Pacific Journal of Medical and Health Sciences
ISSN: 2456-7450 | Vol.9, No. 1, 2024, pp - 36-49

PJMHS
PACIFIC JOURNAL OF MEDICAL AND HEALTH SCIENCES

Review

Magnesium - An Essential Element, Vital for Human Health

Riya Pareek and S.K.Verma

Department of Medicine, Pacific Medical College and Hospital, Udaipur, Rajasthan, Bharat

***Corresponding Author Email:** drskverma77@gmail.com

ABSTRACT

Magnesium is one of the four essential metals for human health vital for numerous physiological functions. Biologically, magnesium is considered a "chronic regulator" and a "forgotten electrolyte," essential for numerous cellular processes. It is central to the activity of around 500 enzymes known as kinases, which regulate complex cellular functions. It is vital for electrolyte homeostasis and plays a critical role in controlling neuromuscular function, regulating heart rhythm, modulating vascular tone, and influencing hormone secretion. Magnesium is necessary for bone health, protein, carbohydrate, and fat metabolism, and energy production. Deficiency in magnesium can lead to a range of health issues, including decreased bone density and an increased risk of various disorders.

KEYWORDS: Essential metal, Kinases, “Forgotten electrolyte”, Electrolyte homeostasis, "chanzymes"

INTRODUCTION

Magnesium is an essential element vital for numerous physiological functions that support overall health. Despite its importance, it often goes unrecognized as a major mineral. Magnesium is one of the four essential metals for human health, alongside calcium, potassium, and sodium, with a relatively high recommended daily allowance (RDA). Its absorption and retention decrease with age, making deficiency more common in the elderly. The magnesium content in drinking water also varies significantly, affecting dietary availability.

Magnesium plays a critical role in controlling neuromuscular function, regulating heart rhythm, modulating vascular tone, and influencing hormone secretion and NMDA release in the central nervous system. It acts as a second messenger in intracellular signaling and regulates cardiac clock genes that control circadian rhythms within biological systems. Magnesium functions in body fluids as hydrated ions, which significantly influence its electrochemical, biochemical, and physiological roles. Its unique ionic hydration form enhances its recognition and transport at the molecular level.

Biologically, magnesium is considered a "chronic regulator" and a "forgotten electrolyte," essential for numerous cellular processes. It is central to the activity of around 500 enzymes known as kinases, which regulate complex cellular functions, including signal transduction, energy production, and cellular communication. Magnesium-dependent kinases are involved in phosphorylation, crucial for activating proteins and other molecules. Magnesium is vital for electrolyte homeostasis, influencing the activity of various ATPase pumps and preventing conditions like hypokalemia and hypocalcemia.

Magnesium is necessary for bone health, protein, carbohydrate, and fat metabolism, and energy production. Deficiency in magnesium can lead to a range of health issues, including decreased bone density and an increased risk of various disorders. Causes of magnesium deficiency include poor dietary intake, excessive renal loss (often due to alcohol consumption), malabsorption, and certain medications. Clinicians often rely on laboratory tests for diagnosis, but lifestyle factors such as diet, exercise, and alcohol consumption can also indicate potential deficiencies. Identifying these factors is crucial for diagnosing and treating magnesium deficiency, which is linked to a wide range of pathologies[1].

Bioavailability and Absorption

Dietary magnesium has decreased due to changes in eating habits and food processing. High-magnesium foods include almonds, bananas, black beans, broccoli, brown rice, cashews, flaxseed, green vegetables, nuts, oatmeal, seeds, soybeans, sweet corn, tofu, and whole grains. Common sources include green vegetables, cereals, fish, nuts, and water, with hard water typically containing more magnesium than soft water. However, magnesium levels in water can vary greatly. Magnesium is abundantly found in foods, especially green vegetables due to its presence in chlorophyll. Daily intake varies from 6 to 20 mmol, with an average of about 12 mmol. Hard water can contain up to 5 mmol/L of soluble magnesium, which might be more bioavailable than magnesium in certain foods.

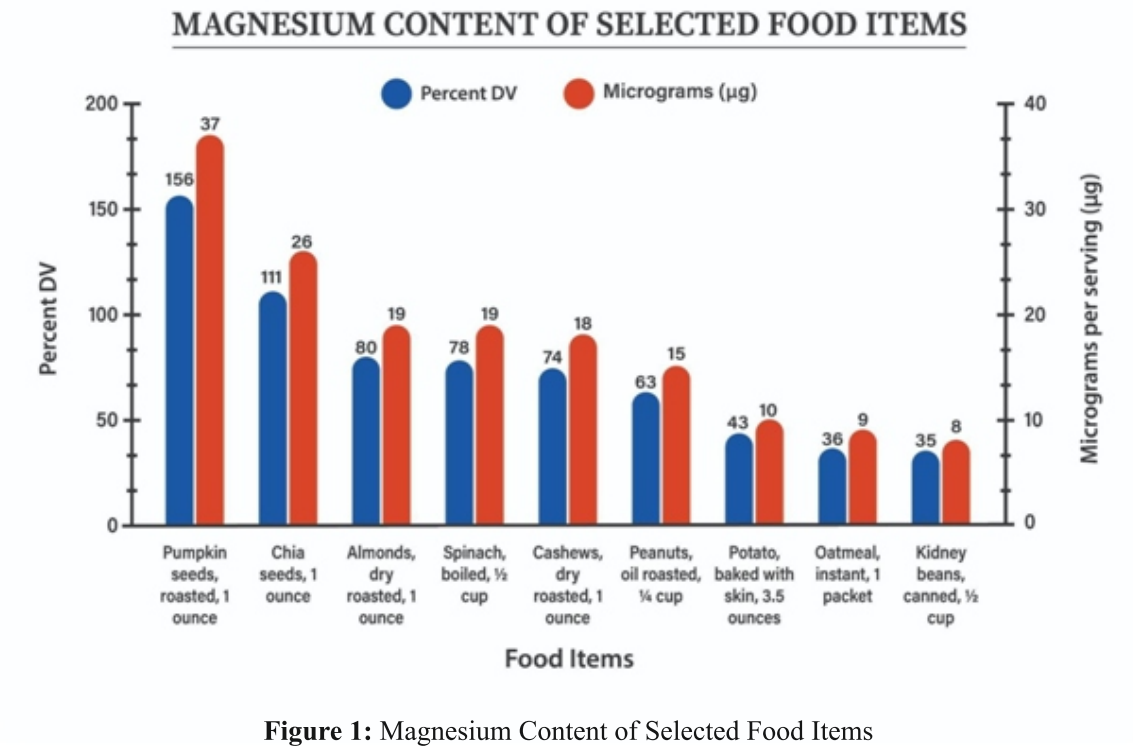

Figure 1: Magnesium Content of Selected Food Items

This figure shows the magnesium content in various food items, measured in both percent daily value (% DV) and micrograms (µg) per serving. The Daily Value (DV) for magnesium is 420 mg for adults and children age 4 years and older. Data for this figure was sourced from the National Institute of Health's Office of Dietary Supplements. [Magnesium Fact Sheet for Health Professionals]

Magnesium deficiency, affecting many cellular functions, is linked to systemic diseases. For instance, a study of over 286,000 individuals showed an inverse relationship between magnesium intake and type II diabetes incidence, suggesting increased consumption of magnesium-rich foods may reduce diabetes risk.

