Annals of International Medical and Dental Research
E-ISSN: 2395-2822 | P-ISSN: 2395-2814
Vol-9, Issue-2 | March- April 2023
DOI: 10.53339/aimdr.2023.9.2.45
Page no- 345-356 | Section- Research Article (Internal Medicine)

Status of Serum Magnesium in Different Stages of CKD Patients: A Tertiary Care Hospital Study in Bangladesh

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Received: 01 December 2022
Revised: 25 January 2023
Accepted: 10 February 2023
Published: 28 February 2023

Abstract

Background: In chronic kidney disease (CKD), renal regulatory mechanisms may be insufficient to balance intestinal magnesium absorption hence insufficient to maintain homeostasis. But related data are relatively sparse and not readily available, especially in Bangladesh context. **Aim of the study**: The aim of the study was to assess the pattern of serum magnesium level in different stages of CKD patients. **Material & Methods:** This descriptive cross-sectional study was conducted in the Department of Medicine and the Department of Nephrology, Dhaka Medical College Hospital (DMCH) for nine months' period. Approval for the study was taken from the ethical review committee of DMC before the commencement of the study. Diagnosed patients of chronic kidney disease (CKD) were approached for the inclusion of the study. Informed written consent was taken from each patient. All patients were subjected to detailed history taking, physical examination, and relevant investigations. For the study purpose, serum magnesium was done for all patients. **Results:** After compiling data from all participants, statistical analysis was performed using the statistical package for social science (SPSS) version 22 for windows, and a $p < 0.05$ was considered statistically significant. Mean age of the patients was 53 years with male predominance (male 64% vs female 36%). Of all, 6.7% of cases had hypomagnesemia and 55.3% had hypermagnesemia. The mean serum magnesium level was 2.68±0.81 mg/dl. Assessment of serum magnesium in a different stages of CKD showed that hypermagnesemia is associated with higher staging ($p<0.05$), and there is a negative correlation between lower e-GFR with serum magnesium (($r=-0.753$, $p<0.01$). **Conclusion:** Nearly two-third of CKD patients were found with altered magnesium level in the form of hypomagnesemia or hypermagnesemia in this study. Serum magnesium was found increased in higher stages of CKD. That means serum magnesium level increases along with higher stage of the disease. Urinary magnesium excretion also decreases when eGFR of patient decreased.

Keywords:- Chronic kidney disease (CKD), Renal regulatory mechanisms, Intestinal magnesium, Homeostasis.

INTRODUCTION

Chronic kidney disease (CKD) has become a global epidemic with an estimated prevalence of 5-15%[1] worldwide with 13.4% in stages 1-5 and 10.6% in stages 3-5.[2] CKD is defined as a reduced glomerular filtration rate, increased

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urinary albumin excretion, or both.[3] Diabetes mellitus and hypertension are the leading causes of chronic kidney disease all over the world, but in some regions like Asia and sub-Saharan Africa, glomerulonephritis and other causes such as herbal and environmental toxins are more common. Complications includes cardiovascular mortality, kidney-disease progression, acute kidney injury, cognitive decline, anaemia, mineral and bone disorders, and fractures. Cardiovascular disease (CVD) is the primary cause of morbidity and mortality where CKD is regarded as an accelerator of CVD risk and an independent risk factor for CVD events.[4] Early identification of chronic kidney disease is needed to prevent disease progression and reduce the risk of cardiovascular morbidity and mortality. As the kidneys play a central role in the regulation of body fluids, electrolytes and acid-base balance, CKD and ESRD predictably result in multiple derangements including hyperkalemia, metabolic acidosis and hyperphosphatemia which, in turn lead to serious complications including muscle wasting, bone-mineral disorder, vascular calcification and mortality. Although, in patients with ESRD some derangements can be corrected by the renal replacement therapy. Integration of screening and management strategies for chronic kidney disease into national programs for non-communicable diseases are needed to identify CKD in early stages and halt the progression to reduce the burden and cost of care of chronic kidney disease. One such predictor of CKD related mortalities that evoked particular interest is magnesium which is the fourth most abundant cation in the body and the second major intracellular divalent cation which is involved in maintaining normal cellular function. Normal serum mg concentrations ranges from 1.7–2.4 mg/dl (0.7 to 1.1 mmol/L or 1.4-2.0 mEq/L).[5] However, serum magnesium (Mg) concentration does not reflect total body magnesium content since 60% is found in the skeleton, 39% is intracellular and only 1% of it is extracellular.[6] Mg has 3 important roles in that it: (1) is a biologic competitor of calcium, antagonizing it in binding cellular membranes and proteins, (2) functions as a cofactor in more than 300 essential enzymatic reactions, and (3) has a role in the regulation of the passages of electrolytes through the cellular membranes.[7] Mg also plays an important role in the regulation of vascular tone and heart rhythm[7] by affecting calcium uptake and distribution in the vascular smooth cells and also has direct effects on the vascular tone and can reduce peripheral resistance by stimulation of nitric oxide synthesis.[8,9] Magnesium deficiency has been reported to promote inflammation, and it decreases the specific immune response magnesium depletion can be associated with cardiovascular disturbances such as ventricular arrhythmias, prolonged QT interval, and torsades de pointes.[10,11] Magnesium not only affects the vascular system, but also reduces triglycerides and low-density lipoprotein cholesterol and increases high-density lipoprotein cholesterol levels.[12,13] There are studies which have shown that magnesium supplementation improves flow-mediated

