

Hypomagnesemia

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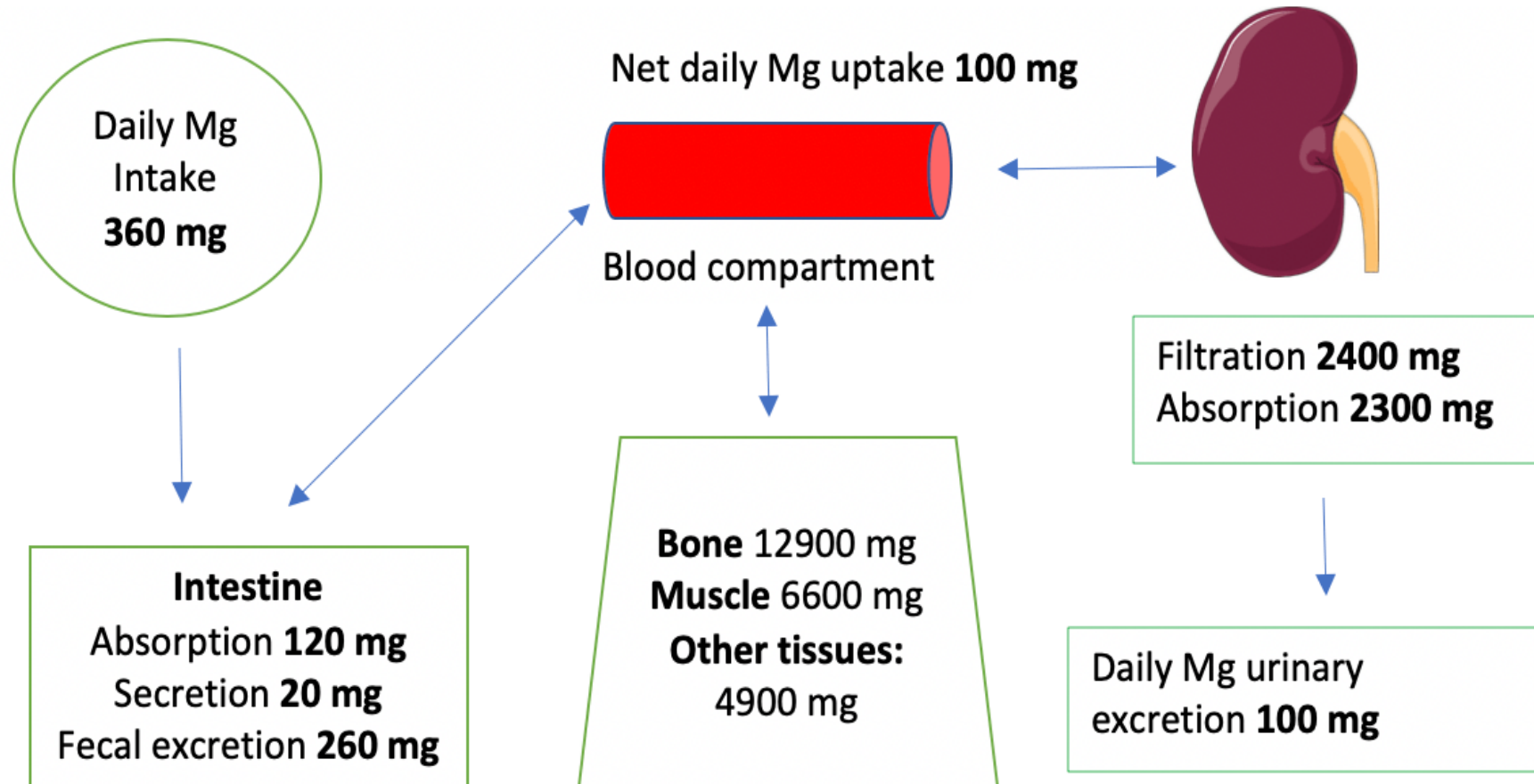
Magnesium Homeostasis

Magnesium is:

- The fourth most abundant cation in the body
- The second most abundant intracellular cation
- Major factor in numerous cellular functions
- Cofactor in hundreds of enzymatic reactions
- Essential for cellular energy production (cofactor for ATP)