Magnesium is vital for electrolyte homeostasis, influencing the activity of various ATPase pumps, and preventing conditions like hypokalemia and hypocalcemia. It is necessary for bone health, protein, carbohydrate, and fat metabolism, and energy production. Magnesium deficiency can lead to a range of health issues, affecting bone density and increasing the risk of disorders.

Magnesium (Mg) absorption in the body primarily occurs in the small intestine, specifically in the ileum and the jejunum. This occurs through tight junctions between enterocytes (intestinal cells) and is driven by the concentration gradient. When dietary Mg is high, passive transport becomes more significant. This involves specific Mg transport channels and occurs mainly when dietary Mg is low. The primary channels responsible for Mg uptake are Transient Receptor Potential Melastatin (TRPM)6 and TRPM7. TRPM6 is primarily expressed in the distal small intestine and colon, while TRPM7 is more widely distributed and supports magnesium absorption. Once absorbed, Mg enters the bloodstream and is distributed to various tissues. Approximately 60% is stored in bones and 20% is located in muscles.

Magnesium homeostasis, crucial for many bodily functions, has only recently been understood in detail. Two ion channels, TRPM6 and TRPM7, have been identified as key players in magnesium transport and homeostasis. These channels, part of the Transient Receptor Potential Melastatin (TRPM) sub-family, facilitate magnesium absorption from the gut and reabsorption by the kidneys.

TRPM6 is primarily expressed in the colon and renal distal tubules, responding to low intracellular magnesium levels by increasing magnesium absorption and reabsorption. TRPM7 is more widespread, found in various organs like the lungs. These channels, termed "chanzymes" due to their dual channel and kinase functions, represent a molecular mechanism that regulates magnesium balance at the cellular level. In the gut, Mg2+ absorption primarily occurs in the distal ileum and colon via the Mg2+ channels TRPM6 and TRPM7.

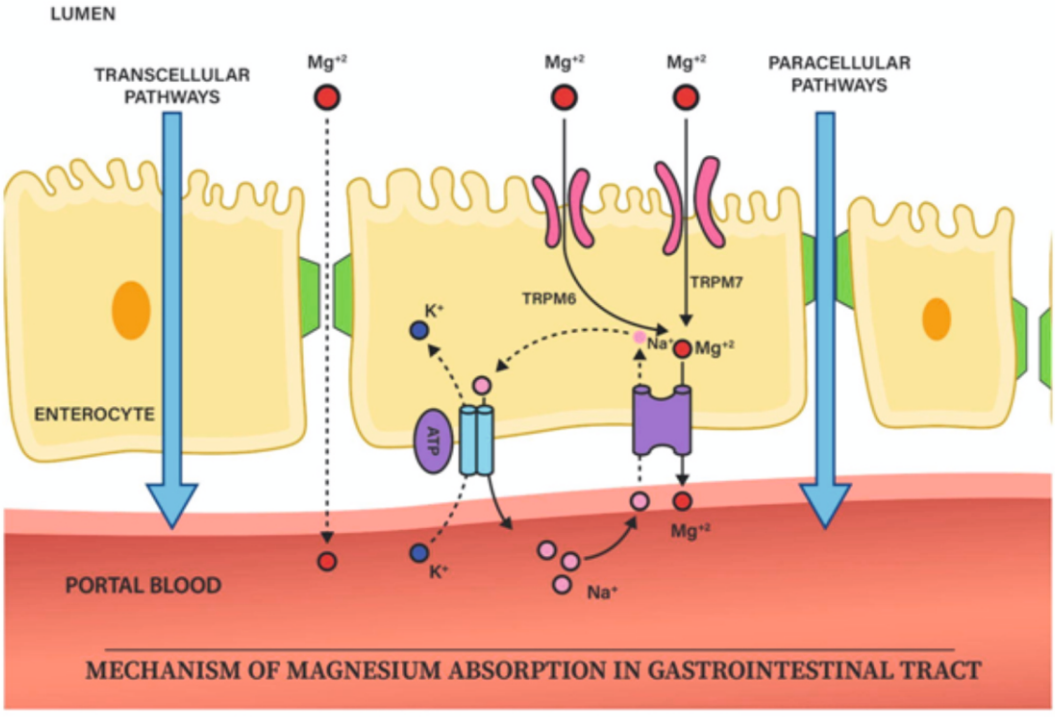

Figure 2: Mechanism of Magnesium absorption in gastrointestinal tract

TRPM6 and TRPM7 are members of the Transient Receptor Potential (TRP) channel family, specifically the TRPM (Melastatin) subgroup, and play critical roles in magnesium transport within enterocytes (intestinal cells).

The recommended daily intake of magnesium for adults is 300-400 mg/day, with absorption rates influenced by intake levels and overall body magnesium status. Dietary intake of magnesium is essential, with 30-70% absorbed by a healthy gut. Absorption occurs both actively and passively, with active uptake facilitated by TRPM6 and TRPM7 channels in the large intestine, and passive absorption in the small intestine [Figure 2]. Magnesium homeostasis is maintained through renal reabsorption and urinary excretion, with renal conservation occurring during deficiency and increased excretion during surplus. Despite renal adjustments, magnesium can be drawn from skeletal storage to maintain serum levels, which may lead to bone issues like osteopenia and osteoporosis. Magnesium is absorbed in the intestines via passive paracellular and active transcellular pathways. TRPM6 expression is influenced by factors such as acid-base status, 17-estradiol, β-adrenergic activity, FK506, and cyclosporine.

SGLT2 inhibitors, used to treat type II diabetes by increasing urinary glucose excretion, have been associated with higher serum magnesium levels. This suggests potential benefits of SGLT2 inhibitors may include altered magnesium homeostasis. Magnesium supplements, such as magnesium citrate, glycinate, threonate, and malate, are available, with organic forms being more bioavailable than inorganic ones. However, some studies report no significant differences in bioavailability among different formulations. Oral magnesium supplements can cause diarrhea, while transdermal applications, such as magnesium oil, may minimize this side effect and have shown benefits in conditions like diaper rash. Epsom salt baths are also used to alleviate various conditions, though excessive ingestion can lead to complications. Hypermagnesemia, although rare, can result from high doses of magnesium, leading to serious health issues like hypotension, bradycardia, and coma.

Individuals with serum magnesium around 1.82 mg/dL are likely deficient, while levels above 2.07 mg/dL are considered adequate. Red blood cell (RBC) magnesium levels are a better indicator of body magnesium status, with normal RBC levels ranging from 4.2 to 6.8 mg/dL[2].

Dietary Influences

- Food Processing: Common food processing methods, such as refining white flour or rice, can reduce Mg content by 300–400%.
- Phytic Acid: Found in nuts, seeds, and grains, it can chelate and diminish the absorption of essential minerals like Ca, Fe, Mg, and Zn.
- Glyphosate: The widely used pesticide can chelate minerals, potentially affecting their availability.
- Traditional Foods: Consuming traditional foods and using methods like sourdough fermentation can improve Mg bioavailability[3].

