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A RETROSPECTIVE STUDY OF CORRELATION BETWEEN SERUM CREATININE, SERUM CALCIUM, SERUM INORGANIC PHOSPHORUS AND SERUM MAGNESIUM LEVELS IN PATIENTS ATTENDING NEPHROLOGY CLINICS IN TERTIARY CARE CENTER

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ABSTRACT **Introduction:** Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide. The global estimated prevalence of CKD is 13.4%. Kidney plays a critical role in regulating serum levels of Calcium, Magnesium and Phosphate. Calcium, phosphorus and magnesium homeostasis is altered in chronic kidney disease(CKD). **Objective:** Objective of the study is to establish the correlation of increase in serum creatinine levels with Calcium, Magnesium and Phosphate levels in patients. **Design & Methods:** This observational retrospective study included patients attending nephrology department in tertiary care centre for a period of two months. In total, 229 patients' data was accessed from the medical records. **Results:** Patients were grouped in 5 groups based on serum creatinine levels. Group I with serum creatinine levels of 0.5mg/dl to 0.8mg/dl, group II with serum creatinine levels of 0.8 to 1.1mg/dl, group III with serum creatinine levels of 1.1 to 3mg/dl, group IV with serum creatinine levels of 3 to 6mg/dl, group V with serum creatinine levels above 6mg/dl. Overall from group I to Group V , Serum Calcium showed negative and significant correlation, Serum phosphorus levels showed positive and significant correlation, Serum magnesium showed negative and insignificant correlation with serum creatinine. **Conclusions:** As serum creatinine increases, more patients show decline in serum calcium levels and serum magnesium levels and increase in serum inorganic phosphorus levels. Hypocalcemia, hypomagnesemia and hyperphosphatemia have been associated with increased risk of cardiovascular morbidity and mortality in cases of CKD. Hypomagnesemia has possible association with rapid decline in kidney function. Therefore, regular analysis of these parameters is important for predicting the prognosis of CKD and cardiovascular risk in cases of CKD.

KEYWORDS : Chronic kidney disease, Hypocalcemia, Hypomagnesemia, Hyperphosphatemia

INTRODUCTION –

Chronic kidney disease (CKD) has been recognized as a leading public health problem worldwide. The global estimated prevalence of CKD is 13.4%, and patients with end-stage kidney disease (ESKD) needing renal replacement therapy is estimated between 4.902 and 7.083 million (1). Through its effect on cardiovascular risk and ESKD, CKD directly affects the burden of morbidity and mortality worldwide (1).

The identification of modifiable risk factors for chronic kidney disease (CKD) progression is important to the design, study and implementation of preventive strategies(2)(3). Disturbances in mineral metabolism are prevalent in advanced CKD and have been suggested not only to be the consequence of CKD, but also a potential cause for a more rapid decline kidney function (4)(5).

Kidney plays a critical role in regulating serum levels of Calcium, Magnesium and Phosphate. Calcium, phosphorus and magnesium homeostasis is altered in CKD (6). In earlier stages of Chronic renal disease, compensatory mechanism maintains the serum levels of calcium, phosphorus and magnesium; the changes in serum levels of calcium, magnesium, phosphorus are not seen until advanced stages of CKD(6).

Aim of the study is to establish the relation of increase in serum creatinine levels with these parameters in patients attending nephrology department in Osmania General Hospital.

MATERIALS AND METHODS – After approval of institutional ethical committee and after taking informed consent from participants, Data is accessed from the medical records from nephrology department of Osmania General Hospital during month of March and April,2022.

Sample size – 229
Study design – Observational retrospective study

Inclusion criteria - All IP and OP cases, adult males and females attending nephrology department in OGH.

Method – Serum Creatinine was analyzed by enzymatic method, serum Calcium was analyzed by Arsenazo method, Serum Magnesium was analyzed by Xylidyl blue and serum phosphorus was analysed by modification of Daly and Ertingshausen with proper quality control with fully automated clinical chemistry analyzer - Beckman coulter Au5800.

RESULTS – Data collected was divided into 5 groups depending on serum creatinine levels.