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vasodilation in stable coronary artery disease patients, which confirms magnesium effect on regulation of vascular tone.[11,12] According to recent studies, magnesium not only has an effect on the bone, serum phosphate, and parathyroid hormone levels, but also is regarded as a cardiovascular risk factor in CKD and dialysis patients.[14] The kidney has a vital role in magnesium homeostasis and although the renal handling of magnesium is highly adaptable, this ability deteriorates when renal function declines significantly. Cardiovascular disease is the leading cause of mortality and morbidity in patients with chronic kidney disease, which is partly explained by the fact that 40–70% of patients receiving dialysis have significant coronary artery disease. Recent clinical studies have shown that lower serum magnesium (Mg) levels are associated with vascular calcification, hospitalization and cardiovascular mortality as well as an accelerated progression of early onset renal disease to RRT among patients with end-stage renal disease (ESRD).[15] Epidemiological studies have also found associations between higher levels of serum magnesium (Mg) and improved survival among patients suffering from CKD5 and end-stage renal disease.[16] Higher levels of serum mg are associated with reduced progression of CKD.[17] These associations are thought to be mediated by an antagonistic effect of Mg on the procalcifying milieu in CKD.[6] In vitro calcifications induced by Ca and high concentrations of PO4 can be prevented or reversed by adding or increasing mg, which appears to be mediated by both upregulation of factors that inhibit calcification and downregulation of factors that promote calcification.[18-21] Moreover, hypermagnesemia inhibits parathyroid hormone secretion, which is considered an important independent risk factor for vascular calcification, left ventricular hypertrophy and mortality in ESRD patients. Also, 2 small clinical trials of mg supplementation in end-stage renal disease have shown reduced progression of vascular calcification.[22] Thus, mg supplementation could potentially be a therapeutic option to attenuate the progression of vascular calcification in CKD.

Objectives

General Objective

General objective of the study was to evaluate the status of serum magnesium in different stages of chronic kidney disease patients.

Specific Objectives

- To measure serum magnesium level of CKD patients in different stages.
- To know the relation of serum magnesium with different stages of chronic kidney disease patients.

MATERIAL AND METHODS

This was a Descriptive cross-sectional study. The patients were selected purposively. A total of 150 patients were included in this study. The study was conducted in the department of Department of Medicine and Department of Nephrology, Dhaka Medical College & Hospital (DMCH), Dhaka. At March 2018 to September 2020 (Actual enrollment started after ERC clearance in December 2019).

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Inclusion Criteria for Case

- Diagnosed CKD for at least 3 months.
- CKD patients did not get dialysis as renal replacement therapy.
- Willing to participate.

Exclusion Criteria for Case

- Patients with CKD receiving any medications (Antacid, Amphotericin, Furosemide, Cisplatin, Aminoglycosides) which can alter magnesium level.
- Pregnant women.

Study Procedure

CKD patients who were admitted or attending in the Department of Medicine, and Department of Nephrology, Dhaka Medical College & Hospital (DMCH) were approached for inclusion of the study. Patients diagnosed with CKD for more than 3 months as documented in their medical records were selected in according to the inclusion and exclusion criteria. Informed consent was taken for each participant. Detailed clinical history, physical examination, relevant investigations were done and required data were recorded in preformed data collection sheet. Information on age, sex, occupation, marital status and health status information like diabetes, hypertension, dyslipidemia and smoking history was collected. Furthermore, serum magnesium was assessed in the clinical pathology department. All information was recorded properly in the preformed data collection sheet. After compiling data from all patients, statistical analysis was done.