The Institute of Medicine (IOM) sets the upper tolerable limit for Mg supplementation at 350 mg/day to avoid gastrointestinal side effects. Individuals with renal impairment are at higher risk for Mg toxicity and should be closely monitored. Gastrointestinal symptoms often indicate excessive Mg levels, but the severity can vary based on the type of Mg salt ingested. Awareness of potential toxicity is crucial, especially for those with compromised kidney function. The lack of practical training in clinical nutritional biochemistry within medical education is a major issue contributing to widespread Mg insufficiency. Mg supplementation is beneficial for conditions such as preeclampsia/eclampsia, cardiac arrhythmias, migraine headaches, metabolic syndrome, diabetes and its complications, premenstrual syndrome, hyperlipidemia, and asthma. No specific hormone regulates Mg, but several hormones (e.g., insulin, PTH, calcitonin, catecholamines) influence Mg homeostasis.

Maintaining Mg sufficiency can significantly impact many common clinical conditions. The lack of practical training in clinical nutritional biochemistry within medical education is a major issue contributing to widespread Mg insufficiency. Higher requirements in conditions like pregnancy, aging, exercise and certain diseases (e.g., type 2 diabetes). High intake of sodium, calcium, protein, alcohol, caffeine, and certain drugs (e.g., diuretics, proton-pump inhibitors) can alter Mg balance. Mg absorption primarily occurs in the small intestine. Daily Mg intake needed: 5–7 mg/kg. Kidney excretes about 120 mg of Mg daily, with reabsorption increasing during Mg depletion[4].

Food processing often reduces magnesium content in cereals and carbohydrate products. The broad reference range for 24-hour urinary magnesium excretion (2.0–7.5 mmol) mainly

reflects dietary variations.

Typically, of the 12 mmol of dietary magnesium, about 6 mmol is absorbed, primarily in the small intestine. Absorption occurs via two mechanisms: an active transport system that saturates at low concentrations and a passive diffusion system that consistently absorbs around 7% of ingested magnesium. Some magnesium can also be absorbed in the large intestine, as evidenced by hypermagnesaemia from magnesium-containing enemas. Approximately 2 mmol of magnesium is secreted into the intestine, resulting in a net absorption of about 4 mmol per day, which is balanced by urinary excretion[5].

Excretion

Magnesium homeostasis is primarily managed by filtration and reabsorption in the kidneys. When magnesium intake is high, urinary excretion increases, and when intake is low, the kidneys conserve magnesium. Typically, 1000 mmol of magnesium is filtered daily, with only 3 mmol excreted in urine. About 10-15% of filtered magnesium is passively reabsorbed in the proximal tubule, while 65% is reabsorbed in the thick ascending loop of Henle via a paracellular mechanism involving paracellin-1, which is dependent on NaCl absorption. Factors disrupting NaCl "chanzymes" reabsorption, like diuretics and fluid expansion, enhance magnesium excretion. Additionally, 10-15% of filtered magnesium is actively reabsorbed in the distal tubule, regulated by divalent cation-sensing receptors, which adjust reabsorption based on plasma magnesium levels [Figure 3]. Hormones such as parathyroid hormone, glucagon, calcitonin, and insulin can increase magnesium reabsorption. Factors like hypercalciuria, hypophosphatemia, and metabolic acidosis also affect magnesium reabsorption, with metabolic acidosis linked to increased urinary magnesium loss, potentially reducing magnesium status in individuals on Western diets.

The blood Mg2+ concentration is regulated through a coordinated process involving intestinal Mg2+ absorption, storage in bones and soft tissues, and renal excretion. Similar to Ca2+, bone is traditionally viewed as the main storage site for Mg2+, containing 50% of the body's Mg2+ content. However, the role of soft tissues, such as muscles and the liver, in Mg2+ storage has gained recognition in recent years.

The proximal tubule (PT) is primarily responsible for the bulk reabsorption of Na+, K+, and Ca2+, but it only reabsorbs 20-30% of the filtered Mg2+ load. When the tubular fluid-to-ultrafiltrate concentration ratio exceeds 1.9 in the late PT, Mg2+ is reabsorbed through a passive paracellular mechanism which reabsorbs 15-25% of filtered Mg2+ mainly through paracellular transport. In the nephron, about 70% of plasma Mg2+ is filtered through the glomerulus. The majority of Mg2+ reabsorption occurs paracellularly, where ions pass between cells, while a smaller fraction is reabsorbed transcellularly, where ions move through the cells [Figure 3]. Magnesium ions (Mg^{2+}) are reabsorbed through solvent drag, where they move along with water via paracellular pathways. Mg^{2} can also passively diffuse from the tubule lumen into the interstitial space.

Proximal Tubule (PT) Magnesium Reabsorption

In the Proximal Convoluted Tubule (PCT), various transporters and channels are crucial for ion and water reabsorption. The NHE3 (Na^{+}/H^{+} Exchanger) facilitates sodium reabsorption by exchanging sodium for hydrogen, while the Na^{+}-K^{+} ATPase pump maintains the electrochemical gradient by pumping sodium out of the cell and potassium into the cell. Aquaporin-1 (AQP1) channels enable water reabsorption, and Kir4.2/Kir5.1 channels manage potassium recycling. Claudin 1/2 proteins are implicated in the paracellular transport of magnesium, though their precise role is unclear. The proximal tubule primarily reabsorbs sodium, potassium, and calcium, but handles only 20-30% of the filtered magnesium load. Initial studies indicated minimal magnesium transport in the early proximal tubule, with passive reabsorption occurring in the late proximal tubule when the tubular fluid-to-ultrafiltrate concentration ratio exceeds 1.9. Clinical studies emphasize the significance of proximal tubule glucose transport in magnesium reabsorption.

Magnesium (Mg^{2+}) Reabsorption and Regulatory Mechanisms in the Thick Ascending Limb (TAL)

The Thick Ascending Limb (TAL) of the Loop of Henle is the primary site for magnesium (Mg^{2+}) reabsorption, handling 50-70% of the filtered Mg^{2+} load via paracellular pathways. This process is facilitated by the cation-selective claudins, CLDN16 and CLDN19. Mutations in these genes cause familial hypomagnesemia, hypermagnesiuria, and nephrocalcinosis (FHHNC). The lumen-positive transepithelial membrane potential, generated by NKCC2 activity and potassium backleak through the ROMK channel, drives paracellular Mg^{2+} reabsorption. Inhibition of NKCC2 by furosemide reduces Mg^{2+} reabsorption in the TAL.

Research using isolated perfused TAL tubules has shown that deleting CLDN16 reduces the Mg^{2+} and Ca^{2+} permeability-to-Na^{+} permeability ratios, underscoring its role in Mg^{2+} reabsorption. TAL tight junctions exhibit a mosaic pattern where CLDN10b and CLDN16/19 are expressed separately, with CLDN10b forming monovalent cation pores and CLDN16/19 forming Ca^{2+}/Mg^{2+}-selective pores.