Group I (59 patients) with serum creatinine levels between 0.5mg/dl to 0.8mg/dl,

Group II (58 patients) with serum creatinine level between 0.8mg/dl to < 1.1mg/dl,

Group III (52 patients) with serum creatinine levels between 1.1mg/dl to < 3mg/dl,

Group IV (34 patients) with serum creatinine level between 3mg/dl to 6 mg/dl,

Group V (26 patients) with serum creatinine above 6 mg/dl.

TABLE1: Following table shows the mean ± 1 SD values of these 5 groups

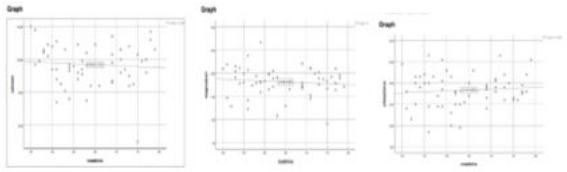
	Group I	Group II	Group III	Group IV	Group V
Serum Creatinine	0.64 ± 0.08mg/dl	0.92 ± 0.08 mg/dl	1.79 ± 0.47 mg/dl	4.20 ± 0.84 mg/dl	9.91 ± 4.35 mg/dl
Serum Calcium	9.6 ± 1.2mg/dl	9.65 ± 1.51 mg/dl	9.06 ± 1.53 mg/dl	8.96± 1.84 mg/dl	8.70 ± 0.78 mg/dl
Serum inorganic phosphorus	3.7± 0.8mg/dl	3.7 ± 0.7 mg/dl	3.96 ±1.5 mg/dl	5.04± 1.80 mg/dl	6.6 ± 2.5 mg/dl
Serum Magnesium	1.8±0.3mg /dl	1.8 ± 0.4 mg/dl	1.75 ± 0.43 mg/dl	1.75 ± 0.43 mg/dl	1.84 ± 0.49 mg/dl

TABLE 2: Showing percentage of patients having hypocalcemia, hypomagnesemia and hyperphosphatemia in each group.

PERCENTAGE OF PATIENTS WITH	Group I	Group II	Group III	Group IV	Group V
HYPOCALCEMIA(<8.4mg/dl)	8.4%	10.3%	26.9%	38.2%	30.8%
HYPERPHOSPHATEMIA(>4.8mg/dl)	8.5%	3.4%	17.3%	44.1%	76.9%

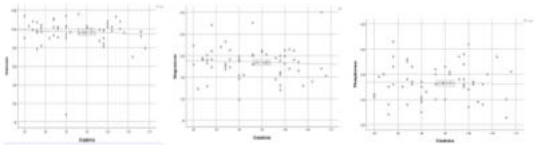
HYPOMAGNESEMIA(<1.8mg/dl)	42.3%	39.6%	51.9%	67.6%	50%

Analysis was done by spearman correlation, which showed In Group I – Serum Calcium and Magnesium have negative and insignificant correlation (>0.05) with serum creatinine. Serum phosphorus levels are positive and insignificant correlation (>0.05) with serum creatinine.



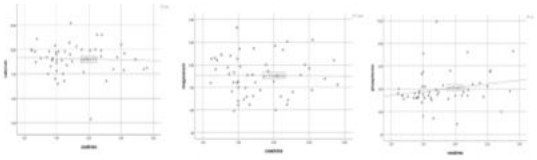
GRAPH 1 : Spearman correlation between sCreatinine with sCa, sCreatinine with sMg and sCreatinine with sP respectively in group I patients.

In Group II - Serum Calcium and Magnesium have negative and insignificant(>0.05) correlation with serum creatinine. Serum phosphorus levels are negative and insignificant (>0.05) correlation with serum creatinine. In this group the negative correlation between creatinine and phosphorus can be due to prolonged poor dietary sources of phosphate, intestinal malabsorption, and intestinal binding by exogenous agents.



