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Prevalence of Hypomagnesemia in Hemodialysis Patient: An Approach to Understand Risk Factors

Conflict of interest: nothing to declare.
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Abstract

Introduction. In medicine, magnesium (Mg) is termed a forgotten ion. Hypomagnesemia is characterized by a serum Mg level of less than 0.65 mmol/l. Intake of alcohol, antibiotics (pentamidine, amphotericin B, and aminoglycosides), digoxin, calcineurin, proton pump inhibitors, diuretics (thiazide and loop), and antineoplastic drugs are major risk factors for hypomagnesemia. Hypomagnesemia causes hypophosphatemia, hypokalemia, nephrocalcinosis, Gitelman syndrome, and EAST syndrome.
Purpose. To assess the factors leading to plasma magnesium deficiency and evaluating the prevalence of hypomagnesemia in CKD patients after hemodialysis.
Materials and methods. The present study examines the occurrence and possible factors influencing hypomagnesemia in CKD patients on hemodialysis. 100 participants with CKD patients under hemodialysis were recruited in the present study. A proper questionnaire and consent forms were obtained from patients. The baseline and chronic diseases (diabetes mellitus, hypertension, and ischemic heart disease) were evaluated. The blood parameters (serum Mg, parathyroid hormone, serum calcium, serum uric acid, serum phosphate, hemoglobin, and ferritin) were analyzed using a biochemical analyzer. The drugs prescribed to CKD patients were also analyzed for their effect on hypomagnesemia.
Results. Findings indicated that the dialysis duration (<1 year) influences the magnesium level. Diabetes mellitus and ischemic heart disease positively correlated with hypomagnesemia in CKD patients. The blood parameters, except serum phosphate, did not present significance with hypomagnesemia. The drug prescribed for CKD patients displayed high significance for hypomagnesemia.
Conclusion. A history of diabetes and IHD may be one of the risk factors for hypomagnesemia in individuals with CKD, and it may also operate as a mediator in the disease's progression.
Keywords: magnesium, Diabetes mellitus, CKD, hypomagnesemia, angiotensin-converting enzyme inhibitors

■ INTRODUCTION

Chronic kidney disease (CKD) is clinically characterized by a deformity in renal function or structure for more than three months, and it is an irreversible and slow process [1]. An individual adult is specified as a CKD patient if they have a glomerular filtration rate (GRF) greater or lesser than 60 ml/min/1.73 m^2 for a duration of three or more months but with damage to the structure of the kidney and filtration below 15 ml/min/1.73 m^2 is kidney failure. Approximately 850 million people worldwide are affected by CKD (1 to 5 stages) [2]. In India, the prevalence of CKD is 17%, according to the International Society of Nephrology's Kidney Disease [3]. The pathogenesis of CKD involves two possible mechanisms: an initial trigger and a perpetuating mechanism. The initial trigger or stimulus is the baseline problem caused by an immune- or inflammation-mediated reaction or toxic substance. Hypertrophy and hyperfiltration perpetuate kidney damage [4]. There are five stages in CKD based on glomerular performance: G1 (high or normal GFR), G2 (mildly decreased GFR), G3a (mildly to moderately decreased GFR), G3b (moderately to severely decreased GFR), G4 (severely decreased GFR), and G5 (kidney failure). The people display symptoms including reduced urine output, albuminuria, shortness of breath, nausea, vomiting, loss of appetite, lethargy, fatigue, and itching. However, CKD patients are usually asymptomatic in their initial stages [5]. Diabetes mellitus (DM) type-2, glomerulonephritis, hypertension, obesity, polycystic kidney disease, heart disease, acute kidney injury, alcoholism, and smoking are vital risk factors for CKD [6, 7]. The uremic syndrome was observed during the last stage of kidney disease. The screening of CKD patients includes a kidney profile test to estimate the serum creatinine and urea levels to measure GFR and albumin to creatinine ratio in urine, and imaging techniques (computerized tomography and ultrasound) are performed [8]. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, β-blockers, and sodium-glucose cotransporter 2 are prescribed to CKD patients in the early stages [9, 10]. Hemodialysis, peritoneal dialysis, and kidney transplantation are the renal therapies that support renal function. Among these dialysis methods, hemodialysis is an effective renal therapy that regulates the electrolyte (chloride, sodium, chloride, magnesium, potassium, and bicarbonate), fluid, acid-base balance, azotemia, and suppresses the conditions of the uremic syndrome [11].