Mg metabolism is linked to potassium and calcium metabolism





Magnesium Homeostasis

Arch Clin Biomed Res 2020; 4 (3): 205-220

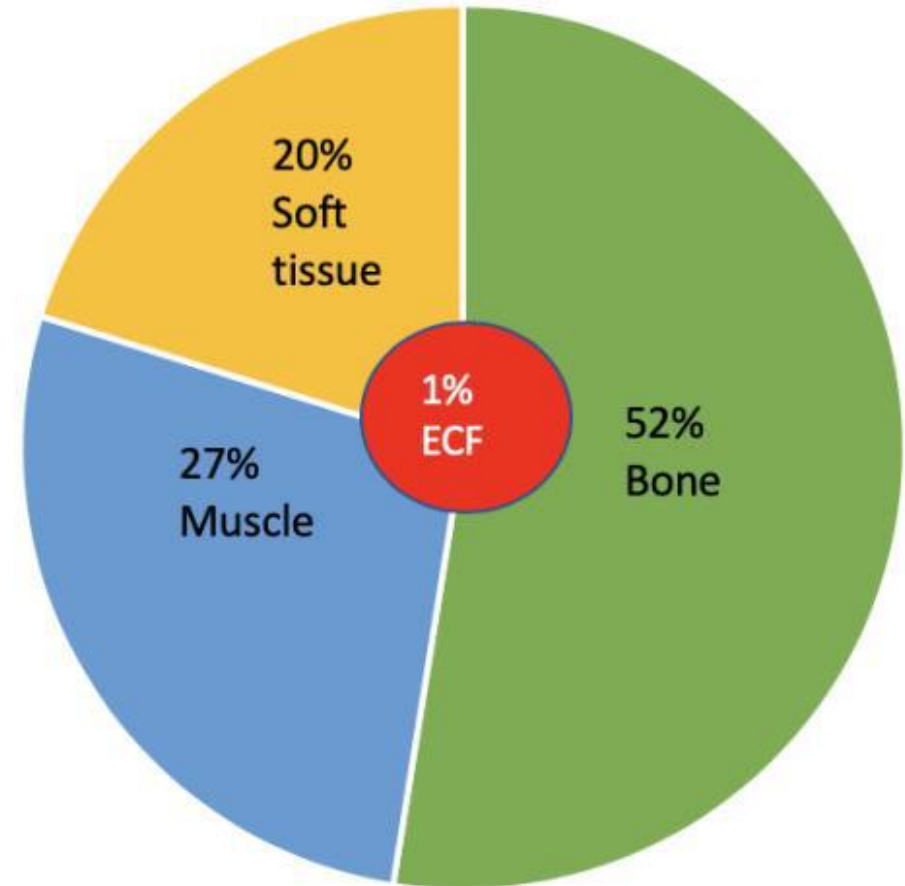


Magnesium Homeostasis

Total body Mg

- 52% is in the bone
- 27% in muscles
- 20% in non-muscular soft tissue
- 1% in ECF

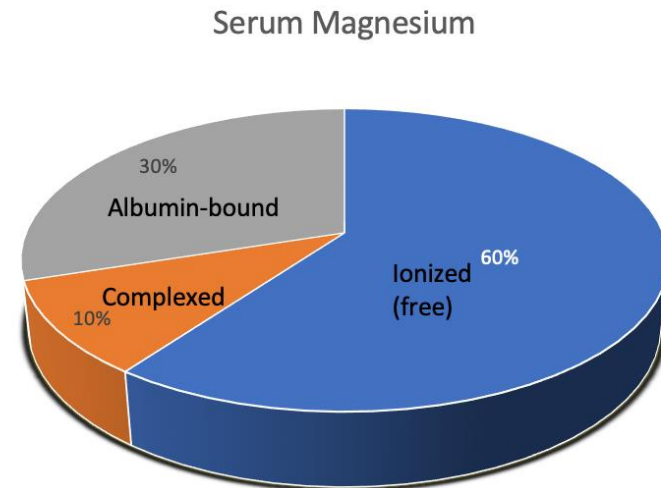
The serum contains only 0.3% of total body Mg, most of it is in the RBCs