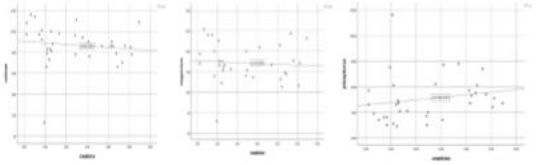
GRAPH 2 : Spearman correlation between sCreatinine with sCa, sCreatinine with sMg and sCreatinine with sP respectively in group II patients.

In Group III - Serum Calcium and Magnesium have negative and insignificant (>0.05) correlation with serum creatinine. Serum phosphorus levels are positive and significant (<0.05) correlation with serum creatinine.



GRAPH 3: Spearman correlation between sCreatinine with sCa, sCreatinine with sMg and sCreatinine with sP respectively in group III patients.

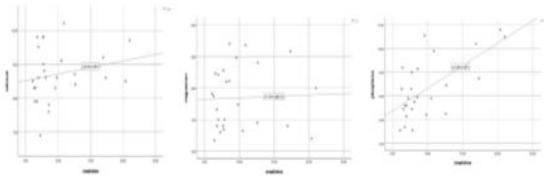
In Group IV - Serum Calcium and Magnesium have negative and insignificant (>0.05) correlation with serum creatinine. Serum phosphorus levels are positive and insignificant (>0.05) correlation with serum creatinine.



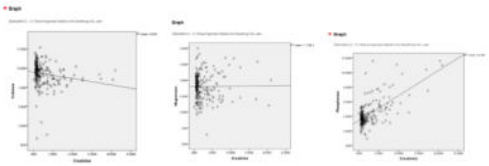
GRAPH 4: Spearman correlation between sCreatinine with sCa, sCreatinine with sMg and sCreatinine with sP respectively in group IV patients.

In Group V - Serum Calcium and Magnesium have positive and insignificant (>0.05) correlation with serum creatinine. Serum phosphorus levels are positive and significant (<0.05) correlation with serum creatinine.

GRAPH 5: Spearman correlation between sCreatinine with sCa, sCreatinine with sMg and sCreatinine with sP respectively in group V patients.



GRAPH 6: Spearman correlation between sCreatinine with sCa, sCreatinine with sMg and sCreatinine with sP respectively overall from group I to group V.



Overall from group I to Group V , Serum Calcium showed negative and significant correlation, Serum phosphorus levels showed positive and significant correlation, Serum magnesium showed negative and insignificant correlation with serum creatinine.

As serum creatinine increases, more patients showing decline in serum calcium levels and serum magnesium levels and increase in serum inorganic phosphorus levels.

DISCUSSION –

This study examined relationship between serum calcium, inorganic phosphorus and serum magnesium levels with serum creatinine levels.

Calcium is the fifth most abundant element in the body with >99% residing in the skeleton as hydroxyapatite, a complex calcium phosphate molecule(7).Three forms of calcium circulate in the blood. These are albumin-bound (40%), ionized (50%) and complexed (10%), primarily with citrate, phosphate, and bicarbonate. The latter two forms of calcium are filterable at the glomerulus(6).

In the initial stages of chronic renal failure, serum calcium levels remain normal as adaptation develops. The primary regulator of serum calcium is parathyroid hormone (PTH) with PTH secretion modulated by the interaction between calcium and the calcium sensing receptor (CaSR) located on the cell surface of the parathyroid gland(6). Hypocalcemia stimulates PTH secretion and hypercalcemia suppresses PTH secretion(6). Parathyroid hormone is secreted in response to low calcium levels and it increases serum calcium levels by acting on bone causing bone resorption, by increasing intestinal absorption of calcium and by increasing reabsorption in renal tubules (6). In late stages of CKD, these compensatory mechanisms fail and serum calcium levels decline.

Our observational study has shown similar results as a study by Felsenfeld et al. (6) which showed negative correlation between serum creatinine and serum calcium levels. Lim et al.(8) reported low serum calcium to be associated with a faster kidney function decline in a pooled cohort of CKD stage 3–4 patients. A study by Cynthia J. Janmaat et al(9) found that the effect of serum calcium on kidney function decline is stronger, for lower baseline eGFR, thus the higher the CKD stage.

