International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

An Overview on Magnesium Homeostasis in Chronic Kidney Disease

Mostafa Mahmoud Salah Ibrahim[1], Ezzat Mostafa Mohammed[1] , Hossam Eldin Mansour Abdel Rahman[2] , Abeer Abd Alla Fikry Abdel-Rahaman [3], George Emad Shaker [1], Amr Galal Ibrahim Yousef [1], Malak Emad Samy, Ahmed Ezzat Mostafa[1], Fatima Al Taher Taha Morsi[1]

1 Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt

2 Radio- Diagnosis Department, Faculty of Medicine, Zagazig University, Egypt

3 Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Amr Galal Ibrahim Yousef

Email: Dramrgalal@gmail.com,

Abstract:

Magnesium is an essential mineral that plays a pivotal role in enzymatic reactions, neuromuscular function, cardiovascular stability, and bone metabolism. In patients with chronic kidney disease (CKD), impaired renal excretion alters magnesium homeostasis, predisposing individuals to either hypomagnesemia or hypermagnesemia depending on the disease stage, comorbidities, and dialysis status.

Keywords: Magnesium, chronic kidney disease, homeostasis, dialysis, mineral metabolism, vascular calcification

Introduction:

Magnesium is the fourth most abundant cation in the human body, serving as a cofactor in more than 300 enzymatic reactions that regulate energy metabolism, protein synthesis, and neuromuscular stability **(1).**

In the kidney, approximately 70% of filtered magnesium is reabsorbed in the loop of Henle, with further fine-tuning in the distal tubules, reflecting a tightly regulated process that maintains serum concentrations within a narrow physiological range **(2).**

Chronic kidney disease (CKD) disrupts this balance due to progressive nephron loss, altered tubular handling, and frequent use of medications that interfere with magnesium absorption or excretion **(3).**

Hypomagnesemia in CKD has been linked to higher cardiovascular risk, increased insulin resistance, and all-cause mortality, highlighting its importance as a prognostic marker **(4).**

Conversely, hypermagnesemia is common in advanced CKD and dialysis patients, often resulting from impaired renal clearance or magnesium-based therapies, and may cause neuromuscular dysfunction and arrhythmias **(5).**

Emerging evidence suggests that maintaining magnesium homeostasis may help mitigate vascular calcification, mineral bone disorder, and inflammation, thus potentially improving long-term outcomes in CKD populations **(6).**

Magnesium Biological Role

Magnesium is the second most abundant intracellular cation and the fourth most abundant cation in the body. About 99% of total magnesium is located in bone, muscles and non-muscular soft tissue. Extracellular magnesium accounts for about 1% and is primarily found in serum and red blood cells. Humans have to consume magnesium regularly to prevent a deficiency. The Institute of Medicine recommends 310–360 mg and 400–420mg for adult women and men, respectively **(7)**.

Magnesium plays an essential physiological role in many intracellular functions of the body. This role is achieved through two important properties of magnesium; the ability to form chelates with important intracellular anionic-ligands, especially ATP, its ability to compete with calcium for binding sites on proteins and membranes, modulates insulin signal transduction and cell proliferation, and is important for cell adhesion and membrane transport **(8).** Magnesium is essential for the synthesis of nucleic acids and proteins, for intermediary metabolism and for specific actions in different organs such as the neuromuscular and cardiovascular systems **(9)**.

Magnesium plays an important role in numerous enzymatic reactions, transport processes and synthesis of proteins, DNA and RNA. Over 300 enzymes are dependent on magnesium. Magnesium containing compounds present promising oral phosphate binders for the treatment of hyperphosphataemia in patients with chronic kidney disease (CKD) **(1)**.

Prevalence of hypomagnesaemia is high in the general population and especially in intensive care unit patients, but often not being detected. Magnesium deficiency increases the risk for several diseases, like diabetes mellitus type 2, hypertension and atherosclerosis. Moderate hypermagnesaemia, however, seems to have beneficial effects on vascular calcification and mortality rates in CKD patients **(10)**.

On the other hand, higher serum magnesium levels are reported to be linked to lower PTH levels and results on the effects on bone are controversial. In addition, low magnesium levels are associated with low bone mass, osteoporosis and vascular calcification. In dialysis patients serum magnesium levels are dependent mainly on the dialysate magnesium concentration **(11)**.