Magnesium Homeostasis

Serum Mg

- 60% of is free (ionized)
- 10% is complexed (bound to anions such as citrate phosphate, bicarbonate or sulfate) and
- 30% is albumin-bound



Magnesium and diet

Recommended Mg consumption :

- Adult males consume 400 to 420 mg daily
- Adult females 310-320 mg daily

Mg rich foods include:

- Green vegetables
- Seeds (such as cashew, almond and brown rice) and nuts
- Cereals, baked potato with skin, oatmeal, yogurt, banana, black beans and peanut butter
- Some meats and sea foods

Processed and refined food is a poor source of Mg



Magnesium Homeostasis

Magnesium absorption

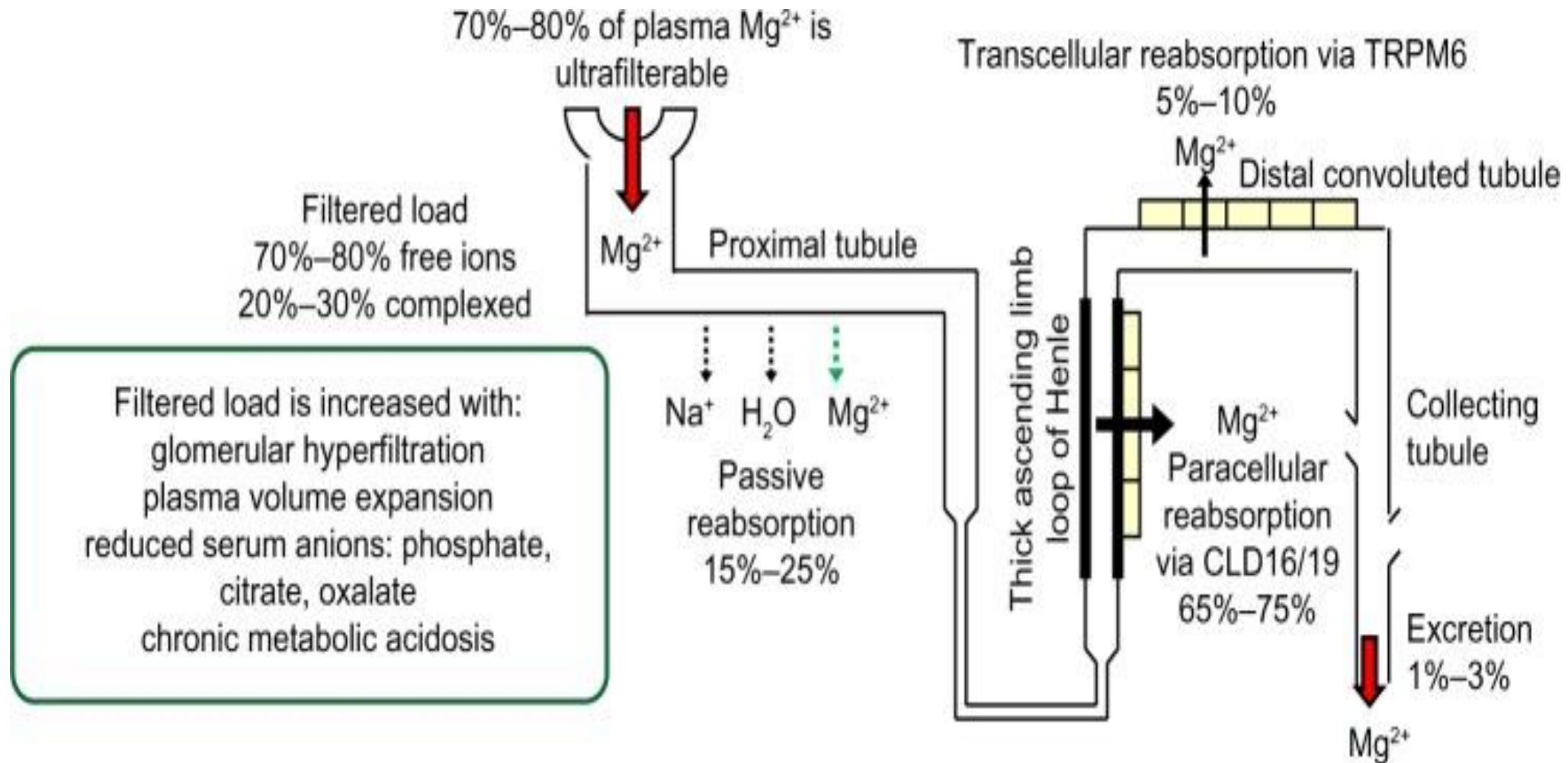
- In the small intestine is absorbed paracellularly, mainly in the late jejunum and in the ileum
- In the colon, both transcellular (via TRPM 6 and 7) and paracellular absorption occur