In this study, overall serum calcium levels have negative and significant correlation with serum creatinine. In group V where mean serum creatinine was 9.91 ± 4.35 mg/dl, less patients were having hypocalcemia compared to previous groups which can be attributed to Calcium supplementations.

Phosphate is important for many physiological processes in body such as cell metabolism, intracellular signaling, bone structure and protein synthesis. Therefore, maintaining phosphate balance is vital for survival(6). Primary regulator of phosphate homeostasis is kidney (6). In early stages of CKD, compensatory mechanisms increase fractional excretion of phosphate and decrease the phosphate threshold clearance to maintain normal phosphorus value (10)(11). Bone also helps in maintenance of serum phosphate levels through fibroblast growth factor23 (FGF23) (6). In early stages of CKD, renal excretion of phosphate is maintained by increased secretion of FGF23 and PTH. In advance stages of chronic renal disease, phosphaturic effect of FGF23

is decreased by downregulation of its cofactor Klotho which is necessary for binding FGF23 to FGF receptors(6). Hyperphosphatemia has been consistently associated with CKD progression(12)(13)(14), as well as FGF-23 excess and the calcium-phosphorus product(15)(12).

A study by Felsenfeld et al. (6) have discussed pathophysiology of hyperphosphatemia in cases of CKD and also shows positive correlation between serum creatinine and serum phosphorus levels, these findings correlate with my study. The study by Antonio Bellasi (12) separately tested the association between serum phosphate and the risk of death or progression to dialysis. As expected, patients with hyperphosphatemia were more likely than peers to experience each of the two events. Chronic kidney disease-mineral and bone disorders (CKD-MBD) is identified by imbalances in serum calcium (Ca), phosphate, and parathyroid hormone (PTH)(16). CKD-MBD are associated with vascular calcification and abnormal electrolytes that lead to cardiovascular disease and mortality(16).

In my study, we found that overall, serum inorganic phosphate having positive and significant correlation with serum creatinine.

Magnesium is second most important intracellular cation in the body(17). Magnesium plays an important role in mineral bone metabolism, adenosine triphosphate metabolism, neurotransmitter release and in the regulation of vascular tone, heart rhythm and platelet activated thrombosis (18). The kidney plays major role in regulation of serum magnesium levels. In early stages of CKD, an increase in fractional excretion of magnesium compensates for the loss of renal function to maintain serum magnesium levels in normal range(19). In advanced CKD cases magnesium cannot be excreted in sufficient quantity as GFR is declined, in such patients hypermagnesemia is only possible outcome(20)(21).

However, both CKD and ESRD patients on dialysis have usually normal serum levels of Mg and sometimes even low serum Mg concentration (hypomagnesaemia)(22)(23). Hypomagnesaemia might be a side effect of a number of different medications, such as thiazide diuretics, proton-pump inhibitors (PPI), cisplatin, aminoglycoside antibiotics and calcineurin inhibitors(24). Patients with CKD normally have severely depressed intestinal Mg absorption compared to healthy individuals, probably due to a deficiency of active vitamin D (25).

Hypomagnesemia might be associated with a more rapid decline in kidney function and mortality or adverse cardiovascular outcome in chronic kidney disease(26). This hypothesis is supported by emerging mostly observational and indirect evidence pointing to a relationship between hypomagnesemia and risk factors for both renal and cardiovascular disease such as dyslipidaemia, endothelial dysfunction, inflammation, oxidative stress, hypertension, hyperparathyroidism, and insulin resistance(27).

Laecke et al.(26) showed that Lower magnesium concentrations remained associated with higher risk of mortality even after adjusting for potential confounders. Also, magnesium concentrations were related to the rate of kidney function decline after adjustment for age, sex, diabetes, and hypertension(26). The lower the serum magnesium concentration at baseline, the faster kidney function declined(26).

Pham et al. (28) demonstrated in a cohort of predominantly Hispanic diabetes patients without known kidney disease (n = 550) that lower magnesium levels were associated with faster deterioration of kidney function, even after correction for age, lipid status and HbA1c.