Among the various electrolytes used in dialysate solution in hemodialysis, magnesium (Mg) levels have a crucial role because they are strongly associated with different risk factors for CKD. Mg is the second most common cation and the fourth most abundant mineral in the human body [12]. Over 300 enzymatic reactions in the body require Mg as a cofactor, synthesis of proteins, modulation of cell proliferation, reproduction, insulin and ATP metabolism, structural maintenance of DNA and RNA, blood pressure, and calcium and potassium ion transport through the transmembrane are major physiological functions controlled by Mg [13]. White and leafy green vegetables and whole grains are good sources of Mg. The optimal amount of Mg dietary intake for adults is 310–420 mg/day [14]. Bone serves as the reservoir for 60% of the Mg in the body, and the remaining is present in the soft tissue and muscles [13]. The three different forms in which serum Mg exists in the human body are: a) 5–15% – Mg attached to negative ions (anions), including sulfates, citrates, phosphates, and bicarbonates; b) 30% – Mg complexed to serum proteins (primarily albumin); and c) about 55–70% – ionized or free Mg, the active form present in total serum Mg [13]. Mg is usually engrossed mainly

in the small intestine and occasionally absorbed in the large intestine [15]. Transcellular and paracellular are two pathways in which Mg is absorbed. In the gastrointestinal tract (distal region), the transcellular absorption of Mg takes place through active transport by transient receptor channels (melastatin subtypes TRPM6 and TRPM7) [16]. 80% to 90% of Mg uptake is aided by paracellular absorption through passive transport. Primarily, the kidney regulates the filtration of Mg, and then it is reabsorbed in the thin limb of Henle's loop across the channels present in the occluding junction. The distal and proximal tubules are absorption sites for remaining Mg [17, 18].

The concentration of serum Mg levels from 0.7 to 1.1 mmol/l is normal. A serum Mg level below 0.66 mmol/l is hypomagnesemia and a serum above 1.1 mmol/l is hypermagnesemia [19]. The prevalence of magnesium deficiency (hypomagnesemia) is reported to be higher when compared to hypermagnesemia [20]. In the general population, 2.5% to 15% of the prevalence of hypomagnesemia and 12% to 20% of hypomagnesemia are reported in hospitalized patients [21]. Hypomagnesemia is associated with DM, cancer, stroke, depression, hypertension, fragility of bone, respiratory syndromes, migraine, dementia, Alzheimer's, and cardiovascular diseases [22]. An inverse relationship is found between DM type-2 and hypomagnesemia, and antidiabetic drugs (sodium-glucose cotransporter-2 inhibitors) can increase the Mg level [23].

An observational study conducted by Larsson et al. [24] in the general population has demonstrated an inverse relationship between heart failure, atrial fibrillation, ischemic stroke, cardiovascular mortality, and serum Mg concentration.

The cardiac system, muscles, and nerve membrane functions are altered due to hypomagnesemia. Hypomagnesemia may be accompanied by neuromuscular conditions (tetany, seizures, weakness, ataxia, psychosis, muscle cramps, vertigo, and depression) and cardiovascular system conditions (sensitivity to digoxin, ventricular arrhythmias, and supraventricular tachycardia) [25]. A recent study has suggested that Mg can reduce the vascular calcification mediated by phosphate, causing phosphate toxicity in the kidney. The phosphate and calcium crystallization, particularly caliprotein maturation, are deteriorated by Mg [26].

A mild elevation in plasma Mg concentration is observed during the advanced stages of renal disease because of the minimal excretion rate. The gastrointestinal absorption and concentration of Mg in dialysate determine the amount of Mg in hemodialysis patients [27]. Usually, Mg concentration in patients on hemodialysis is below the acceptable level of the treatment itself, diuretics, and proton pump inhibitors (PPI) [28–30].

The dietary intake of Mg and decreased serum Mg levels are associated with the progression of kidney disease and elevate the risk of CKD.

■ PURPOSE OF THE STUDY

To assess the factors leading to plasma magnesium deficiency and evaluating the prevalence of hypomagnesemia in CKD patients after hemodialysis.

■ MATERIALS AND METHODS

The samples were collected from 100 individuals under hemodialysis regularly after obtaining a questionnaire and consent form. The samples were collected for one year, from March 2022 to March 2023, from the Department of Nephrology, Basrah Teaching Hospital, based on the inclusion and exclusion criteria (Table 1). The questionnaire

contains information including basic details (age and gender), medical history, duration of dialysis, and drug history.