Diarrhea fluid contains significant Mg (15 mEq/l)

vomit contains only 1 mEq/l

❖ TRPM channels are mammalian transient receptor potential melastatin non-selective cation channels





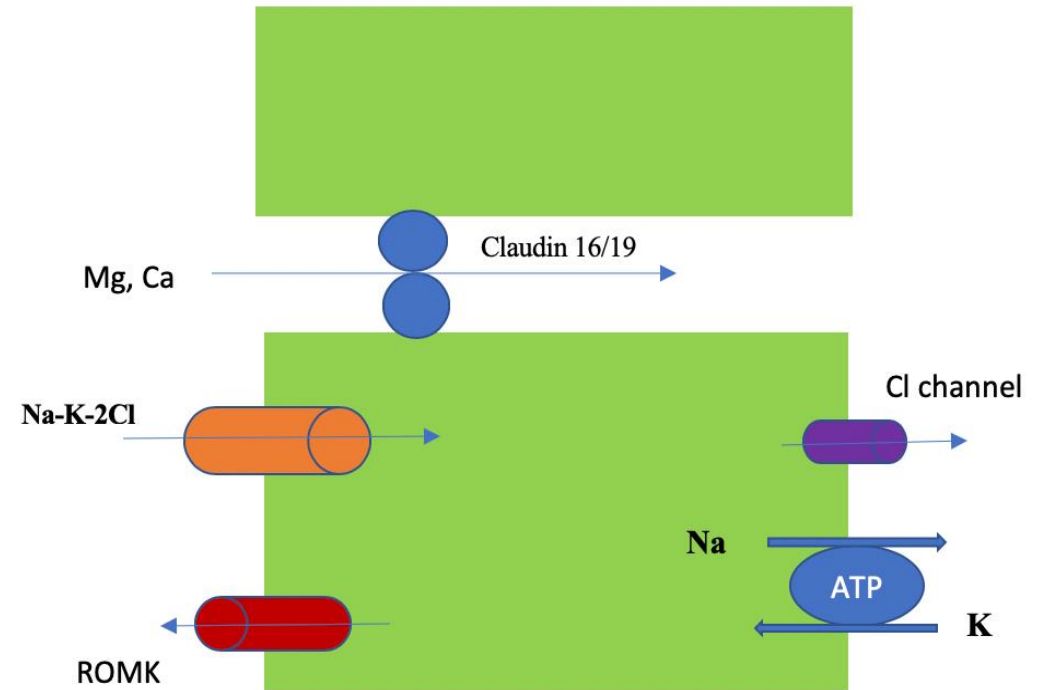
Kidney handling of magnesium

Abbreviations: CLD, claudin; TRPM6, transient receptor potential channel 6
International Journal of Nephrology and Renovascular Disease 2014;7 219–230



Magnesium Homeostasis

- Mg reabsorption in the TAL via the paracellular route
- Mg reabsorption is passive and depends on Na and K uptake via the Na-K-2Cl pump
- Mg inhibits ROMK channels



Hypomagnesemia

Definition

- serum Mg < 1.7 mg/dl (0.7 mmol/l)
- Normal serum Mg: 1.7-2.6 mg/dl (1.4-2.2 mEq/l or 0.7-1.1 mmol/l)
- Significant symptoms and signs are seen when serum Mg is < 1.2 mg/dl (0.5 mmol/l)

1mmol= 2mEq= 24.3 mg

1mmol/L =2mEq/L=2.4mg/dl



Hypomagnesemia

In Mayo Clinic review the risk of hypomagnesemia include:

- 2% in the general population
 - 10-20% in hospitalized patients
 - 50-60% in intensive care unit (ICU) patients
 - 30-80% in persons with alcoholism
 - 25% in outpatients with diabetes
-
- Mayo Clin Proc. 2015 Aug. 90 (8):1001-10



Hypomagnesemia: causes

1. Dietary deficiency: malnutrition, TPN, chronic alcoholism.

2. Gastrointestinal: chronic diarrhea, proton pump inhibitors (PPI), malabsorption, laxatives, short bowel syndrome, intestinal fistulas, nasogastric suction, primary infantile hypomagnesemia, patiromer (a potassium binder).

3. Renal wasting:

- Diuretics: loop and thiazide
- Diuretic phase of acute tubular necrosis (ATN) and post-obstructive diuresis
- Bartter syndrome and Gitelman syndrome
- Aminoglycosides
- Cyclosporine A and tacrolimus
- Epidermal growth factor receptor [EGFR] inhibitors such as cetuximab
- Cisplatin
- Amphotericin B
- Pentamidine
- Foscarnet
- Congenital or acquired tubular defects

4. Redistribution: acute pancreatitis, hungry bone syndrome, refeeding syndrome, blood transfusions, insulin.

5. Endocrine: primary and secondary hyperaldosteronism, hyperparathyroidism, hyperthyroidism, diabetes mellitus, syndrome of inappropriate anti-diuretic hormone secretion (SIADH).



Hypomagnesemia

Diabetes Mellitus:

13.5% to 47.7% of nonhospitalized patients with type 2 diabetes

Contributing factors include:

- Decreased oral intake of magnesium rich foods
- Poor intestinal absorption due to diabetic autonomic neuropathy
- Increased renal excretion caused by:

 Glomerular hyperfiltration

 Osmotic diuresis

 Decreased TAL and distal tubule Mg reabsorption caused by functional insulin deficiency



Post transplant hypomagnesemia

Primarily caused by **calcineurin inhibitors**

- Down regulate TRPM6 in DCT
- Increase claudin-14 expression(inhibit paracellular Mg transport)
- The incidence with tacrolimus may be 43 percent is higher than cyclosporine
- The incidence with calcineurin inhibitors is higher than mTOR inhibitor

- Transplant Proc. 2010;42(8):3047–3049



Hypomagnesemia: Symptoms and complications

Neuromuscular Manifestations

Tremors

Tetany, including positive Trousseau and Chvostek signs, muscle spasms, muscle cramps, muscle weakness

Seizures

Vertical nystagmus

Apathy

Delirium

Coma



Hypomagnesemia: Symptoms and complications

Cardiovascular Manifestations

Electrocardiogram changes including

widening of the QRS complex, peaked T waves, prolongation of the PR interval

Atrial and ventricular premature systoles

Atrial fibrillation

Ventricular arrhythmias, including torsades de pointes

Other electrolyte and hormone abnormalities

Hypocalcemia

Hypoparathyroidism

Hypokalemia



Hypomagnesemia: Symptoms and complications

Hypokalemia

Incidence: 40 to 60 %

Mechanisms:

- Due to disorders that cause both magnesium and potassium loss (such as diarrhea and diuretics)
- Renal K loss: Potassium secretion
by the cells of the connecting tubule and cortical collecting (ROMK channels)

hypokalemia is relatively refractory to potassium supplementation



Hypomagnesemia: Symptoms and complications

Hypocalcemia

Major factors:

- Hypoparathyroidism
- Parathyroid hormone resistance
- Vitamin D deficiency(calcitriol)

(epidemiologic studies suggest a correlation between bone mass and dietary magnesium intake)



Hypomagnesemia: Symptoms and complications

Magnesium depletion is also associated with :

- Insulin resistance and the metabolic syndrome
- New-onset diabetes after liver and kidney transplantation
- Hypertension

Patients with primary hypertension may have reduced free magnesium concentrations in RBCs

Magnesium supplementation can reduce blood pressure

- Eur J Clin Nutr. 2012 Apr;66(4):411-8. Epub 2012 Feb 08



Hypomagnesemia: Symptoms and complications

- Migraine headaches
- Asthma

magnesium therapy is effective in these disorders

- Low magnesium levels have been associated with higher mortality in hemodialysis patients

