

RELATIONSHIP BETWEEN SERUM LEVEL OF IONIZED CALCIUM, MAGNESIUM, PHOSPHATE, VITAMIN D AND PARATHYROID HORMONE WITH STAGES OF CKD.

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ABSTRACT

Background: Chronic kidney disease is defined as either damage or a decreased Glomerular Filtration Rate of less than 60ml/min/1.73m² for 3 or more months. There is destruction of renal mass with irreversible sclerosis and loss of nephron leading to a progressive decline in GFR. Secondary hyperparathyroidism hyperphosphataemia, hypocalcaemia and vitamin-D deficiency are common complications of CKD. Objective: To determine relationship between serum level of ionised calcium, magnesium, phosphate, vitamin-D and parathyroid hormone with stages of CKD. Method: This study was conducted at ABUTH Zaria. 125 consecutive adult patients in various stages of CKD who presented were enrolled and 125 apparently healthy matched for sex and age controls were also recruited. Results: 9% of patients were in stage-1, 16% in stage-2, 22% in stage-3, 12% in stage-4 and 41% in stage-5. Serum ionised calcium, vitamin-D and eCrCl showed a progressive decline as the stage of CKD advances, while serum phosphate, creatinine and iPTH showed a progressive increase as the stage of CKD advances. Changes in serum magnesium showed a slight change with advancing stages of CKD. The difference in mean serum levels of calcium, phosphorus, vitamin-D, parathyroid hormone, creatinine and eCrCl with different stages of CKD were statistically significant. eCrCl correlated negatively with phosphate and iPTH while serum creatinine correlated negatively with calcium and positively with phosphate and iPTH. Conclusion: Majority of CKD patients were in late stage. Correlation of analytes with stages was more in late stages and biochemical derangements occurred in late, rather than early stages of CKD.

Keywords: Chronic kidney disease, Calcium, Phosphate, Vitamin D, Magnesium, Parathyroid hormone

INTRODUCTION

Chronic damage to the kidney also known as chronic kidney disease (CKD) has serious implication for systematic functions, growth and existence.¹ Chronic kidney disease (CKD) is defined

as either damage or a decreased Glomerular Filtration Rate (GFR) of less than 60ml/min/1.73m² for 3 or more months. With underlying aetiology, the destruction of renal mass with irreversible sclerosis and loss of nephron leads to a progressive decline in GFR. The different stages of kidney disease form a continuum in time.²

In 2002 K/DOQI published its first classification of the stages of chronic kidney disease (which was updated in 2012) as follows.

- Stage 1; kidney damage with normal or increased GFR (≥ 90ml/min

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/1.73m²)

- Stage 2; kidney damage with mild reduction in GFR (60-89ml/min/1.73m²)
- Stage 3; moderate reduction in GFR (30-59ml/min/1.73m²)
- Stage 4; severe reduction in GFR (15-29ml/min/1.73m²)
- Stage 5; kidney failure with GFR (<15ml/min/1.73m²)

Nevertheless, the global increase in the incidence and prevalence of CKD is being driven by the global increase in the prevalence of diabetes mellitus, hypertension, obesity and aging.³ Globally CKD represents the 12th cause of death and 17th cause of disability.^{4,5} It is almost a truism to say that patients with end-stage renal failure (ESRD) are thought to represent the tip of the iceberg of the entire burden of CKD.¹

The major common causes of the CKD in our environment include hypertension, diabetes mellitus and chronic glomerulonephritis.

Disorders of mineral metabolism, secondary hyperparathyroidism, hyperphosphatemia, hypocalcaemia and deficiencies of vitamin D are common complications of CKD. Elevations in the calcium-phosphorus product are clearly associated with calcification of coronary arteries and with cardiovascular-related mortality in patients undergoing dialysis.⁶ Cardiovascular-related deaths remain the primary cause of mortality in patients with end-stage renal disease. Hyperphosphataemia, hyper- or hypocalcaemia, hypomagnesaemia and increased parathyroid hormone (PTH) plasma concentrations, all commonly observed in CKD, are also associated with increased mortality.⁷ Thus, prevention of the disturbances in mineral and bone metabolism and their management early in the course of CKD are vital for improving the patient's quality of life and longevity.

MATERIALS AND METHOD

This study was conducted at the departments of Chemical Pathology and Medicine of Ahmadu Bello University Teaching Hospital, Shika – Zaria within fifteen months. One hundred and twenty-five (125) consecutive adult patients 18 years and above in various stages of CKD who presented at the nephrology clinic of ABUTH Shika Zaria were enrolled into the study. Equal number of apparently healthy matched for sex and age controls were also recruited. Patient with acute renal failure, primary hyperparathyroidism and those who are pregnant were excluded from the study.