Common variants in CLDN14 are linked to differential Mg^{2+} and Ca^{2+} excretion. Although CLDN14 expression is low in the kidney, it is induced by high Ca^{2+} levels through the Ca^{2+}-sensing receptor (CaSR). Over expression of CLDN14 in the TAL decreases plasma Mg^{2+} and increases Mg^{2+} excretion, suggesting a regulatory role for CLDN14.

The NKCC2 (Na^{+}-K^{+}-$2Cl^{-}$ Co-transporter) and ROMK channels are essential for TAL function. NKCC2 transports Na^{+}, K^{+}, and Cl^{-} from the lumen into cells, while ROMK recycles K^{+} back into the lumen. The Na^{+}-K^{+} ATPase pump maintains Na^{+} and K^{+} gradients, and ClC-Kb and Barttin channels facilitate chloride reabsorption. Although the CaSR regulates divalent cation reabsorption, its specific impact on Mg^{2+} reabsorption in the TAL is not clear. Gain-of-function mutations in CaSR can inhibit NKCC2 activity, leading to hypomagnesemia and hypocalcemia.

Parathyroid hormone (PTH) significantly enhances Mg^{2+} reabsorption in the TAL, with low serum Mg^{2+} levels common in hypoparathyroidism. Mutations in the RRAGD gene, which affect the mTOR complex 1 (mTORC1) pathway, are linked to autosomal dominant hypomagnesemia. Hyperactivation of mTORC1 influences Mg^{2+} and Ca^{2+} reabsorption in the TAL, and mTORC1 inhibition is associated with hypomagnesemia and reduced NKCC2 expression, indicating a complex regulatory role for mTORC1.

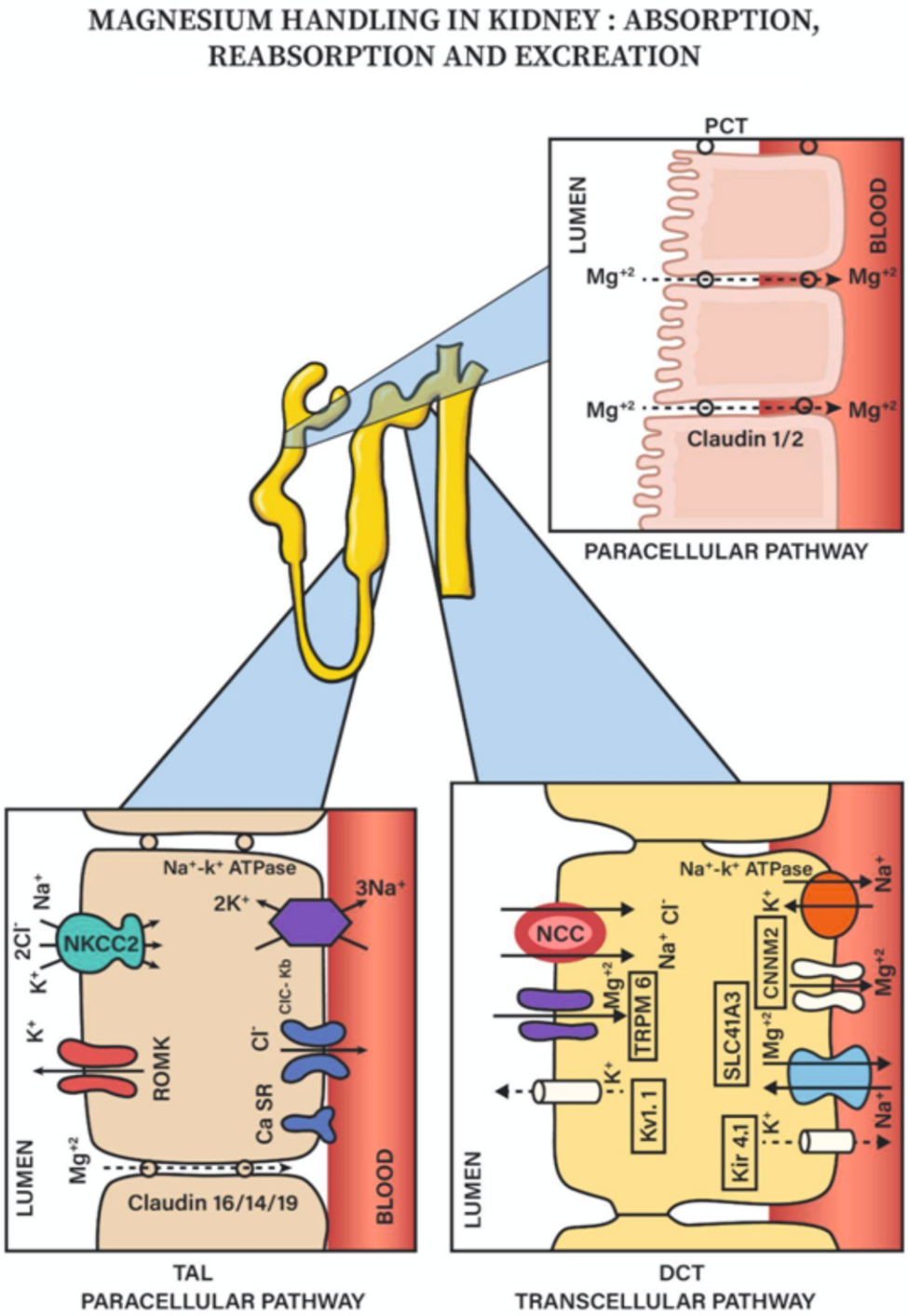

Figure 3: Mechanisms of Magnesium Handling in the Kidney

The diagram shows magnesium (Mg^{2+}) transport in the nephron. In the Proximal Convoluted Tubule (PCT), Mg^{2+} is reabsorbed via the paracellular pathway with Claudin 1/2. The Thick Ascending Limb (TAL) involves Claudin 16/14/19, NKCC2 (Na^+-K^+-$2Cl^-$ co-transporter), ROMK (renal outer medullary potassium channel), and ClC-Kb (chloride channel). The Distal Convoluted Tubule (DCT) features TRPM6 (transient receptor potential melastatin 6), NCC (sodium-chloride co-transporter), Kv1.1 (voltage-gated potassium channel subfamily A member 1.1), SLC41A3 (sodium-magnesium exchanger), CNNM2 (sodium-magnesium exchanger 1), and Kir4.1 (inwardly rectifying potassium channel subfamily J member 10).

Mg^{2+} Reabsorption and Regulatory Mechanisms in the Distal Convoluted Tubule (DCT)

In the Distal Convoluted Tubule (DCT), the NCC (Na^+-Cl^- Co-transporter) and other channels manage the reabsorption of sodium (Na^+), chloride (Cl^-), and magnesium (Mg^{2+}). The TRPM6 channel is crucial for transcellular Mg^{2+} reabsorption, with its activity enhanced by Epidermal Growth Factor (EGF). Mutations in TRPM6 cause familial hypomagnesemia with secondary hypocalcemia, leading to muscle cramps and seizures. TRPM7, often forming heterotetramers with TRPM6, also plays a role in Mg^{2+} reabsorption, with pathogenic variants linked to hypomagnesemia.