(in 2,636 individuals died over 5 years, serum Mg levels <2.0mg/dL)

- Am J Kidney Dis. 2015 Dec;66(6):1047-55. Epub 2015 Jul 14



Hypomagnesemia: Diagnosis

Serum Mg measurement should be ordered in:

- Patients with electrolyte disorders especially recalcitrant hypokalemia and hypocalcemia
- Patients with the symptoms, signs or complications of hypomagnesemia
- high index of suspicion in base of the clinical settings



Hypomagnesemia: Diagnosis

Normomagnesemic magnesium depletion

- Had low mononuclear cell magnesium levels
- As a possible cause of refractory hypokalemia or unexplained hypocalcemia in patients at high risk for magnesium loss



Hypomagnesemia: Diagnosis

- Hx taking

If no etiology is apparent:

- Fractional excretion of magnesium on a random urine specimen

$$\text{FEMg} = \frac{\text{UMg} \times \text{PCr}}{(0.7 \times \text{PMg}) \times \text{UCr}} \times 100 \text{ percent}$$

FEMg < 2 % indicates an extrarenal losses (typically GI)

FEMg > 3 to 4 % indicates renal magnesium wasting

- 24-hour urine collection for Mg
Urine Mg > 30 mg/ 24 h in renal Mg wasting



Hypomagnesemia: Treatment

- Underlying causes
- Oral Mg replacement
- IV Mg replacement
- Dietary counseling to increase Mg intake
- K sparing diuretics: amiloride, spironolactone, triamtrene



Hypomagnesemia: Treatment

- IV magnesium:
- Magnesium sulfate: 10%, 20%, 50%

1mmol= 2mEq= 24 mg of elemental mg= 240 mg of mgSO₄

1000mg of mgSO₄(2ml mgso₄; 50%) = 98.4 mg of elemental mg



Hypomagnesemia: Treatment

Patients with severe symptoms

- Hemodynamically unstable: such as those with tetany, arrhythmias, or seizures
1 to 2 grams Mg sulfate over 2-15 minutes
- Hemodynamically stable patients (less than or equal to 1 mg/dL)
1 to 2 grams of Mg sulfate in 50 to 100 mL of D5%W) over 5 to 60 minutes followed by an infusion



Hypomagnesemia: Treatment

- Plasma magnesium <1 mg/dL: 4 - 8 grams over 12 to 24 hours
(This dose can be repeated to maintain the plasma Mg > 1 mg/dL)
- In the normomagnesemic patient with hypocalcemia,
repeat this dose daily for three to five days

- plasma magnesium is 1 - 1.5 mg/dL: 2 - 4 grams over 4 -12 hours

- plasma magnesium is 1.6 - 1.9 mg/dL: 1 - 2 grams over 1-2 hours



Hypomagnesemia: Treatment

Follow up:

- Serum magnesium should be measured 6 to 12 hours after each dose of intravenous magnesium
- Repeat doses are given based upon the follow-up measurement

In Patients with renal insufficiency (Cr clearance < 30 mL/min/1.73 m)

- reduce IV magnesium dose by 50 percent or more
- closely monitoring magnesium concentrations

In children, slow infusion, dose is 25 to 50 mg/kg with a maximum single dose of 2 g is recommended



Hypomagnesemia: Treatment

- Magnesium repletion(nonemergency):

MgSO₄ 64 mEq (8 g) over the first 24 hours

and

32 mEq (4 g) daily for the next 2 to 6 days

- Magnesium repletion should continue for at least 1 to 2 days after the serum magnesium level normalizes



Hypomagnesemia: Treatment

Magnesium sulfate adverse effects:

Hypermagnesemia:

- include facial flushing
- loss of deep tendon reflexes
- hypotension
- atrioventricular block

Acute decrease in the serum ionized Ca²⁺ level

- which is related to increased urinary calcium excretion
- complexing of calcium by sulfate

in an asymptomatic patient who is already hypocalcemic, administration of MgSO₄ may further lower the ionized Ca²⁺ level and precipitate tetany