Ethical Implications

Formal ethical clearance was taken from the ethical review committee of the Dhaka Medical College for conducting the study.

Statistical Analysis

All statistical analysis was performed using the statistical package for social science (SPSS) program, version 22 for Windows. Baseline patient characteristics were reported as a frequency (%) for categorical variables and mean (standard deviation [SD]) for continuous variables. Differences and/or relation in baseline characteristics were compared using proper statistical test as needed. Results were presented with a 95% confidence interval (95% CI). A p value of <0.05 was considered significant.

RESULTS

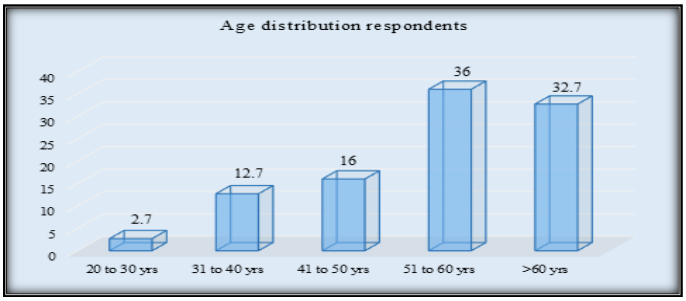

Figure 1: Bar chart showed age wise respondents. (N=150)

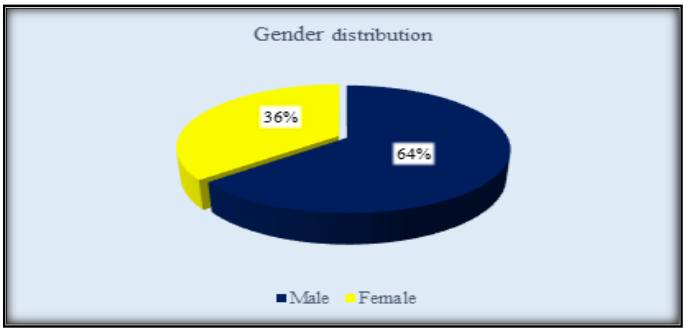

Figure 2: Pie chart showed gender wise respondents. (N=150)

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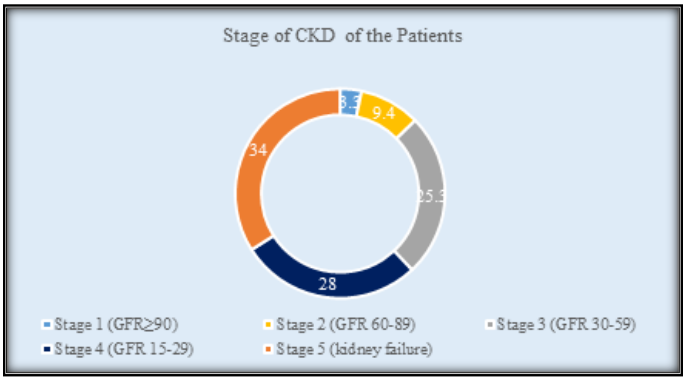

Figure 3: Ring chart showed stage of CKD of the respondents. (N=150)

This cross sectional observational study was conducted in Department of Medicine and Department of Nephrology, Dhaka Medical College & Hospital (DMCH), Dhaka. Total number of respondents were 150.

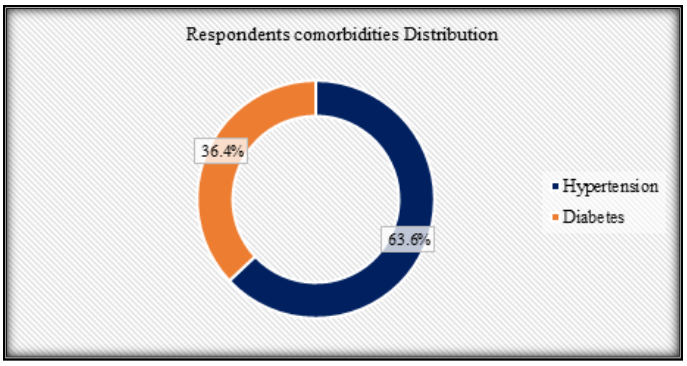

Figure 4: Ring chart showed Clinical feature wise respondents comorbidities. (N=150)