Approval was obtained from Ethical and Scientific committee of ABUTH Zaria before embarking on the study.

Five millilitres (5 mL) blood specimen was collected from a prominent peripheral vein. The antecubital fossa was cleaned with 70% methylated spirit and allowed to dry. Blood was taken using a sterilized 5 mL syringe and 21 G needle. 5 ml of the blood sample was transferred into a plain sample bottle and allowed to stand for 30 minutes to clot and thereafter was centrifuged at 4000rpm for 10 min. The serum was separated immediately and transferred into a serum bottle. Analysis of serum calcium was carried out immediately and the remaining serum was stored frozen at -20°C until time for analysis.

The data obtained were cleaned and entered into Statistical Package for the Social Sciences 17.0 (SPSS 17.0) for windows (SPSS Inc. Chicago, 17). Results were expressed as absolute numbers, percentages, means and standard deviations and ranges as appropriate. Serum calcium, phosphate, magnesium, vitamin D, parathyroid and creatinine obtained from the patients were compared with those of the controls using the two tailed Student's t-test. p-value of equal to or less than 0.05 ($p \leq 0.05$) was considered statistically significant. Categorical data were presented as frequencies and percentages while continuous data were summarized as mean \pm standard deviation. Discrete variables were analysed using χ^2 . Student's t-test was used to analyse continuous normally distributed variables.

The chemicals and kits used for the measurement of serum calcium, phosphate, magnesium, creatinine, were procured from LABKIT Barcelona while that for parathyroid hormone and vitamin D were procured from WKEA medical supplies (China).

Adequate quality control was observed when carrying out the analysis of the samples to ensure that the results obtained are reliable. This was done by analysing the samples in batches together with quality control sera from labkit for specific analytes using multi control. Pooled sera were used for parathyroid hormone and vitamin D.

RESULTS

One hundred and twenty-five (125) CKD patients aged 18 to 85 years were enrolled for the study CKD patients were in different stages, with 9% in stage 1, 16% in stage 2, 22% in stage 3, 12% in stage 4 and 41% in end stage renal disease (stage 5) (table 1). Hypertensive nephropathy is the leading cause of CKD with 45.6%, followed by diabetic nephropathy and adult polycystic kidney disease occurring with similar frequency of 16.8% each, while chronic glomerulonephritis accounted for the fourth cause with a frequency of 12%. Other sundry causes comprising sickle cell nephropathy, etc accounted for 5.6%.

Treatment modalities of CKD patients indicated that majority of the patients were on conservative treatment with 108 (86.4%) on conservative treatment, and 16 (12.8%) were on dialysis and 1(0.8%) had transplant.

Serum ionised calcium, vitamin D and eCrCl showed a progressive decline as the stage of CKD advances, while serum levels of phosphate, creatinine and iPTH showed a progressive increase as the stage of CKD advances. Serum magnesium showed a slight change even with advancing stages of CKD. The difference in mean serum levels of calcium, phosphorus, vitamin D, parathyroid hormone, creatinine and estimated creatinine clearance with different stages of CKD were statistically significant ($p < 0.05$). (table 2) Serum ionised calcium showed statistical significance difference between stages 1 and 4, 1 and 5, 2 and 4, 2 and 5 and stage 3 and 5. Serum phosphorus showed

statistical significance difference between stages 1 and 4, 1 and 5, 2 and 4, 2 and 5, 3 and 4, 3 and 5 and stage 4 and 5. Serum vitamin D and intact parathyroid hormone showed statistical significance difference between stages 1 and 3, 1 and 4, 1 and 5, 2 and 3, 2 and 4, 2 and 5 and stages 3 and 5. The difference in estimated creatinine clearance and serum creatinine were statistically significant across all the stages of CKD. (Table 3)

Table 4 showed that Estimated creatinine clearance (eCrCl) correlated negatively with phosphate ($r = -0.350$, $p = 0.00$), and iPTH ($r = -0.621$, $p = 0.00$) while serum creatinine correlated negatively with calcium ($r = -0.599$, $p = 0.00$) and positively with phosphate ($r = +0.526$, $p = 0.00$) and iPTH ($r = +0.449$, $p = 0.00$).