Hypomagnesemia: Treatment

Oral repletion

- limited bioavailability
- Daily dose : 240 to 1000 mg of elemental magnesium
- Sustained-release preparations are slowly absorbed and thereby minimize renal excretion of magnesium and better tolerated
- If a sustained-release preparation is **not** available, magnesium oxide 800 to 1600 mg daily in divided doses



Hypomagnesemia: Treatment (oral)

Mg formulation	Dosage forms	Elemental Mg content	Typical dose
Mg Oxide	Cap: 250 mg, 400 mg, 500 mg Tab: 241.3 mg, 250 mg, 253 mg, 500 mg	60% is elemental Mg. e.g. 400 mg cap contains 240 mg (~20 mEq or 10 mmol)	1-4 tab or cap/day divided in 1-4 doses Bioavailability: 4%
Mg Gluconate (available OTC)	Tab: 500 mg	5.4% elemental Mg. e.g. 500 mg tab contains 27 mg (2.25 mEq or 1.12 mmol)	1-2 tab/day divided in 1-2 doses Bioavailability: Human data not available
Mg Chloride (also available OTC in combination with Ca carbonate)	Extended release tab: 535 mg Mg content varies in OTC products	12% elemental Mg. Each extended release tab contains 64 mg elemental Mg	2 tab/day Bioavailability: 12%
Mg Lactate (available OTC)	Ex: Mag-Tab SR ®	12% elemental Mg. Each tablet contains 84 mg of elemental Mg	2-4 tab in 2 doses Bioavailability: 12%



Hypomagnesemia: Treatment

Potassium-Sparing Diuretics

In patients:

- with inappropriate renal magnesium wasting
- who are refractory to oral repletion or require such high doses of oral magnesium that diarrhea develops
- Amiloride
- Triamterene
- Spironolactone



Hypomagnesemia: Treatment

Proton pump inhibitors

Mechanism: impaired absorption of magnesium by intestinal epithelial cells caused by inhibition of TRPM6 and TRPM7 channels

- Prevalence of hypomagnesemia was significantly higher in patients taking **PPI+ diuretics** as compared with those who only used **diuretics** (15.6 versus 11 percent)
- In patients not taking diuretics, use of PPIs was not associated with the prevalence of hypomagnesemia
- Kidney Int. 2013 Apr;83(4):692-9



Hypomagnesemia: Treatment

FDA safety warning suggesting:

- Measure serum magnesium levels prior to initiation of PPI therapy and periodically during treatment

in patients expected to be on PPIs for long periods of time and in those taking other medications associated with hypomagnesemia eg, diuretics



Food	mg per serving	Percent daily value
Almonds, dry roasted, 1 ounce	80	20
Spinach, boiled, ½ cup	78	20
Cashews, dry roasted, 1 ounce	74	19
Peanuts, oil roasted, ¼ cup	63	16
Cereal, shredded wheat, 2 large biscuits	61	15
Soy milk, plain or vanilla, 1 cup	61	15
Black beans, cooked, ½ cup	60	15
Edamame, shelled, cooked, ½ cup	50	13
Peanut butter, smooth, 2 tablespoons	49	12
Bread, whole wheat, 2 slices	46	12
Avocado, cubed, 1 cup	44	15
Potato, baked with skin, 3.5 ounces	43	11
Rice, brown, cooked, ½ cup	42	11
Yogurt, plain, low fat, 8 ounces	42	11
Breakfast cereals, fortified with magnesium	40	10

Selected food sources of magnesium

Adapted from US Department of Health and Human Services. National Institutes of Health. *Magnesium fact sheet for health professionals*



Magnesium & Covid 19

Magnesium supplementation protects organs and tissues from damage through multiple mechanisms including:

- Anti-inflammation

lung inflammation possibly by inhibiting IL-6 pathway, NF- κ B pathway, and L-type calcium channels

- Anti-oxidation
- Immune-regulation
- Inhibit bronchial smooth muscle contraction

- *European Journal of Pharmacology 886 (2020) 173546*



Hypomagnesemia: Treatment

A cohort study with combination of:

- Magnesium (150 mg daily)
- Vitamin D (1000 IU daily)
- Vitamin B12 (500 mcg daily)