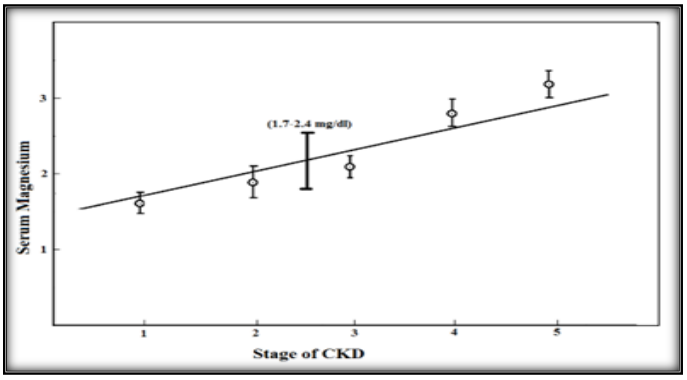

Figure 5: Stage of CHD (N=150)

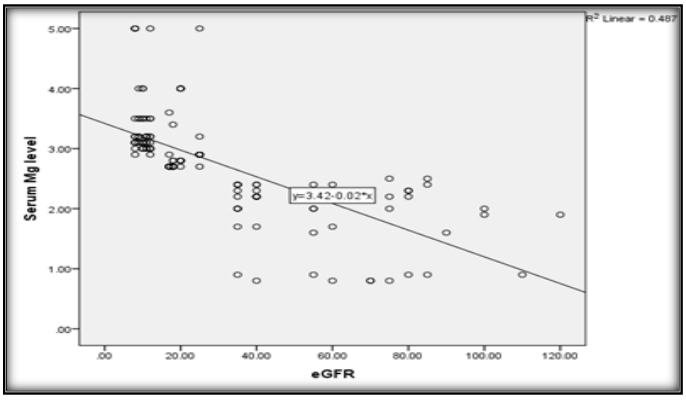

Figure 6: Correlation between serum magnesium level and eGFR of CKD patients using scatter plot diagram (N=150)

[Figure 5] showed Mean serum magnesium level significantly changes in different stages of CKD where higher value of serum magnesium is associated with higher stage of disease.

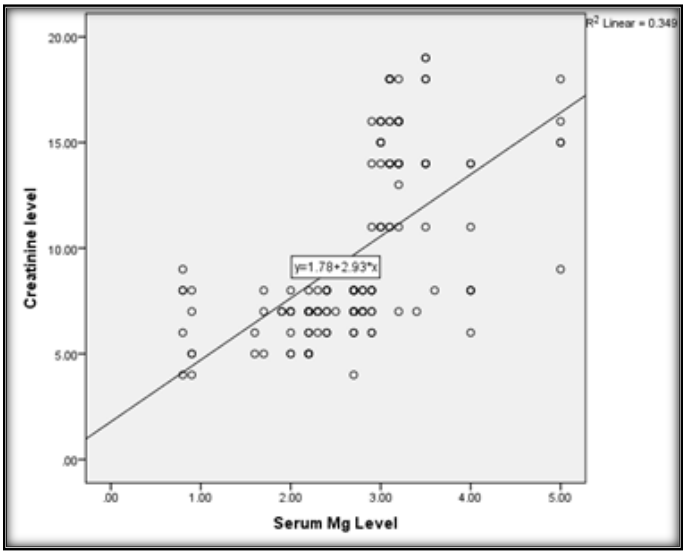

Figure 7: Correlation between serum magnesium level and serum creatinine level in patients using scatter plot diagram (N=150)

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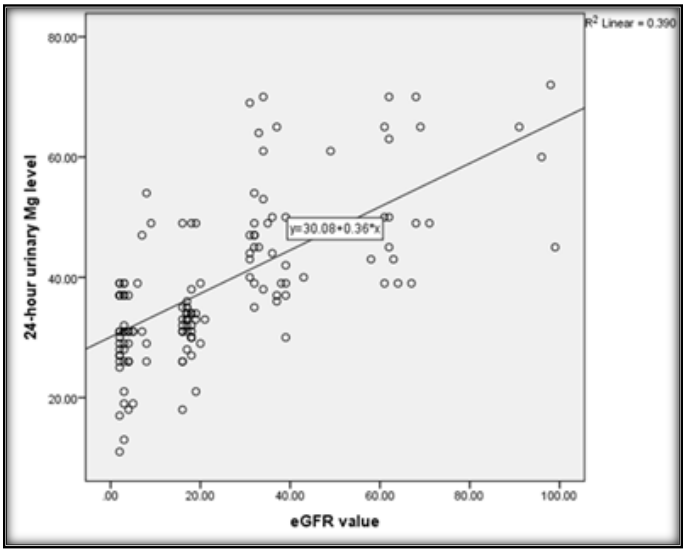