Kv1.1, encoded by the KCNA1 gene, supports TRPM6-mediated Mg^{2+} reabsorption by maintaining the electrochemical gradient. TRPM6/7 activity is influenced by intracellular Mg^{2+}, Mg-ATP, fluid shear stress, and hormonal regulators like EGF, insulin, estrogens, and β-adrenergic signaling. EGF increases TRPM6 membrane expression and is essential for Mg^{2+} homeostasis.

Basolateral Mg^{2+} transport involves proteins like CNNM2 and the solute carrier 41 protein family (SLC41A1−SLC41A3). CNNM2 is a candidate for Mg^{2+} extrusion, though its exact function is debated. SLC41A3 is enriched in the DCT, and knockout mice show hypomagnesemia. Na^+/K^+ exchange proteins, such as Na^+-K^+-ATPase subunits and Kir4.1/Kir5.1 K^+ channels, are vital for Mg^{2+} reabsorption, with mutations causing syndromes like EAST/SeSAME and Gitelman, leading to hypomagnesemia.

Mitochondrial function also plays a role in Mg^{2+} reabsorption, with mutations in mitochondrial tRNAs and tRNA synthases linked to hypomagnesemia. The DCT adapts to Na^+ or Mg^{2+} wasting by increasing its reabsorptive capacity in response to stimuli like diuretics or dietary restrictions. Further research is needed to fully elucidate the molecular processes involved in Mg^{2+} transport in the DCT[6].

Crucial Role of Magnesium in Neuronal Development and Neurological Disorders

Magnesium (Mg^{2+}) is crucial for various diseases, including cancers, diabetes, and neurodegenerative disorders like Parkinson's, Alzheimer's, and demyelination diseases. Its regulation is complex, leading to ongoing debates in research. However, Mg^{2+} plays essential roles in neuronal development, normal functioning, and disease states. Mg^{2+} supplementation often has neurotrophic effects, indicating that maintaining Mg^{2+} balance could be a potential therapeutic target for neuronal diseases.

In the central nervous system (CNS), the extracellular fluid (ECF) is separated from the blood by the blood-brain barrier (BBB). The BBB, made up of brain capillary endothelial cells, regulates the passage of nutrients and electrolytes to maintain ECF homeostasis. Due to the close proximity of neuronal and glial cells (20 to 50 nm apart) and the small volume of extracellular space in the brain, ECF component concentrations fluctuate significantly. Therefore, the BBB actively transports various molecules to maintain ECF stability. ECF Mg^{2+} concentrations are higher than those in plasma or cerebrospinal fluid (CSF), indicating active Mg^{2+} transport across the BBB [Figure 4]. In vitro models of the BBB with human brain endothelial cells have shown the presence of active Mg^{2+} transporters, such as transient receptor potential melastatin 7 (TRPM7) and MagT1. However, the mechanisms of Mg^{2+} transport in the BBB are not well understood. Research has mainly focused on Mg^{2+} absorption and excretion in the small intestine and kidneys, so further studies are needed to explore these processes in the CNS. Additionally, gap-junction-mediated cytosolic Mg^{2+} ([Mg^2] cyto) regulates the circadian rhythm of BBB permeability in Drosophila, suggesting that intracellular Mg^{2+} levels in the BBB affect the neuronal environment in the brain.

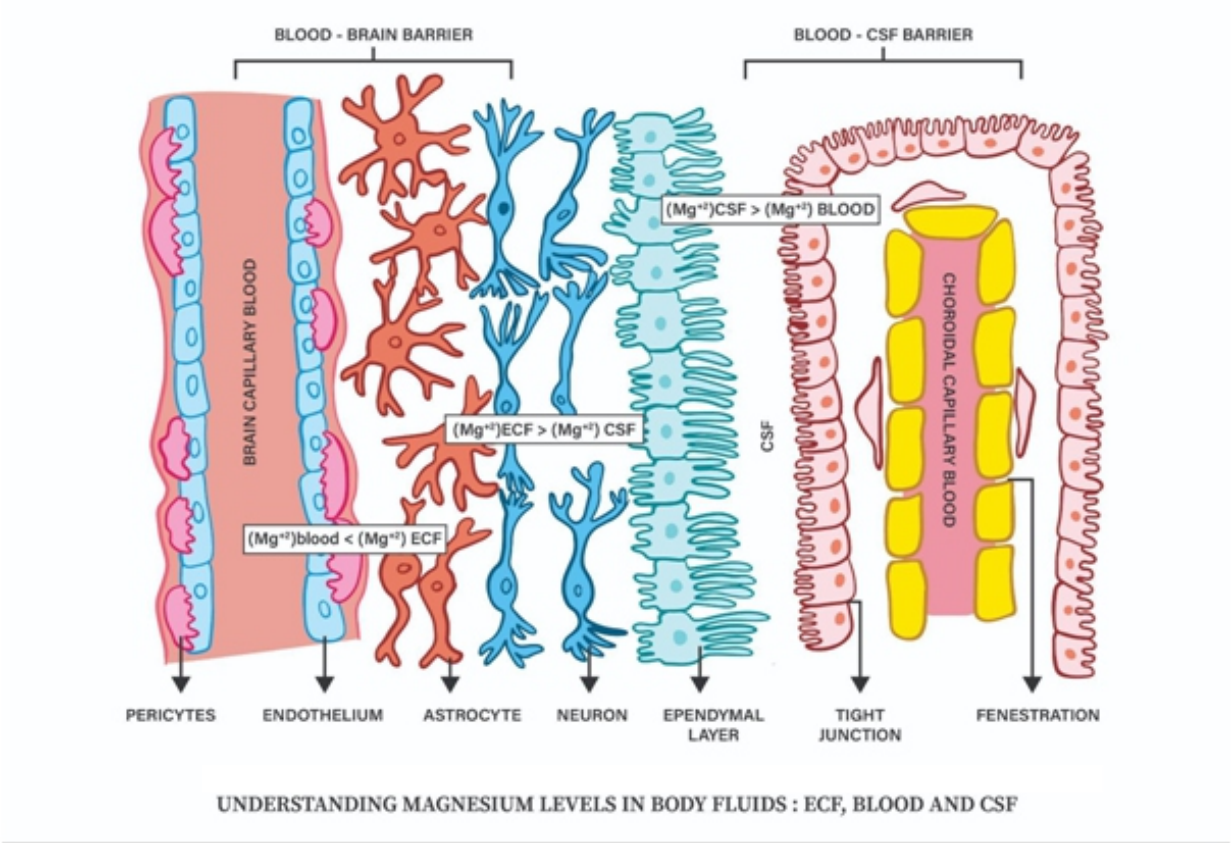

Figure 4: Understanding Magnesium Levels in Body Fluids
The diagram illustrates magnesium (Mg^{2+}) distribution across the blood-brain barrier, blood-cerebrospinal fluid (CSF) barrier, and within extracellular fluid (ECF), highlighting the higher Mg^{2+} concentration in ECF compared to blood, and in CSF compared to blood.