Significantly reduces the proportion of older COVID-19 patients with clinical deterioration requiring oxygen support and/or intensive care support

- Tan et al., 2020, medRxiv. <https://doi.org/10.1101/2020.06.01.20112334>



Hypomagnesemia: Treatment

Recommendation for COVID-19 patients with respiratory symptoms

- Adults:

Oral Mg supplementation 340 mg daily

- Children:

Nebulised magnesium supplementation treatment 150 mg daily

- *European Journal of Pharmacology 886 (2020) 173546*



Hypomagnesemia: case presentation

آقای 60 ساله با سابقه بیماری قلبی و فشار خون بالا و دیابت به علت ضعف و بی حالی مراجعه کرده است مشکلات گوارشی را ذکر نمیکند.

در بررسی های اولیه فشار خون 110 /70 و آزمایشات به شرح زیر میباشد:

BUN:30mg/dl, Cr: 1.5mg/dl, Na:135mEq/L, K:2.9mEq/L, BS:300mg/dl

بیمار تحت درمان با لوزارتان، هیدروکلرتیازید، کارودیلول، آسپیرین، انسولین و پنتوپرازول میباشد.

1- اندازه گیری منیزیم سرم؟



Hypomagnesemia: case presentation

- Serum Mg: 1mg/dl
- اندازه گیری کلسیم و فسفر
- ECG
- FEMg و اندازه گیری منیزیم ادرار 24 ساعته ؟
- درمان:
- رفع عوامل زمینه ای
- استفاده از ترکیبات منیزیم علاوه بر پتاسیم (سولفات منیزیم 4-8 گرم طی 12-24 ساعت)
- ادامه درمان و پیگیری طی بستری و سرپایی
- ترکیبات منیزیم خوراکی:
- استفاده از Potassium- sparing diuretics



Hypomagnesemia: case presentation

بیمار خانم 50 ساله که به علت کاهش سطح هوشیاری از یک هفته قبل در ICU بستری
میباشد، تحت تنفس مصنوعی قرار دارد، فشار خون 120/70mmHg
آزمایشات به شرح زیر میباشد:

BUN:15mg/dl, Cr: 1mg/dl, Na:135mEq/L,

K:2.8mEq/L, BS:140mg/dl, Ca:7.4mg/dl, Alb:3.6 g/dl

بیمار تحت درمان با پتاسیم کلراید قرار میگیرد که پس از دو روز و علیرغم افزایش دوز،
پتاسیم به 3mEq/L افزایش می یابد. جهت بیمار مشاوره نفرولوژی درخواست میگردد.



Hypomagnesemia: case presentation

منیزیم سرم: 0.9mg/dl

• بررسی علل هیپومنیزیمی و هیپوکالمی
علل گوارشی مانند اسهال، استفراغ و یا ساکشن ترشحات معده، استفاده از PPI و سوء تغذیه
باید بررسی شود. بیمار طی 4 روز گذشته اسهال داشته است و از پنتوپرازول استفاده
میکند.

علل کلیوی: بیمار تحت درمان با فورسماید با دوز کم میباشد

• ECG: مختصر آریتمی دهلیزی و پهن شدن QRS را نشان میدهد

• ABG: مختصر اسیدوز متابولیک



Hypomagnesemia: case presentation

درمان:

- رفع عوامل زمینه ای و درمان هیپوکالمی
- با توجه به شدت هیپومنیزیمی و آریتمی 1-2 گرم منیزیم سولفات طی 10-15 دقیقه تزریق می‌گردد و سپس 4-8 گرم طی 12-24 ساعت داخل سرم نمکی تزریق می‌گردد
- روز بعد منیزیم سرم 1.2 mg/dl و پتاسیم 3.4mEq/L
- سولفات منیزیم 2-4 گرم طی 4-12 ساعت روزانه ادامه میابد
- پس از 3 روز منیزیم 1.8mg/dl بوده است
- 2 روز دیگر جهت جبران منیزیم داخل سلولی منیزیم سولفات 1-2 گرم طی 2 ساعت روزانه تجویز می‌گردد.
- ترکیبات منیزیم خوراکی:
- استفاده از Potassium- sparing diuretics



اللهم اغفر لكل مريض

