hypomagnesemia, hypercalciuria, and nephrocalcinosis
- Progressive chronic kidney disease

Other Inherited Causes of Hypomagnesemia

- Hypomagnesaemia With Secondary Hypocalcemia (HSH): Autosomal recessive mutations in TRPM6
- Isolated Dominant Hypomagnesemia: AD mutations affecting different genes which regulates the Na-K-ATPase in the DCT
- Isolated Recessive Hypomagnesemia: mutation that affects the cytoplasmic domain of pro-EGF

When to suspect Hypomagnesemia

- Hypomagnesemia should be suspected in patients who have risk factors for it such as chronic diarrhea , PPI therapy , Alcohol use disorder , Diuretic use or clinical manifestations of hypomagnesemia (unexplained hypocalcemia , refractory hypokalemia , neuromuscular disturbances , ventricular arrythmias)

Evaluation of hypomagnesemia

- Fractional excretion of magnesium (FeMg) is calculated from blood and urine chemistries as follows

$$\frac{(\mathrm{uMg} \times \mathrm{pCr})}{(0.7 \times \mathrm{pMg} \times \mathrm{uCr})}$$

- where u is urine, p is plasma, Mg is magnesium, Cr is creatinine, and 0.7 represents the average free fraction of plasma free magnesium

Evaluation of hypomagnesemia

- In a patient with hypomagnesemia, FeMg > 3%-4% generally indicates renal magnesium wasting, and a value < 2% shows an alternative cause.

- In a 24-hour urine, magnesium excretion of <10 or > 30 mg is consistent with extrarenal and renal causes of hypomagnesemia, respectively.

Dietary Sources of Magnesium

- Some of the foods with the highest magnesium content include:

- Dark chocolate
- Avocados
- Nuts
- Legumes
- Seeds

CONCLUSION

- Mg^{2+} is essential for the physiological function of the human body and is tightly regulated by an interplay between intestinal Mg^{2+} absorption and renal Mg^{2+} excretion.
- Hypomagnesemia can either be genetic, acquired, or drug-induced by drugs such as PPIs, immunosuppressive drugs and diuretics. It often goes along with other comorbidities such as diabetes, metabolic syndrome or age.
- SGLT2 inhibitors, however, shows promising effects in clinical case studies to increase serum Mg^{2+} levels in diabetic patients with hypomagnesemia.

Thanks for your attention

References

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