Table 1
Inclusion and exclusion criteria for sample recruitment

Inclusion criteria	Exclusion criteria
Age (18–70 years)	Salt wasting nephropathy
	Sepsis
Stable patient with euvolemic	Patients with critical illness
Patients on hemodialysis for more than three months with CKD (stage 5)	Elevated C-reactive protein
	History of kidney transplant
	Polycystic kidney disease

Treatment protocol

The machine used in the present study is the B Braun Dialog+ (2021) with a high-flow filter; the Diacap Ultra hemodialyzer filter used in our study has a surface area of 1.9 m, 1.6 m and 1.3 m. Average blood flow is 250±50 ml/min, and dialysate flow is 500–800 ml/min. The dialysis solution composition used in the present study is given in Table 2.

Table 2
Dialysate solution composition

Component	Concentration (mmol/l)
Magnesium	0.5
Sodium	138
Chloride	109
Potassium	2.0
Calcium	1.5
Bicarbonate	32
Glucose	1000
Acetate	3

Study variables

The following parameters were considered in the present study: baseline parameters (age 11–34, 35–59 and 60–84 years), gender, and duration of dialysis (>6 months and >1 year), chronic disease (DM, hypertension, and ischemic heart disease (IHD)), blood parameters (serum Mg, parathyroid hormone, serum calcium, serum uric acid, serum phosphate, hemoglobin, and ferritin), and drug history (PPI, loop diuretics, and ACE1/ARB). The results for the baseline parameters were obtained from the questionnaire. The chronic diseases were elevated using electrocardiograms and echocardiograms. The blood parameters were estimated using the Cobas C111 analyzer machine. All the blood parameters were categorized as normal, high, and low based on their normal range (1.6–2.5 mg/dl, 10–55 pg/ml, 8.5–10.5 mg/dl, 2.7–8.5 mg/dl, 2.8–4.5 mg/dl, 12.1–17.2 g/dl, and >200 ng/ml, respectively). The history of drugs involved was mostly prescribed to hemodialysis patients.

Statistical analysis

The data obtained from the present study was analyzed in SPSS version 21. The statistical significance among the various parameters was evaluated using Pearson's Chi-Square test at four different p values (P<0.05, P<0.01, P<0.005, and P<0.001).

■ RESULTS

This cross-sectional study used samples from 100 CKD patients on regular hemodialysis. The baseline parameters – gender, age, and duration of dialysis were coordinated with serum Mg levels in the patients to check whether these parameters affected the serum Mg level. Of 100 patients, 53% were male and 47% were female. CKD patients with three different age groups (11 to 34, 35 to 59, and 60 to 84 years) were considered in the present study; among these, 16% of patients fall under 11 to 34, 48% in 35 to 59, and 36% in 60 to 84 years. The results of the present study revealed that age (P=0.667) and gender (P=0.174) do not influence the serum Mg of CKD patients. The samples were divided into two groups (>6 months and <1 year) according to the duration of dialysis. The findings revealed that the duration of dialysis (<1 year) has a significant influence on serum Mg levels in CKD patients (P=0.0001). The CKD patients (63.2%) under dialysis for more than one year have displayed hypomagnesemia compared to another group.

The CKD patient's history of chronic diseases (DM, IHD, and hypertension) was correlated with serum Mg levels. Among the 100 patients, 54% had DM, 74% had high blood pressure, and 60% had IHD. The observation of the present study showed that 72.2% (P<0.0001) of CKD patients with DM had a low magnesium level. No significant difference (P=0.351) was observed between hypomagnesemia and CKD patients with hypertension. The present study's findings demonstrated significance (P=0.0001) that 85.0% of CKD patients with IHD displayed hypomagnesemia (Table 3).

Table 3
Comparison between serum magnesium and baseline parameters and chronic diseases

Baseline parameter		X^2 value	df	Total number (%)	Serum magnesium		p-value
					Normal	Low	
Gender	Male	1.846	1	53	21 (39.6%)	32 (60.4%)	0.174[f]
	Female			47	25 (53.2%)	22 (46.8%)	
Age (Year)	11–34	0.810	2	16	6 (37.5%)	10 (62.5%)	0.667[f]
	35–59			48	24 (50.0%)	24 (50.0%)	
	60–84			36	16 (44.4%)	20 (55.6%)	
Duration of Dialysis	>6 months	10.692	1	24	18 (75.0%)	6 (25.0%)	0.001[d]
	<1 year			76	28 (36.8%)	48 (63.2%)	
Diabetes mellitus	DM	15.692	1	54	15 (27.8%)	39 (72.2%)	0.0001[e]
	Non-DM			46	31 (67.4%)	15 (32.6%)	
Hypertension	Normal BP	0.871	1	26	14 (53.8%)	12 (46.2%)	0.351[f]
	High BP			74	32 (43.2%)	42 (56.8%)	
Ischemic Heart Disease	IHD	58.031	1	60	9 (15.0%)	51 (85.0%)	0.0001[e]

Notes: sample size n=100, Significance levels at P<0.05[a], P<0.01[b], P<0.005[c], P<0.001[d], P<0.0001[e], and non-significant [f], X^2 value – Chi-squared value; df – degrees of freedom; DM – diabetes mellitus; BP – blood pressure; IHD – ischemic heart disease.

