Magnesium Balance and Disorders: A Nephrologist Perspective

Introduction: Magnesium is a cofactor required for large number of enzymes and vital to their appropriate function. It is the most abundant divalent cation in human body, but often neglected in clinical practice. It also plays a significant role in bone formation and regulation of PTH hormone. Extracellular concentration represents only 1-2% of total body stores and thus normal values (1.8-2.4 mg/dL) may not be a true representative of overall total body stores as 60% of the magnesium is stored in bones and rest of the magnesium resides intracellularly\(^1,2\). A nephrologist may come across magnesium disorders in the clinical practice more often than thought before.

Magnesium Transport: Once magnesium is orally ingested, it is absorbed in gastrointestinal tract mostly by paracellular route\(^1,2\) (80-90%). In the blood, only 20-30% of magnesium is bound to proteins and rest is presented to glomerulus for filtration. Contrary to most other electrolytes, only 10-30% of magnesium is reabsorbed in proximal tubule. Major site of magnesium reabsorption is thick ascending loop of Henle whereby active sodium reabsorption by Na-K-2Cl channel creates a negative intraluminal potential which is assisted by luminal renal outer medullary potassium channel (ROMK), basolateral Na-K-ATPase, basolateral Cl channel and Calcium sensing receptor. Luminal magnesium is passively reabsorbed along with the calcium via paracellular route through tight junction proteins\(^2\) Claudin 16 (paracellin-1 protein) and claudin 19. Magnesium also inhibits ROMK channel and thus hypomagnesaemia contributes to hypokalemia via increased potassium efflux through ROMK channels in to the tubular lumen\(^3\).

In the distal convoluted tubule\(^1,2,4\) (DCT), rest of the 5-10% of magnesium is actively reabsorbed via electrical gradient through luminal protein known as transient receptor potential melastatin, subtype 6 (TRPM 6) which is modulated by epidermal growth factor (EGF) and assisted by TRPM 7. Once inside the cell, it is extruded through basolateral membrane possibly via a sodium magnesium transporter. Potassium channels such as...
Kv1.1 (luminal) and Kir 4.1 (basolateral) recycles intracellular potassium into the tubular lumen and interstitial space and play a critical role in the magnesium reabsorption via maintaining a favorable negative intracellular electrical gradient. Furthermore, hepatocyte nuclear factor homeobox 1B (HNF-1B) plays a role by in magnesium handling by modulating FXYD2 gene which encode the gamma subunit of Na-K-ATPase, as gamma unit is postulated to play a role in basolateral magnesium extrusion.

Finally, magnesium concentration in itself may regulate its transport by affecting calcium sensing receptor and TRPM 6 function.

**Causes of magnesium Disorders:**

**Hypomagnesaemia**5: Common causes are chronic GI losses due to malabsorption, diarrheal illness, and low intake as in chronic alcoholics. It is also common in patients with diabetes mellitus, pancreatitis and admitted to intensive care units. Medications which may cause low magnesium levels are diuretics, proton pump inhibitors6 (through decreased gastrointestinal absorption), cisplatin (renal wasting of magnesium), calcineurin inhibitors (down regulates TRPM 6), aminoglycosides, amphotericin-B and cetuximab (inhibition of VEGF). Vitamin D deficiency may cause hypomagnesaemia as it also modulates magnesium reabsorption in DCT.

**Hypermagnesaemia**: It is mostly due to inadvertent intake of magnesium based antacids, enema, phosphate binders or the iatrogenic magnesium infusion in the presence of renal failure. Uncommon causes are massive hemolysis, lithium, milk alkali syndrome. High magnesium levels are also usually maintained for the treatment of eclampsia.

**Genetic Disease associated with hypomagnesaemia**1,2: Some of the genetic diseases with associated low magnesium levels are as follows: Gitelman syndrome (mutation in Na-Cl contransporter), Bartter syndrome (mutation in Na-K-2Cl contransporter), Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (mutation in Paracellin 1), hypomagnesaemia with secondary hypocalcaemia (mutation in TRPM 6), autosomal dominant hypomagnesaemia (mutation in Kv1.1), and SeSAME syndrome (mutation in Kir 4.1)

**Clinical Features (depending upon the severity):**

**Hypomagnesaemia**: muscle weakness, tetany, chovstek sign, convulsions, arrhythmias, PR prolongation and QRS widening.

**Hypermagnesaemia**: hypotension, respiratory depression arrhythmia, heart block, absent or diminished deep tendon reflex, PR prolongation and QRS widening
Evaluation should include assessment of serum potassium, calcium, vitamin D and PTH level and EKG analysis. Also urine factional excretion of magnesium may be helpful to differentiate between gastrointestinal versus renal loss of magnesium.

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\text{Fractional Excretion of Magnesium} = \frac{\text{Urine Mg} \times \text{serum creatinine}}{(0.7 \times \text{Urine creatinine} \times \text{serum Mg})} \text{ all units in mg/dL}
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**Treatment:**

**Hypomagnesaemia:** Depending upon the clinical status or severity, patients may be given magnesium supplements orally or intravenously. In the presence of hypokalemia, caution should be paid while giving magnesium with non-reabsorbable anions such as sulphate or oxide as these may promote potassium losses in collecting tubules and worsens hypokalemia hence should prefer to give magnesium chloride or lactate.

**Hypermagnesaemia:** In the presence of normal renal function, it may be conservatively managed with diuretics however in patients with renal failure or life threatening symptoms, emergent hemodialysis may be necessary. In meantime, temporary measures such as intravenous calcium gluconate or chloride to stabilize the cardiac membrane should be utilized.

**References:**