Cerebrospinal fluid (CSF), which surrounds the brain and spinal cord, exists in a normal adult human body at about 100 to 150 mL It serves as a mechanical barrier and is produced by the filtration of blood and active transport of molecules such as nutrients, hormones, metal ions, and metabolites across the ependymal cells in the choroid plexus at a rate of 0.2 to 0.7 mL per minute. CSF Mg^{2+} concentrations are higher than those in blood, indicating active Mg^{2+} transport from the blood into CSF. Changes in CSF Mg^{2+} levels correlate with extracellular Mg^{2+} around neurons, affecting neural activities. Thus, CSF Mg^{2+} is closely related to various brain functions. Notably, CSF Mg^{2+} levels and cognitive functions have shown a positive correlation. Additionally, intracellular Mg^{2+} levels in erythrocytes significantly correlate with CSF Mg^{2+} in the hippocampus and with hippocampal synapse density and recognition and memory performance, suggesting that erythrocyte Mg^{2+} levels are a good indicator of recognition and memory. These findings highlight the importance of Mg^{2+} homeostasis in the human body for brain functions, particularly synaptic connectivity.

The magnesium concentration in cerebrospinal fluid (CSF) is 1.3 times higher than in the blood. This indicates a selective transport mechanism at the choroid plexus epithelium. Magnesium concentration in the extracellular fluid is higher than in the blood but lower than in the CSF[7].

Cellular Distribution and Physiological Roles of Magnesium

Magnesium (Mg2+) stands as the most abundant divalent cation within mammalian cells, with a total concentration typically ranging between 17 and 20 mM . Maintaining a relatively stable gap between the cytosolic magnesium concentration ([Mg2+] cyto) and extracellular free magnesium concentration ([Mg2+] ex) is vital, usually within less than twofold. Despite the

electrochemical equilibrium suggesting a resting concentration of 50 mM for Mg2+ in the cytosol, only a slight change in [Mg2+] cytosol is observed even under conditions of Mg2+ mobilization. Cells employ various mechanisms to maintain intracellular magnesium within a narrow range, balancing influx, efflux, and stored magnesium levels. Mg2+ transport requires considerable energy due to its unique properties, including tight binding to water molecules and a large hydrated radius compared to its ionic radius. Although several Mg2+-transporting proteins are identified, their association with neurophysiology remains largely unexplored.

Cellular Distribution

1. *Cytosol*
   Mg2+ in the cytosol forms complexes with a wide array of biomolecules, with adenosine 5′-triphosphate (ATP) serving as a major intracellular pool due to its abundance and high binding affinity . Fluctuations in [Mg2+]cyto, even minor ones, can significantly impact cellular processes due to changes in the distribution of Mg-complexed biomolecules.

2. *Nuclei*
   Nuclear magnesium concentration ([Mg2+]nuc) varies depending on physiological conditions, with Mg2+ playing a crucial role in neutralizing the negative charges of chromatin, nucleic acids, and free nucleotides. [Mg2+]nuc affects cell mitosis, chromatin folding, and gene expression regulation.

3. *Mitochondria*
   Mitochondria serve as a major cellular magnesium pool and are key regulators of intracellular magnesium homeostasis. Mg2+ in mitochondria influences various functions, including mitochondrial energy metabolism, the apoptotic process, mitochondrial calcium homeostasis, and mitochondrial DNA functions.

4. *Endo(sarco)plasmic Reticulum*
   The endoplasmic reticulum (ER) accumulates Mg2+ and contributes to intracellular magnesium homeostasis. Mg2+ inhibits inositol-1,4,5-trisphosphate receptors (IP3R) and ryanodine receptors (RyR), which play essential roles in Ca2+ signaling in neurons.

5. *Ribosomes*
   Ribosomes, essential for protein synthesis, chelate significant amounts of Mg2+ and are closely associated with cytosolic magnesium levels. Mg2+ regulates protein synthesis via its effects on ribosomal functions through the mechanistic target of rapamycin (mTOR) pathway.

Physiological Roles of Cellular Mg2+

Magnesium interacts with numerous biomolecules, serving as a modulator of enzymatic activities, a cell protector against stress, a regulator of ion channels, and a stabilizer of DNA/RNA structures. Dysregulation of Mg2+ homeostasis is implicated in various diseases, including neurodegenerative diseases, diabetes mellitus, and metabolic syndrome.
Intracellular Mg^{2+} plays crucial roles in various biochemical processes due to its ability to neutralize negatively charged biomolecules like RNA/DNA, reactive oxygen species (ROS), and ATP. It acts as a counterion for these molecules, ensuring their stability and functionality. Dysregulation of Mg^{2+} homeostasis is linked to several disease conditions, including neurodegenerative diseases, diabetes mellitus, and metabolic syndrome.

Biochemical Reactions in Cells
Mg^{2+} influences over 600 enzymatic reactions, particularly those involved in energy metabolism, protein synthesis, and signal transduction. Its presence is essential for ATP-related biochemical reactions, as it stabilizes ATP molecules. Fluctuations in intracellular Mg^{2+} levels affect the energetic of these reactions. Mg^{2+} also competes with other ions like Ca^{2+} and protons, impacting cellular biochemistry in organelle-specific manners.

Intracellular Signaling
Mg^{2+} enhances the activity of protein kinases and thus modulates intracellular signal transduction. While its role as a second messenger has been debated, Mg^{2+} mobilization in response to biological stimuli suggests its involvement in cellular responses. Mg^{2+} regulates cellular processes in a cell-type specific manner and may function as a signal amplifier, particularly in neural development and plasticity.

Reactive oxygen species (ROS) Toxicity
Mg^{2+} suppresses the production of reactive oxygen species (ROS) in various tissues, including the brain. Its physicochemical properties allow it to react with ROS intermediates, protecting cells from oxidative damage.

Channel Regulation

Mg^{2+} regulates ion channels, such as the N-methyl-D-aspartate (NMDA) receptor in neurons. Its presence blocks the NMDA receptor, affecting neuronal excitability and neurotransmission.

DNA Protection and Genome Stability

Mg^{2+} stabilizes DNA and chromatin structures, protecting them from damage caused by ROS. It also serves as a cofactor in DNA replication and repair processes, ensuring accurate transfer of genetic information and maintaining genome stability.

In a nutshell, cellular Mg^{2+} plays diverse and essential roles in maintaining cellular function and homeostasis, impacting processes ranging from energy metabolism to DNA stability. Its dysregulation can lead to various pathological conditions, emphasizing the importance of maintaining adequate Mg^{2+} levels for overall health.

Formation of Neural Networks and Synaptic Activities

Role of Mg^{2+} in Neural Development

Mg^{2+} is crucial for cellular and tissue-level growth and differentiation. In developing neurons, neurotransmitter-induced increase in cytoplasmic Mg^{2+} mobilized from mitochondria stimulates mTOR activities, facilitating neural network maturation. mTOR activation promotes dendritic arborization and protein synthesis, essential for neurogenesis.