Figure 8: Correlation between 24-hour urinary magnesium level and eGFR of CKD patients using scatter plot diagram (N=150)

[Figure 6] showed Serum magnesium level and eGFR of the patients were negatively associated (r = -0.753, p<0.01) that means serum magnesium level increases while eGFR of CKD patients decrease ed.

[Figure 7] showed Serum magnesium level and serum creatinine level were significantly associated (r=0.550, p<0.01) that means serum magnesium level increases along with serum creatinine level.

[Figure 8] showed 24-hour urinary magnesium level and eGFR of the patients were positively associated (r=0.625, p<0.01) that means 24-hour urinary magnesium level decreases while eGFR of CKD patients decreased.

[Table 1] showed 32.7% respondents were more than 60 years old, 36% were in age group 51 to 60 years, 16% were in age group 41 to 50 years, 12.7% were in age group 31 to 40 years and only 2.7% were in age group 20 to 30 years. Mean age of the respondents was 53.31±10.28 year of SD.

Table 1: Distribution of the respondents by age. (N=150)

Age group	Frequency (n)	Percentage (%)	Mean Age ±SD
20 to 30 yrs.	4	2.7	3.31±10.28
31 to 40 yrs.	19	12.7	
41 to 50 yrs.	24	16	
51 to 60 yrs.	54	36	
>60 yrs.	49	32.7	

Table 2: Distribution of the respondents according to demographic characteristics. (N=150)

	Frequency (n)	Percentage (%)
Gender		
Male	96	64
Female	54	36
Occupation		
Unemployed	65	43.3
Housewife	32	21.3
Business	24	16
Service holder	15	10
Day laborer	14	9.4
Marital status		
Married	106	70.7

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Unmarried	15	10
Widow	29	19.3

Table 3: Distribution of the respondents by serum magnesium level. (N=150)

Serum magnesium level	Frequency (n)	Percentage (%)
Hypomagnesemia	10	6.7
Normal	57	38
Hypermagnesemia	83	55.3

[Table 3] showed 6.7% had hypomagnesemia, 38% had normal magnesium level and 55.3% had hypermagnesemia.

Table 4: Distribution of the respondents by stage of CKD. (N=150)

Stage	Frequency (n)	Percentage (%)
Stage 1 (GFR≥90)	5	3.3
Stage 2 (GFR 60-89)	14	9.4
Stage 3 (GFR 30-59)	38	25.3
Stage 4 (GFR 15-29)	42	28
Stage 5 (kidney failure)	51	34

[Table 4] showed among the respondents 34% respondents had CKD stage 5, 28% had CKD stage 4, 25.3% had CKD stage 3, 9.3% had CKD stage 2 and only 3.3% had CKD stage 1.

Table 5: Distribution of the respondents according to clinical features. (N=150)

	Frequency (n)	Percentage (%)
Nausea	120	80
Fatigue and weakness	112	74.7
Oliguria	98	65.3
Oedema	76	50.7
Fever	42	28%
Confusion	27	18%

[Table 5] showed 80% respondents had nausea, 74.7% had fatigue and weakness, 65.3% had oliguria, 50.7% had oedema, 28% had fever and 18% had confusion.

Table 6: Distribution of the respondents according to comorbidities. (N=150)

Clinical feature	Frequency (n)	Percentage (%)
Hypertension	104	69.3
Diabetes	61	40.7

[Table 6] showed 69.3% had hypertension, 40.7% had diabetes.

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Table 7: Distribution of the respondents according to mean serum magnesium in different stages of CKD patient (N=150)

Stage of CKD	Mean (mg/dl) ±SD
Stage 1	1.62±0.44
Stage 2	1.87±0.87
Stage 3	2.00±0.49
Stage 4	2.94±0.54
Stage 5	3.29±0.55

[Table 7] showed mean serum magnesium level was 1.62±0.44mg/dl in patients having CKD stage 1, 1.87±0.87 mg/dl in stage 2, 2.00±0.49 mg/dl in stage 3, 2.94±0.54 mg/dl in stage 4 and 3.29±0.55 mg/dl in stage 5.