In this study, serum magnesium levels were low in 41.02% patients with normal serum creatinine levels. In Group III, 51.9% patients had low serum magnesium levels. In Group IV, 67.6% patients had low serum magnesium levels. In Group V, 50% patients had low serum magnesium levels. This shows that serum magnesium can be used to predict the decline in renal function.

CONCLUSION -

In early stages of CKD, levels of serum creatinine, serum phosphorus and serum magnesium are maintained in normal range by compensatory mechanisms. In advanced CKD, abnormalities in levels of these parameters are seen, as compensatory mechanisms fail. In this study, decline in levels of serum calcium and serum magnesium and increase in levels of serum phosphorus is observed at serum creatinine level of >1.1 mg/dl (Group III, IV, V). Some studies have suggested hypocalcemia and hyperphosphatemia is associated with increased risk of cardiovascular mortality in patients with chronic kidney disease, hence estimation of serum calcium and serum phosphorus levels in early stages of CKD is important to predict the risk of cardiovascular morbidity and mortality in cases of CKD. Hypomagnesemia is also associated with mortality or adverse cardiovascular outcome in chronic kidney disease. Hypomagnesemia has possible association with rapid decline in kidney function. Detection of hypomagnesemia at early stage can act as a whistle-blower to take necessary steps and further evaluate the patients for decline in renal function and monitor their cardiovascular health. Magnesium can be used as a parameter for early detection of impaired renal function.

Further studies are required to provide insight into the role of Calcium – phosphorus product and hypomagnesemia together in the development of cardiovascular risk in cases of CKD which is the limitation of my study and opportunity for further research. There was no conflict of interest while conducting the study.

Abbreviations : CKD – chronic kidney disease; sCa – Serum calcium; sMg – serum magnesium; sP – serum phosphorus, FGF23 – fibroblast growth factor 23; CaSR - calcium sensing receptor ; PTH – parathyroid hormone; GFR- glomerular filtration rate