Involvement of TRPM7 Channel in Neuronal Development

TRPM7 channel plays a significant role in intracellular Mg^{2+} homeostasis. Its contribution to embryonic development remains debated, but studies suggest its involvement in Mg^{2+} transport and neural development. TRPM7-mediated Mg^{2+} influx is crucial for growth cone pathfinding and neurite outgrowth by enhancing mTOR activation while preventing axonal overgrowth via ROS regulation.

Regulation of Electrical and Chemical Synapses by Mg^{2+}

Mg^{2+} controls the strength of electrical gap junctions, influencing long-term plasticity.

Action potential-triggered Mg^{2+} influx coordinates chemical and electrical synaptic activities, contributing to synaptic plasticity and neural network formation.

Neural Cell Fate Determination

Magnesium-L-threonate (MgT) increases neural stem cell (NSC) numbers and promotes differentiation into neurons in vivo, but not in vitro.

Mg2+ levels decline during brain development, correlating with the sequence of NSC differentiation into neurons and glia.

TRPM7 channels are involved in the proliferation and migration of astrocytes via ERK and JNK signaling pathways, impacting neuronal cell proliferation and differentiation.

In short, Mg^{2+} plays diverse roles in neural development, including regulating mTOR activity, guiding neurite outgrowth, controlling synaptic strength, and influencing NSC fate determination. TRPM7 channels are central to Mg^{2+} homeostasis and contribute significantly to various aspects of neural development and function.

Role of Magnesium in Parkinson`s Disease

Parkinson's disease (PD) is a debilitating neurodegenerative disorder characterized by symptoms like tremors and rigidity. These symptoms primarily arise from the loss of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies. Recent research has highlighted the significant role of magnesium ions (Mg^{2+}) in PD pathology.

Low levels of Mg^{2+} in the cerebrospinal fluid (CSF) of PD patients, along with evidence linking magnesium deficiency to a higher risk of developing PD, underscore the importance of this mineral in the disease. Additionally, mutations in Mg^{2+}-transporting proteins such as TRPM7 and SLC41A1 have been found in some familial PD cases, indicating a genetic link to magnesium dysregulation in PD.

Mg^{2+} has been shown to protect dopaminergic neurons from neurotoxicity caused by toxins like MPP+, suggesting it has a neuroprotective role. Furthermore, impaired Mg^{2+} influx has been associated with reduced cell viability in PD models, highlighting the critical role of Mg^{2+} homeostasis. Mg^{2+} also directly inhibits the aggregation of α-synuclein, a protein closely linked to PD pathology, suggesting its potential therapeutic importance in slowing PD progression.

These findings collectively emphasize the multifaceted role of Mg^{2} in PD, suggesting further research and potential therapeutic strategies targeting Mg^{2+} dysregulation could be beneficial in managing PD. Mutations in Mg^{2+}-transporting proteins, low Mg^{2+} levels, and impaired Mg^{2+} influx are correlated with neuronal toxicity and α-synuclein aggregation,

key aspects of PD pathology.

Role of Magnesium in Alzheimer's Disease

Alzheimer's disease (AD) is characterized by the accumulation of amyloid β (Aβ) plaques and hyperphosphorylated tau proteins, leading to neuronal degeneration and cognitive decline, especially in individuals over 65 years old. AD patients often exhibit lower levels of Mg^{2+} in cerebrospinal fluid and brain tissue, correlating with more severe symptoms. Mg^{2+} deficiency is linked to emotional memory dysfunction, while Mg+2 supplementation improves learning, memory, and cognitive function, even after brain injury. In AD pathology, Aβ accumulation is influenced by extracellular Mg^{2+} levels, with higher Mg^{2+} concentrations preventing Aβ-induced reduction of synaptic NMDA receptors. MgT treatment reduces Aβ aggregation and neuronal toxicity, preventing cognitive deficits and synaptic loss in transgenic mouse models of AD. Additionally, Mg^{2+} in the blood-brain barrier reduces Aβ influx and promotes its clearance. MgSO4 treatment attenuates impairments in long-term potentiation and dendritic abnormalities in AD model rats by inhibiting GSK-3β and activating the PI3K/Akt signaling pathway. Furthermore, MgT suppresses inflammation triggered by Aβ oligomers by reducing TNF-α expression and inhibiting factors promoting Aβ synthesis, thus protecting neuronal function in AD pathology. Overall, Mg^{2+} influx appears to play a crucial role in mitigating the inflammatory mechanisms and preserving neuronal function in Alzheimer's Disease[8].

Association between Serum Magnesium and Type 2 Diabetes

The prevalence of diabetes has been escalating as an epidemic in India and world over. Magnesium plays a significant role in glucose and insulin metabolism and therefore, maintaining an appropriate level of serum magnesium is crucial for diabetic individuals[9]. There is a recognized relationship between serum magnesium levels and type 2 diabetes. Recent studies have indicated that low serum level of magnesium may contribute to insulin resistance and increases the risk of diabetes[10,11]. A retrospective, observational, cross-sectional study was conducted on 1694 patients. A linear regression analysis indicated associations between serum magnesium levels and fasting plasma glucose and HbA1c. The study found that serum magnesium levels decrease with increasing HbA1c. The exact mechanisms are not completely understood, but elevated urinary magnesium loss may account for observed low serum magnesium levels in diabetic patients with poor glycemic control[12].

Magnesium Deficiency: An Overview

Magnesium is a vital mineral involved in numerous bodily functions. It is essential for over 300 enzymatic reactions, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation. Magnesium is also required for energy production, oxidative phosphorylation, and glycolysis.

Hypomagnesemia and Magnesium Deficiency

While hypomagnesemia (low serum magnesium levels) and magnesium deficiency (total body magnesium depletion) are often used interchangeably, they are not the same. A person can have normal serum magnesium levels despite total body magnesium depletion, and significant hypomagnesemia can occur without a total body deficit. Hypomagnesemia often goes undetected, with studies showing that only 10% of hypomagnesemic patients had magnesium requested for testing.

Etiology and Pathogenesis of Hypomagnesemia

1. Redistribution
   Hypomagnesemia can result from the shift of magnesium from extracellular fluid into cells or bones. This is seen in refeeding syndrome (in starved patients), treatment of metabolic acidosis and`Hungry bone syndrome` (post-parathyroidectomy or in patients with osteoblastic metastases)

2. Gastrointestinal Causes
   Pure magnesium deficiency from reduced dietary intake is rare in healthy individuals. It can occur in patients on magnesium-free intravenous fluids or total parenteral nutrition, particularly those with initially low serum magnesium. An inherited disorder of isolated magnesium malabsorption can cause hypomagnesemia with hypocalcemia, tetany, and seizures, usually presenting in infants with convulsions and other symptoms due to a mutation in the TRPM6 gene.

3. Renal Causes
   Proximal tubular reabsorption of magnesium is proportional to sodium reabsorption, and reductions in sodium reabsorption can lead to magnesium deficiency. Chronic renal failure can lead to obligatory renal

magnesium loss. In diuretic phase of acute renal failure, post-obstructive diuresis, and renal transplantation can also result in hypomagnesemia. Inherited disorders of renal tubular reabsorption of magnesium do exist but lack a consensus on classification.

4. Drugs

Several drugs, including antibiotics and chemotherapeutic agents, cause magnesium wasting.