Table 8: Mean value of investigations among the respondents (N=150)

Investigation	Mean ±SD
Serum Magnesium (mg/dl)	2.68±0.81
24 hours urinary Magnesium(mg/day)	38.91±13.29
Serum Sodium (mEq/L)	140.90±2.86
Serum Potassium (mEq/L)	4.81±0.83
Calcium (mg/dl)	8.71±0.71
Phosphate (mg/dl)	5.07±0.70
Creatinine (mg/dl)	9.72±4.08
Haemoglobin (gm/dl)	10.94±1.23

[Table 8] showed mean serum magnesium level was 2.68±0.81 mg/dl, 24 hrs urinary magnesium level was 38.91±13.29 mg/day, serum sodium was 140.90±2.86 mEq/L, serum potassium was 4.81±0.83mEq/L, calcium was 8.71±0.71mg/dl, phosphate was 5.07±0.70m, s. creatinine was 9.72±4.08 mg/dl and hemoglobin was 10.94±1.23 gm/dl.

DISCUSSION

Chronic kidney disease (CKD) is becoming a major public health problem around the world. In CKD patients, magnesium is important in regulating some aspects of mineral bone disorders associated with chronic renal failure, in cardiovascular health and also in survival. This study aimed to evaluate the level of serum magnesium in different stage of chronic kidney disease patients admitted in Department of Medicine and department of Nephrology, Dhaka Medical College Hospital (DMCH), Dhaka. In this study total number of respondents was 150. Among them 64% were male and 36% were female. Previous 3 studies by Patel et al (2018), Anand et al (2014) and Fatema et al (2013)[23-25] also found male predominance. In this study 32.7% respondents were more than 60 years, 36% was age between 51 to 60 years, 16% was age between 41 to 50 years, 12.7% was age between 31 to 40 years and only 2.7% was age between 20 to 30 years. Mean age of the

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respondents was 53.31±10.28 years of SD. In a previous study by Patel et al (2018)[23] observed majority of patients were in age group >60 years. The mean age of the patients was close to this study. Another study by Anand et al (2014)[24] observed mean age was 49.5(±12.7) years. In another previous study by Fatema et al (2013)[25] age range was between 18 and 70 years but mean age was 37 ± 11. This may be due to large number of cases was or geographic difference. In this study 34% respondents had CKD stage 5, 28% had CKD stage 4, 25.3% had CKD stage 3, 9.3% had CKD stage 2 and only 3.3% had CKD stage 1. A previous study by Fatema et al 2013[25] observed majority of the patients was in stage 3 CKD followed by stage 2 and stage 1 CKD. Besides no subject was found to be having Stage 4 or Stage 5 CKD. Another study by Kanbay et al (2012)[26] most of the respondents were in stage 5 CKD followed by stage 4, stage 3, stage 2 and stage 1 CKD. Which is similar to this study. Another previous study by Patel et al 2018[23] also observed majority of patients were in stage 5 followed by stage 4, stage 3, stage 2 and stage 1. Most of the studies found less number of respondents in stage 1 and stage 2. Reason behind this includes in case of stage 1 and stage 2 CKD, diagnosis is incidental, as in majority of cases clinical features for CKD first appear in stage 3. In this study about 80% respondents had nausea, 74.7% had fatigue and weakness, 65.3% had oliguria, 50.7% had oedema, 28% had fever, 18% had confusion, 69.3% had hypertension and 40.7% had diabetes. In a previous study by Patel et al 2018[23] found majority of patient presented with nausea and were followed by vomiting. The other clinical presentation was similar to this study. In this study less number of patient found with vomiting. They also observed majority of patients were having hypertension followed by diabetes mellitus. (Patel et al., 2018).[23] In a previous study they also observed the risk for developing CKD was almost two fold higher in subjects with high SBP, high RBS.[25] In this study total mean serum magnesium level was 2.68±0.81 mg/dl, 24 hour's urinary magnesium level was 38.91±13.29 mg/day, serum sodium was 140.90±2.86 mEq/L, serum potassium was 4.81±0.83 mEq/L, calcium was 8.71±0.71 mg/dl, phosphate was 5.07±0.70m, creatinine was 9.72±4.08 mg/dl and hemoglobin was 10.94±1.23 gm/dl. Anaemia and hypocalcaemia was more evident in case of stage 4 and stage 5 CKD. Though most of the patient was receiving treatment for anaemia and hypocalcaemia correction. Hyperkalemia was found most of the patient with stage 5 CKD and some of stage 4 CKD. Hyperphostaemia also found among the CKD patients despite of receiving treatment. In a previous study, results of various investigations among CKD patients showed similarity with this study.[23] In this study also observed that among the respondents 35 in stage 4 and 48 in stage 5 had hypermagnesemia. 4 in stage 1, 10 in stage 2 and 33 in stage 3, 7 in stage 4 and 3 in stage 5 had normal magnesium level also 1 in stage 1, 4 in stage 2 and 5 in stage 3 had hypomagnesemia. Whereas mean serum magnesium level was 1.62±0.44mg/dl in stage 1, 1.87±0.87 mg/dl in stage 2, 2.00±0.49 mg/dl in stage 3, 2.94±0.54