Table 1. Stages of CKD in studied patients

STAGES	n	Percentage (%)
1	11	9
2	20	16
3	27	22
4	15	12
5	52	41
Total	125	100

n = frequency CKD =Chronic Kidney Disease % = percentage

TABLE 2. Serum levels (mean± SD) of measured analytes in different stages of CKD

STAGES OF CKD	n	Ca ²⁺ (mmol/L)	Po ⁴⁻ (mmol/L)	Mg ²⁺ (mmol/L)	Vit D pg/mL)	iPTH (pg/mL)	Cr (µmol/L)
1	11	1.06±0.93	0.80±0.12	0.62±0.41	54.83±3.76	91.75±1.10	71±21
2	20	1.04±0.80	1.00±0.30	0.69±0.34	50.60±5.8	99.42±29.1	110±33
3	27	0.99±0.93	1.50±0.55	0.69±0.42	42.3±8.33	181.61±68.95	141±39
4	15	0.88±0.15	1.56±0.39	0.78±0.40	39.78±6.8	209.87±68.97	317±155
5	52	0.81±0.16	2.04±0.75	0.79±0.40	37.02±5.4	262.27±69.45	1278±604
p value		0.000	0.000	0.713	0.000	0.000	0.000

iPTH = intact parathyroid

vit D = vitamin D

CKD = chronic kidney disease

Cr = creatinine

Ca²⁺ = calciumMg²⁺ = magnesiumPo⁴⁻ = phosphate

p value = statistically significant if < 0.05

n = frequency

Table 3. Post hoc analysis between the studied analytes and various stages of CKD.

STAGE	eCrCl (mL/min/ 1.73m ²)	Ca ²⁺ (ionised) (mmol/L)	Po ⁴⁻ (mmol/L)	Mg ²⁺ (mmol/L)	Vit D (ng/mL)	iPTH (ng/mL)	Cr (µmol/L)
1 Vs 2	< 0.01	NS	NS	NS	NS	NS	< 0.00
1 Vs 3	< 0.00	NS	NS	NS	0.00	0.00	< 0.00
1 Vs 4	< 0.00	0.00	0.00	NS	0.00	0.00	< 0.00
1 Vs 5	< 0.00	0.01	0.00	NS	0.00	0.00	< 0.00
2 Vs 3	< 0.00	NS	NS	NS	0.00	0.00	< 0.00
2 Vs 4	< 0.00	0.01	0.00	NS	0.00	0.00	< 0.00
2 Vs 5	< 0.00	0.00	0.00	NS	0.00	0.00	< 0.00
3 Vs 4	< 0.00	NS	0.01	NS	NS	NS	< 0.00
3 Vs 5	< 0.00	0.02	0.00	NS	0.03	0.00	< 0.00
4 Vs 5	< 0.00	NS	0.01	NS	NS	NS	< 0.00

Ca²⁺ = calcium

vit D = vitamin D

NS = not significant

Po⁴⁻ = phosphorus

Cr = creatinine

Mg²⁺ = magnesium

Table 4. Correlation between the different measured analytes in CKD patients

Variables	r - value	p - value
Po ⁴⁻ / eCrCl	-0.340	0.00
iPTH/eCrCl	-0.621	0.00
Po ⁴⁻ /iPTH	0.332	0.00
iPTH/creatinine	0.449	0.00
Ca ²⁺ /iPTH	-0.325	0.00
Ca ²⁺ /Po ⁴⁻	-0.410	0.00
Ca ²⁺ /creatinine	-0.599	0.00
Po ⁴⁻ /creatinine	0.520	0.00

Ca²⁺ = calcium

iPTH = intact parathyroid hormone

Po⁴⁻ = phosphorus

Cr = creatinine

eCrCl = estimated creatinine clearance

DISCUSSION

Majority of the patients presented in late stages of CKD, with over 40% in ESRD requiring any form of kidney replacement treatment. Such trend was observed in the studies conducted in South Western Nigeria by Akinsola et al, in Ile-Ife 2004⁸ and Alebiosu et al, in Sagamu 2006.⁹ who also indicated in their series that majority of patients were in advanced stages of CKD. This is hardly surprising since CKD is asymptomatic in the early stages coupled with poor health seeking behaviour in this part of the country.

The high mean serum creatinine and eCrCl, found in patients with CKD in this study was similar to the findings of Chijioko et al, in Ilorin 2011 who also estimated eCrCl by the Cockcroft and Gault formula.¹⁰ This high mean creatinine levels may reflect the late presentation of majority of CKD patients in the study. This was similarly reported by Ifeoma et al, in Enugu in 2010 while assessing the enormity of CKD in south eastern Nigeria.⁴ This might be because many of the patients with advanced CKD were managed conservatively because they could not afford the cost of renal replacement therapy (RRT). The mean serum magnesium levels in patients showed no significant difference between the various stages of CKD neither was there any correlation with other analytes. This is similar to the work of Ortega et al in 2013 in Spain who found all the CKD patients in stages 4 and 5 (study population) had normal baseline serum magnesium and there was no correlation with serum calcium, phosphorus and parathyroid hormone.¹¹ The regulation and elimination of magnesium in patients with renal disease is somewhat understudied. However, in moderate CKD, the increase in the fractional excretion of magnesium compensates for the loss of renal function, such that serum levels are maintained within the normal range.