Loop diuretics inhibit magnesium transport in the TAL, causing magnesium depletion, especially with long-term use. Thiazide diuretics, which act on the DCT, may not cause immediate magnesium wasting, but long-term use can lead to substantial depletion.

Cisplatin, a chemotherapy agent, frequently causes magnesium wasting, leading to hypomagnesaemia, hypocalciuria, and hypokalemia. The incidence of hypomagnesaemia increases with cumulative doses, with chronic hypomagnesaemia developing around three weeks after initial chemotherapy and usually persisting.

In a nut shell, hypomagnesaemia can arise from redistribution of magnesium within the body, reduced dietary intake, impaired intestinal absorption, increased gastrointestinal or renal loss, and the use of certain drugs. It often goes undetected but can have significant health impacts, particularly in acutely ill patients or those undergoing specific treatments.

Despite the normal serum range being 1.5 to 3.0 mEq/L, serum magnesium is a poor indicator of total body magnesium, as only a small fraction is present in serum. Magnesium distribution in the body is approximately 53% in bone, 27% in muscle, 19% in soft tissues, and just 3% in serum. Magnesium deficiency is relatively common, particularly among critically ill patients, with incidence rates reported as high as 65%. This deficiency significantly impacts mortality rates, as seen in the doubling of mortality in affected individuals.

Clinical Manifestations of Magnesium Deficiency

Biochemical Effects

1. Hypokalemia caused by renal potassium wasting and decreased intracellular potassium levels
2. Hypocalcemia results from impaired secretion of parathyroid hormone, resistance to its effects in the kidneys and bones, and resistance to vitamin D

Neuromuscular Symptoms

1. Tetany that causes spontaneous carpal-pedal spasms
2. Seizures
3. Movement Disorders: Vertigo, ataxia, nystagmus, as well as athetoid and choreiform movements
4. Muscle Issues: Muscular weakness, tremors, fasciculations, and muscle wasting
5. Psychiatric Manifestations: It include Mood and Cognitive Disorders, Depression and Psychosis

Cardiovascular Problems

1. Dysrhythmias: These includes ventricular tachycardia (*torsade de pointes*), atrial fibrillation, and supraventricular tachycardia
2. Hypertension and Vasospasm
3. ECG Changes: Prolonged QT and PR intervals, widened QRS complex, peaked T waves, and ST depression

Risk Groups for Magnesium Deficiency

1. Older Adults: Decreased dietary intake and absorption
2. People with Gastrointestinal Diseases: Conditions that impair absorption
3. Individuals with Type 2 Diabetes: Increased urinary loss
4. Alcoholics: Increased excretion and decreased absorption
5. People on Certain Medications: Diuretics, proton pump inhibitors, and some antibiotics
6. Athletes: Increased magnesium loss through sweat

Diagnosis of Magnesium Deficiency

- Clinical Assessment: Evaluation of symptoms and dietary intake
- Laboratory Tests: Serum magnesium levels, although these may not always accurately reflect total body magnesium stores

Treatment and Management

1. *Dietary Changes*: Increasing intake of magnesium-rich foods such as:
   - Green leafy vegetables (spinach, kale)
   - Nuts and seeds (almonds, sunflower seeds)
   - Whole grains (brown rice, quinoa)
   - Legumes (black beans, chickpeas)
   - Dairy products (milk, yoghurt)

- Fish (mackerel, salmon)
- Fruits (bananas, avocados)

2. *Supplementation*: Magnesium supplements may be recommended for those at risk of deficiency. Common forms include magnesium oxide, magnesium citrate, and magnesium chloride.

3. Addressing Underlying Conditions: Managing conditions that affect magnesium absorption or increase magnesium loss.

4. Lifestyle Modifications: Reducing alcohol intake, managing diabetes effectively, and being cautious with medications that affect magnesium levels.

Recommended Dietary Allowance (RDA)

The RDA for magnesium varies by age, sex, and life stage. For adult men, it is 400-420 mg per day, and for adult women, it is 310-320 mg per day. Higher amounts are recommended for pregnant (350-360 mg/day) and lactating women (310-320 mg/day).

Prevention

- Balanced Diet: Consuming a variety of magnesium-rich foods
- Awareness of Magnesium Inhibitors: Reducing intake of magnesium inhibitors like excessive alcohol and certain medications
- Supplementation When Necessary: Using magnesium supplements in populations at risk for deficiency

Magnesium deficiency can lead to a range of health issues, particularly affecting muscle and nerve function, cardiovascular health, and metabolic processes. Ensuring adequate magnesium intake through diet or supplements is crucial for maintaining overall health and well-being [13].

CONFLICTS OF INTEREST: None

FINANCIAL SUPPORT: None

REFERENCES

1. Ismail AA, Ismail NA. Magnesium: A mineral essential for health yet generally underestimated or even ignored. J. Nutr. Food Sci. 2016 Oct 12; 6(2):1-8.
2. Razzaque MS. Magnesium: are we consuming enough? Nutrients. 2018; 10(12):1863.
3. Schwalfenberg GK, Genuis SJ. The importance of magnesium in clinical healthcare. Scientifica. 2017; 2017(1):4179326.
4. Barbagallo M, Veronese N, Dominguez LJ. Magnesium in aging health and diseases. Nutrients. 2021; 13(2):463.
5. Watson H. Magnesium metabolism. In: Reference Module in Biomedical Sciences [Internet]. Elsevier; 2014 [cited 2024 Jun 7].
6. de Baaij JH. Magnesium reabsorption in the kidney. Am. J. Physiol. Renal Physiol. 2023; 324(3):F227-44.
7. Yamanaka R, Shindo Y, Oka K. Magnesium is a key player in neuronal maturation and neuropathology. International journal of molecular sciences. 2019 Jul 12; 20(14):3439.
8. Maier JA, Locatelli L, Fedele G, Cazzaniga A, Mazur A. Magnesium and the brain: A focus on neuroinflammation and neurodegeneration. International journal of molecular sciences. 2022 Dec 23; 24(1):223.
9. Yang J, Zhang H, Cao Y, et al. The association of dietary magnesium and prediabetes in childbearing Chinese women: results from China Nutrition and Health Surveillance (2015-2017) Nutrients.2022; 14 (21).doi:10.3390/nu14214580.
10. Li W, Jiao Y, Wang L, et al. Association of serum magnesium with insulin resistance and type 2 diabetes among adults in China. Nutrients. 2022; 14(9). Doi: 10.3390/nu 14091799.
11. Ng HY, Kuo WH, Tain YL, et al. Effect of dapagliflozin and magnesium supplementation on renal magnesium handling and magnesium homeostasis in metabolic syndrome. Nutrients. 2021; 13(11). Doi: 3390/nu 13114088.
12. Luo B, Pan B, Zhao G Li J, Sun Li. Association between serum magnesium levels and glycemic control in type 2 diabetes. Diabet Metab Synd Ob. 2024; 17:2823-2829.
13. Seo JW, Park TJ. Magnesium Metabolism. Department of Internal Medicine, College of Medicine and Kidney Research Institute, Hallym University, Seoul, Korea.