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mg/dl in stage 4 and 3.29±0.55 mg/dl in stage 5. In stage 4 and 5 magnesium level was higher than stage 1, 2 and 3 ($p<0.01$). In a previous study they observed 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 hypermagnesemia.[27] In another study they also observed serum magnesium among CKD patients showed that majority of patients presented with hypermagnesemia followed by normal magnesium levels.[23] Serum magnesium level had a negative correlation with stage of the CKD ($r=-0.753$ and $P<0.01$). That means serum magnesium level increases wile eGFR of CKD patients decreases. While eGFR decreases stage of CKD get worst that means serum magnesium increases while CKD stages get worst. Also observed that serum magnesium level and serum creatinine level were significantly associated ($r = 0.550$, $p<0.01$) that means serum magnesium level increases along with serum creatinine level. Another study by Patel et al (2018)[23] also observed the same findings. In this study 24-hours urinary magnesium level and eGFR of the patients were positively associated ($r = 0.625$, $p<0.01$) that means 24-hour urinary magnesium level decreases while eGFR of CKD patients decreases. That means in case of higher stage of CKD urinary excretion of magnesium decreases. This study found almost all patients with hypermagnesemia urinary magnesium excretion is decreased. Previous study by A journal article written by Esther R. van de Wal-Visscher state that, in case of chronic kidney disease (CKD), renal regulatory mechanisms may be insufficient to balance intestinal mg absorption. Usually mg remains normal. However, when glomerular filtration rate declines, changes in serum mg are observed. Maintenance of magnesium homeostasis depends on intestinal absorption and renal excretion which is highly adjustable in healthy state. But in case of renal insufficiency this compensatory mechanism fails and excretion of magnesium is interrupted. Other previous studies by Bressendorff et al. 2017; Giménez-Mascarell et al. 2018; De Francisco and Rodríguez 2013[27-29] found most of the circulating mg, approximately 70% filtered by glomerulus and 90-95% of filtered mg is reabsorbed. Only 10-25% reabsorbed through proximal convoluted tubule and 70% through ascending limb of loop of henle in paracellular pathway. Healthy kidney can balance mg level by increasing or decreasing mg reabsorption in according to the level of mg ingestion. But in case of decline renal function urinary excretion decreases. This study also observed that with the higher stage of disease urinary magnesium excretion decreases.

Limitations

Single centered study. Required number of samples could not be collected due to COVID 19 pandemic situation.

CONCLUSIONS

In this study, nearly two third of CKD patients had magnesium derangement in the form of hyper or hypomagnesemia. Serum magnesium

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was found significantly associated with stage of CKD where serum magnesium level increases with higher stage of disease. Positive correlation also was found between serum creatinine and serum magnesium level. So, present study can conclude that serum magnesium among patients with chronic kidney disease tends to be higher with the higher stage of chronic kidney disease.

Recommendation

As this study found significant correlation of serum magnesium with stages of CKD patients so, its evaluation may play a vital role in management of CKD. Larger studies should be done involving larger sample to evaluate clinical impact.

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Annals of International Medical and Dental Research
E-ISSN: 2395-2822 | P-ISSN: 2395-2814
Vol-9, Issue-2 | March- April 2023
DOI: 10.53339/aimdr.2023.9.2.45
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Source of Support: Nil, Conflict of Interest: None declare