Magnesium Metabolism and Physiology

Intestine, bone and kidneys maintain magnesium homeostasis (Figure 1): Magnesium is absorbed in the gut, stored in bone and muscles and excreted by the kidneys. The majority of magnesium is absorbed by a passive paracellular mechanism in the ileum and distal parts of the jejunum, while a smaller amount is actively transported in the large intestine **(12)** .

Around 24–76% of ingested magnesium is absorbed in the gut and the remaining is eliminated in the feces. The proportion of absorbed magnesium from the gut depends on the amount of ingested magnesium and the status of magnesium in the body. The lower the magnesium level, the more is absorbed **(1)**.

Besides intestinal uptake renal excretion is crucial in maintaining magnesium balance. In kidneys a mechanism comparable to the intestinal uptake regulates magnesium reabsorption. The glomeruli filter around 2400 mg of magnesium per day. About 95% of excreted magnesium is reabsorbed, mainly by the thick ascending limb of the loop of Henle (65%) and to a lesser extent in the distal tubules (30%). the filtered magnesium is reabsorbed in a passive paracellular fashion. Only around 100 mg of magnesium is excreted in the urine each day, and the kidneys can regulate the amount excreted, depending on the serum level of magnesium **(13)**.

In moderate CKD (stage 1-3) loss of renal function is compensated by an increased fractional excretion of magnesium, while this mechanism fails in advanced CKD resulting in hypermagnesaemia. In dialysis patients, serum magnesium levels mainly depend on dialysate magnesium and dietary intake. The most common test for the assessment of the magnesium status is the measurement of serum magnesium levels – a practicable and inexpensive test **(14)**.

However, it should always be kept in mind that serum magnesium levels do not reflect the total body magnesium status. Reference ranges for serum magnesium levels are 0.65–1.05mmol/L for total magnesium and 0.55–0.75mmol/L for ionized magnesium in adult blood serum. The prevalence of hypomagnesaemia in hospitalized patients is high especially in patients on postoperative intensive care units **(15)**.

In the general population, hypomagnesaemia frequently occurs in patients with diabetes, chronic gastrointestinal diseases, alcoholism and after the use of certain types of drugs. A small but interesting group of patients have a hypomagnesaemia that is the result of genetic mutations. Specifically, mutations in genes that encode ion transporters in the distal convoluted tubule can explain many familial forms of hypomagnesaemia **(16)**

In particular mutations in the TRPM6 magnesium channel have been shown to account for the largest part of the genetic forms of hypomagnesaemia. **(17)** .

Clinical signs of both hypo- & hypermagnesemia are non-specific, can be similar or even absent. Signs include loss of appetite, fatigue and weakness, later on, as magnesium deficiency worsens, numbness, cramps, seizures, personality changes, arrhythmias and coronary spasms. Severe hypermagnesaemia might lead to CNS depression or loss of deep tendon reflexes, hypotension, gut paralysis and ECG-changes. At very high and very low serum magnesium levels severe neuromuscular dysfunction, hypotonia and even pseudoparalysis, respiratory depression, areflexia and coma may develop **(18)**.

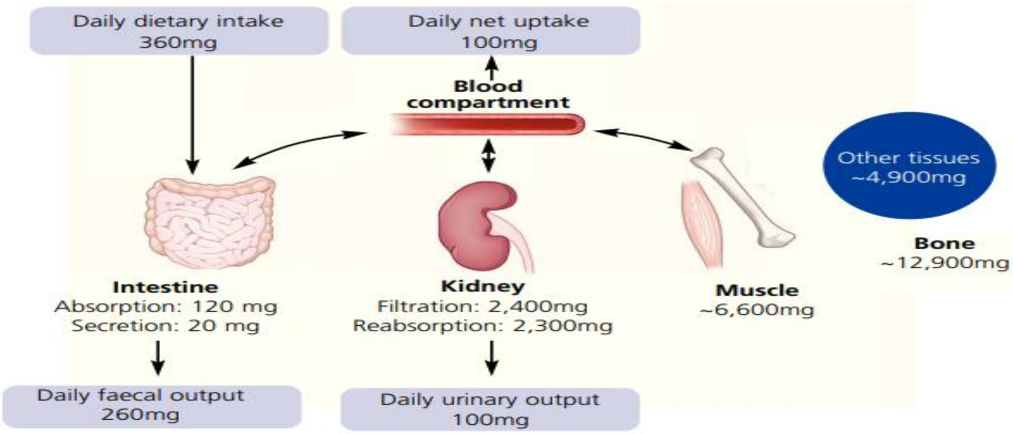

Figure 1: Regulation of magnesium homeostasis (13).