References-

1. Lv JC, Zhang LX. Prevalence and Disease Burden of Chronic Kidney Disease [Internet]. Vol. 1165, Advances in Experimental Medicine and Biology. Springer Singapore; 2019. 3–15 p. Available from: http://dx.doi.org/10.1007/978-981-13-8871-2_1
2. Termorshuizen F, Dekker FW, Van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT. Relative Contribution of Residual Renal Function and Different Measures of Adequacy to Survival in Hemodialysis Patients: An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. J Am Soc Nephrol. 2004;15(4):1061–70.
3. Milik A, Hrynkiewicz E. On translation of LD, IL and SFC given according to IEC-61131 for hardware synthesis of reconfigurable logic controller. IFAC Proc Vol. 2014;19(1):4477–83.
4. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death in individuals with chronic kidney disease. JAMA. 2011;305(11):1119–27.
5. O'Neill WC. Targeting serum calcium in chronic kidney disease and end-stage renal disease: Is normal too high? Kidney Int [Internet]. 2016;89(1):40–5. Available from: http://dx.doi.org/10.1016/j.kint.2015.10.001
6. Felsenfeld AJ, Levine BS, Rodriguez M. Pathophysiology of Calcium, Phosphorus, and Magnesium Dysregulation in Chronic Kidney Disease. Semin Dial. 2015;28(6):564–77.
7. Zimmermann M, R. Trumbo P. Nutrient Information. Am Soc Nutr [Internet]. 2013;4(1):262–4. Available from: www.ebscohost.com
8. Lim LM, Kuo HT, Kuo MC, Chiu YW, Lee JJ, Hwang SJ, et al. Low serum calcium is associated with poor renal outcomes in chronic kidney disease stages 3-4 patients. BMC Nephrol. 2014;15(1):1–9.
9. Janmaat CJ, Van Diepen M, Gasparini A, Evans M, Qureshi AR, Ärnlöv J, et al. Lower serum calcium is independently associated with CKD progression. Sci Rep. 2018;8(1):1–9.
10. Drüeke TB, Massy ZA. Phosphate binders in CKD: Bad news or good news? J Am Soc Nephrol. 2012;23(8):1277–80.
11. Baczynski R, Massry SG, Kohan R, Magott M, Saglikes Y, Brautbar N. Effect of parathyroid hormone on myocardial energy metabolism in the rat. Kidney Int [Internet]. 1985;27(5):718–25. Available from: http://dx.doi.org/10.1038/ki.1985.71
12. Bellasi A, Mandreoli M, Baldrati L, Malmusi MC, Di Nicolo P, Malmusi G, et al. Chronic kidney disease progression and outcome according to serum phosphorus in mild-to-moderate kidney dysfunction. Clin J Am Soc Nephrol. 2011;6(4):883–91.
13. Caravaca F, Villa J, García de Vinuesa E, Martínez del Viejo C, Martínez Gallardo R, Macías R, et al. Asociación entre fósforo sérico y progresión de la enfermedad renal crónica avanzada. Nefrologia. 2011;31(6):707–15.
14. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, Van Manen JG, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007;22(10):2909–16.
15. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006;1(4):825–31.
16. Miura S, Yoshihisa A, Takiguchi M, Shimizu T, Nakamura Y, Yamauchi H, et al. Association of Hypocalcemia with Mortality in Hospitalized Patients with Heart Failure and Chronic Kidney Disease. J Card Fail [Internet]. 2015;21(8):621–7. Available from: http://dx.doi.org/10.1016/j.cardfail.2015.04.015
17. Van De Wal-Visscher ER, Kooman JP, Van Der Sande FM. Magnesium in Chronic Kidney Disease: Should We Care? Blood Purif. 2018;45(1–3):173–8.
18. Cunningham J, Rodríguez M, Messa P. Magnesium in chronic kidney disease Stages 3 and 4 and in dialysis patients. CKJ Clin Kidney J. 2012;5(SUPPL. 1).
19. Coburn JW, Popovtzer MM, Massry SG, Kleeman CR. The Physicochemical State and Renal Handling of Divalent Ions in Chronic Renal Failure. Arch Intern Med. 1969;124(3):302–11.
20. Massy ZA, Nistor I, Apetrii M, Brandenburg VM, Bover J, Evenepoel P, et al. Magnesium-based interventions for normal kidney function and chronic kidney disease. Magnes Res. 2016;29(4):126–40.
21. Massry SG. Magnesium homeostasis in patients with renal failure. Contrib Nephrol. 1984;38:175–84.
22. Alhosaini M, Walter JS, Singh S, Dieter RS, Hsieh A, Leehey DJ. Hypomagnesemia in hemodialysis patients: Role of proton pump inhibitors. Am J Nephrol. 2014;39(3):204–9.
23. Ejaz AA, McShane AP, Gandhi VC, Leehey DJ, Ing TS. Hypomagnesemia in continuous ambulatory peritoneal dialysis patients dialyzed with a low-magnesium peritoneal dialysis solution. Perit Dial Int J Int Soc Perit Dial. 1995;15(1):61–4.
24. Hashizume N, Mori M. An Analysis of Hypermagnesemia and Hypomagnesemia. Jpn J

Med. 1990;29(4):368–72.
25. Brannan PG, Vergne-marini P, Pak CYC, Hull AR, Fordtran JS. Magnesium Absorption in the Human Small Intestine DISEASE , AND PATIENTS WITH ABSORPTIVE HYPERCALCIURIA. J Clin Invest. 1976;57(June):1412–8.
26. Van Laecke S, Nagler E V., Verbeke F, Van Biesen W, Vanholder R. Hypomagnesemia and the risk of death and gfr decline in chronic kidney disease. Am J Med [Internet]. 2013;126(9):825–31. Available from: http://dx.doi.org/10.1016/j.amjmed.2013.02.036
27. Van Laecke S, Van Biesen W, Vanholder R. Hypomagnesaemia, the kidney and the vessels. Nephrol Dial Transplant. 2012;27(11):4003–10.
28. Pham PCT, Pham PMT, Pham PAT, Pham S V, Pham H V, Miller JM, et al. Lower serum magnesium levels are associated with more rapid decline of renal function in patients with diabetes mellitus type 2. Clin Nephrol. 2005 Jun;63(6):429–36.