The serum Mg level in CKD patients was correlated with blood parameters like parathyroid hormone, serum calcium, serum uric acid, serum phosphate, hemoglobin, and serum ferritin. The study revealed no significance between serum Mg and blood parameters except for serum phosphate (P=0.019; Table 4).

Table 4
Comparison of serum magnesium and blood parameters

Blood parameter		X^2 value	Df	Total number (%)	Serum magnesium		p-value
					Normal	Low	
Parathyroid Hormone	Normal	0.483	1	34	14 (41.2%)	20 (58.8%)	0.487[f]
	High			66	32 (48.5%)	34 (51.5%)	
Serum Calcium	Normal	0.961	1	69	34 (49.3%)	35 (50.7%)	0.327[f]
	Low			31	12 (38.7%)	19 (61.3%)	
Serum Uric Acid	Normal	0.000	1	74	34 (45.9%)	40 (54.1%)	0.985[f]
	High			26	12 (46.2%)	14 (53.8%)	
Serum Phosphate	Normal	5.487	1	43	14 (32.6%)	29 (67.4%)	0.019[b]
	High			57	32 (56.1%)	25 (43.9%)	
Hemoglobin	Normal	0.000	1	24	11 (45.8%)	13 (54.2%)	0.985[f]
	Low			76	35 (46.1%)	41 (53.9%)	
Ferritin	Normal	0.015	1	45	21 (46.7%)	24 (53.3%)	0.904[f]
	Low			55	25 (45.5%)	30 (54.5%)	

Notes: sample size n=100, Significance levels at P<0.05[a], P<0.01[b], P<0.005[c], P<0.001[d], P<0.0001[e], and non-significant[f], X^2 value – Chi-squared value; df – degrees of freedom.

The association between drugs (PPI, diuretics, and ACE1/ARB) prescribed to CKD patients on hemodialysis and hypomagnesemia was determined in the present study. The omeprazole and loop diuretics were given as PPI and diuretics, respectively. Among 100 patients, 59% were on omeprazole (20 mg to 80 mg), 67% were on loop diuretics, and 44% were on ACE1/ARB. According to the observations, 83%, 67% and 9.0% of patients were on PPI, diuretics, and ACE1/ARB drugs, respectively. The findings revealed that a higher significance (P<0.0001; Table 5) was found between the drug history of CKD patients and hypomagnesemia.

Table 5
Comparison of serum magnesium and drug history

Drug history		X^2 value	df	Total number (%)	Serum magnesium		p-value
					Normal	Low	
Proton Pump Inhibitor	On PPI	48.892	1	59	10 (16.9%)	49 (83.1%)	0.0001[e]
	Not On PPI			41	36 (87.8%)	5 (12.2%)	
Diuretics	On Diuretics	34.776	1	67	17 (25.4%)	50 (74.6%)	0.0001[e]
	Not On Diuretics			33	29 (87.9%)	4 (12.1%)	
ACE1/ARB	On ACE1	63.794	1	44	40 (90.9%)	4 (9.1%)	0.0001[e]
	Not On ACE1			56	6 (10.7%)	50 (89.3%)	

Notes: sample size n=100, Significance levels at P<0.05[a], P<0.01[b], P<0.005[c], P<0.001[d], P<0.0001[e], and non-significant[f], X^2 value – Chi-squared value; df – degrees of freedom; PPI – proton pump inhibitor.

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DISCUSSION

The present investigation uses various parameters to evaluate the causes of serum Mg insufficiency and the frequency of hypomagnesemia in patients with chronic kidney disease (CKD) following hemodialysis. The findings have revealed that a few parameters (DM, cardiovascular disease, and drugs prescribed) potentially correlate with hypomagnesemia in CKD patients. In the present study, positive inverse significance has been observed between IHD and hypomagnesemia in CKD patients. The previous study demonstrated by Dey et al. [31] showed that the low magnesium levels observed in CKD patients also positively correlated with cardiovascular risk, suggesting low magnesium levels are a marker of elevated cardiovascular risk in CKD. It is found that magnesium can increase the high-density lipoprotein and suppress the low-density lipoprotein and triglyceride. Thus, declining magnesium may have a pathogenic role in cardiovascular disease. The study has also demonstrated an association between hypertension and hypomagnesemia in CKD. However, the findings of the current study contradicted the results of Dey et al. [31].