The finding of this study regarding iPTH and eCrCl was comparable with a previous study done by Rahman et. al in India, in 2005, who correlated the serum parathyroid hormone level with biochemical parameters in chronic renal failure in children.¹² Ian H. de Boer et al, also observed increased iPTH levels as the stage of CKD advances.¹³ This study has further confirmed that high PTH is a prominent feature in CKD as documented by Stalopoulos et al, (1996).¹⁴ The increased levels of mean serum iPTH may be related to reduction in serum calcium level and progressive rise of serum inorganic phosphate from early to advanced renal failure.

Looking at Renal capacity of handling calcium varies in the different stages of CKD, from at least CKD Stage 3 and onwards this trend was noticed in this work with increasing levels from stage 3 onwards. Other factors taken into consideration could be attributed to the black race and other factors other than the traditional markers like FGF23. The findings in this study on the correlation of biochemical analytes with stages of CKD with the exception of vitamin D agrees with that of Rahman et al, in 2005 and also with that of Malawadi et al, in India 2014.^{12,15}

Hypocalcaemia, hyperphosphataemia and hyperparathyroidism cuts across the stages of CKD with the exception of stage 1 while deficiency of vitamin D and magnesium derangement was noted in stages 3, 4 and 5. A greater percentage of hypocalcaemia occurred in stage 5 no comparable local Nigeria study was found in literature search.

CONCLUSION

From this present study, it was found that majority of the CKD patients are in the late stage of CKD with correlation of analytes more evident in the late stages of the disease. Biochemical derangements occurred in late, rather than early stages of CKD.

REFERENCES

1. Afolabi MO, Abioye-Kiteyi EA, Arogundade FA, Bello IS. Prevalence of chronic kidney disease in a Nigeria family practice population. SA Farm Pract. 2009; 51(2): 132-137.
2. Foundation, National Kidney. "KDOQI clinical practice guideline for diabetes and CKD: 2012 Update." American Journal of Kidney Diseases 60.5 (2012): 850-886
3. Olugbenga EA, Alebiosu CO. Burden of chronic kidney disease; An international perspective. ACKDJ 2010;17 (3);215-224

4. Ifeoma I U, Chinwuba K I, The enormity of chronic kidney disease in Nigeria: The situation in a teaching hospital in south east Nigeria. *J Trop Med*. 2010; 2010:1-6
5. World health organization, " global burden of disease march, 2006.
6. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality and morbidity in maintenance haemodialysis. *J Am Soc Nephrol* 2004; 15(8):2208-18.
7. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic haemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31(4):607-617.
8. Akinsola W, Odesanmi WO, Ogunniyi JO, Ladipo GO. Diseases causing chronic renal failure in Nigerians-a prospective study of 100 cases. *Afr J Med Sci* 1989; 18:131-7.
9. Alebiosu CO, Ayodele OO, Abbas A, Olutoyin A. Chronic renal failure at the Olabisi Onabanjo university teaching hospital, Sagamu, Nigeria. *Afr Health Sci* 2006;6(3):132-8.
10. Chijioke, A., Aderibigbe, A., Olarenwaju, T. O., Makusidi, A. M., Oguntoyinbo, A. E. Prevalence and pattern of cystic kidney diseases in Ilorin, Nigeria. *Saudi J Kidney Dis Transpl* 2010 21(6), 1172.
11. Ortega, Olimpia, Isabel Rodriguez, Gabriela Cobo, Julie Hinostroza, PalomaGallar, Carmen Mon, Milagros Ortiz et al. "Lack of Influence of Serum Magnesium Levels on Overall Mortality and Cardiovascular Outcomes in Patients with Advanced Chronic Kidney Disease." *IntScholarly Res Notices* 2013 (2013).
12. Rahman MH, Hosain MM, Sultana S, Jamal CY, Karim MA. Correlation of Serum parathormone level with biochemical parameters in chronic renal failure. *Indian Pediatrics* 2005; 42:250-54.
13. Ian H, IninaGorodetskaya, Belinda Young, Chi-yuan, Glenn MC. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR dependent, race dependent and associated with cardiovascular disease. *J Am Soc Nephrol* 2002; 13:2762-69.
14. Slatopolsky E, Firch J, Denda M, Ritter C, Zhong M, Dusso A, et al. Phosphate restriction prevents parathyroid gland growth. High phosphorus directly stimulates PTH secretion invitro. *J Clin Invest* 1996; 97(11):2534.
15. Malawadi, BN, SumaMN, PrashantV, Akila P, Anjalidevi BS, Manjunath S. "Secondary hyperparathyroidism in all the stages of chronic kidney disease in southern indian population." *IJPPS* 2014; 4:6

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