References:

1. de Baaij, J. H. F., Hoenderop, J. G. J., & Bindels, R. J. M. (2015). Magnesium in man: Implications for health and disease. Physiological Reviews, 95(1), 1–46.
2. Quamme, G. A. (2010). Molecular identification of ancient and modern mammalian magnesium transporters. American Journal of Physiology-Renal Physiology, 298(6), F1071–F1081.
3. van Laecke, S. (2019). Hypomagnesemia and hypermagnesemia. Acta Clinica Belgica, 74(1), 41–47.
4. Pham, P. C. T., Pham, P. M. T., Pham, S. V., Miller, J. M., & Pham, P. T. T. (2014). Hypomagnesemia in patients with type 2 diabetes. Clinical Journal of the American Society of Nephrology, 2(2), 366–373.
5. Markovits, N., Loebstein, R., Bank, I., Halkin, H., & Loebstein, R. (2014). Clinical manifestations of hypermagnesemia in chronic kidney disease. American Journal of Medicine, 127(1), 1–6.
6. Sakaguchi, Y., Hamano, T., Isaka, Y. (2018). Magnesium and progression of chronic kidney disease: Benefits beyond cardiovascular protection. Advances in Chronic Kidney Disease, 25(3), 274–280.
7. Nielsen, F. H. 2017. Magnesium: Basic Nutritional Aspects. Molecular, Genetic, and Nutritional Aspects of Major and Trace Minerals. Elsevier. 307-317.
8. Zhang, Y., Xu, J., Qin, L. & Jiang, Q. 2016. Magnesium and osteoarthritis: from a new perspective. Annals of Joint, 1.
9. Dent, A. & Selvaratnam, R. 2022. Measuring magnesium–Physiological, clinical and analytical perspectives. Clinical Biochemistry, 105, 1-15.
10. Fritzen, R., Davies, A., Veenhuizen, M., Campbell, M., Pitt, S. J., Ajjan, R. A., et al. 2023. Magnesium Deficiency and Cardiometabolic Disease. Nutrients, 15.
11. Hori, M., Yasuda, K., Takahashi, H., Yamazaki, C., Morozumi, K. & Maruyama, S. 2021. Impact of serum magnesium and bone mineral density on systemic fractures in chronic hemodialysis patients. PLoS One, 16, e0251912.
12. Gröber, U., Schmidt, J. & Kisters, K. 2015. Magnesium in Prevention and Therapy. Nutrients, 7, 8199-226.
13. Al Alawi, A. M., Majoni, S. W. & Falhammar, H. 2018. Magnesium and human health: perspectives and research directions. International journal of endocrinology, 2018, 9041694.

14. Matias, P., Ávila, G., Ferreira, A. C., Laranjinha, I. & Ferreira, A. 2023. Hypomagnesemia: a potential underlooked cause of persistent vitamin D deficiency in chronic kidney disease. Clinical Kidney Journal, 16, 1776-1785.
15. Elkady, G. A., GabAllah, R. R. & Mansour, A. Z. 2017. Magnesium in intensive care unit: a review. The Egyptian Journal of Hospital Medicine, 68, 1497-1504.
16. Gragossian, A., Bashir, K., Bhutta, B. & Friede, R. 2023. Hypomagnesemia. 2022. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
17. Si, G.-F., Ge, Y.-X., Lv, X.-P., Li, Y.-Q., Chen, X.-M. & Yuan, X.-M. 2024. Case report: Near-fatal hypermagnesemia resulting from the use of Epsom salts in a patient with normal renal function. Frontiers in Medicine, 11, 1416956.
18. Van Laecke, S. 2023. An Update on Hypomagnesemia and Hypermagnesemia. Kidney and Dialysis, 4, 1-14.