The regulation of glucagon and insulin signaling, phosphorylation of the insulin receptor, and cellular glucose uptake require normal Mg homeostasis. It is stated that a decrease in the incidence of DM can be mediated by regular intake of Mg [32]. A study conducted by Sakaguchi et al. [33] stated that a deficiency of Mg is a novel risk for renal disease patients with DM. A total of 455 subjects were involved in the study; they were grouped as diabetic and non-diabetic samples with CKD. The findings revealed that higher significance was observed in the group with Mg deficiency than in the high Mg group in primary characteristics in CKD patients with DM. The present study also presented a strong correlation between the decline in Mg levels and the progression of CKD with DM. Pham et al. [34] stated that there is a negative correlation between the GFR and hypertension, diuretics, hemoglobin, calcium, and Mg in DM patients between hypomagnesemia and renal disease.

Two mechanisms – oral phosphate binder and simply increasing the Mg concentration – were proposed to increase the Mg concentration in dialysate fluid. First, the calcium-phosphate crystal growth may be delayed by phosphate-Mg binding, thus allowing the Mg to affect the deposition of the crystal. Secondly, Mg promotes calcification and suppresses the differentiation of vascular smooth muscle into an osteogenic phenotype [35]. Fang et al. [36] suggested that bone and mineral disease are critical complications in the advanced stages of kidney disease, the effects of hypomagnesemia in CKD patients with secondary hyperthyroidism were analyzed using parameters including parathyroid, hemoglobin, uric acid, and calcium. The results demonstrated a significant correlation between Mg disturbance and hemoglobin, uric acid, and calcium, but no significance was observed between Mg decline and parathyroid hormone.

However, Ohya et al. [37] reported that hypermagnesemia is observed in patients with low parathyroid hormones. However, in the present study, no significant correlation was found between hypomagnesemia in CKD patients and blood parameters (parathyroid hormone, calcium, uric acid, and hemoglobin). Jandaghi et al. [38] studied the effect of sevelamer and calcium carbonate on preventing hypomagnesemia in CKD patients under hemodialysis. The outcome of the study revealed that both drugs had a positive influence on serum Mg. However, calcium carbonate and sevelamer drugs did not change serum calcium and phosphate levels.

Cardiac arrhythmias, CKD, gastroesophageal reflux disease patients treated with PPI and heart disease, and hypertensive patients treated with higher doses of diuretics are prone to depletion in their Mg levels [39]. The pH of the intestine changes the administration of PPI; a rise in gastric pH leads to an elevation in the small intestine, which affects the solubility and absorption of Mg in the intestine. The PPI also can increase the colonic pH, which in turn reduces TRPM6 activity and the absorption of Mg [40, 41]. A decline in the reabsorption of paracellular Mg induced by diuretics leads to a loss of serum Mg and hypomagnesemia [42].

A recent study by Zhang et al. [40] suggests the monitored and optimal use of PPI in CKD patients because it can lead to conditions like abdominal aortic calcification, hip fracture, and hypomagnesemia. In CKD patients, hypomagnesemia results from using drugs, including PPI, calcineurin inhibitors, and diuretics. Hypomagnesemia is associated with an elevated mortality rate in CKD patients, significantly increasing cardiovascular mortality. A potential relationship has been observed between hypomagnesemia and drugs (beta-blockers, diuretics, ACE1/ARB, and PPI) prescribed to CKD patients [43]. In the present study, a higher significance is seen between the hypomagnesemia and drug history of CKD patients. In previous literature, patients with drug history, DM, hypertension, and cardiovascular disease with hypomagnesemia have been analyzed for the development of CKD. The current study has given new insight: CKD patients under hemodialysis with comorbidities including DM, hypertension, and cardiovascular disease are checked for hypomagnesemia conditions and their role in CKD progression.

■ CONCLUSION

The duration of dialysis has shown potential significance for hypomagnesemia in CKD patients. The blood parameters did not correlate with the decline in Mg. The present outcome implies that the deficiency in serum Mg is due to the loss of efficiency in the reabsorption of Mg. Monitoring PPI and diuretics drugs is essential for CKD patients. Chronic diseases, including a history of DM and IHD, are possible risk factors that induce hypomagnesemia in CKD patients and may also mediate the progression of CKD. In the future, to conform to this finding, the work has to be carried out with an increased sample size and parameters.

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