Original Research Article

Serum calcium and phosphorous balance in diabetic nephropathy and its correlation with glycated hemoglobin

Liji Kavuparambil1*, Ashok Kumar P.2, Jithesh T. K.1, Shifa Kollathodi1

1Department of Biochemistry, MES Medical College, Perinthalmanna, Kerala, India
2Department of Biochemistry, Rajah Muthiah Medical College, Annamalai University, Tamil Nadu, India

Received: 30 September 2021
Revised: 05 October 2021
Accepted: 06 October 2021

*Correspondence:
Liji Kavuparambil,
E-mail: lijinair05@gmail.com

ABSTRACT

Background: Timely control of hemoglobin A1c (HbA1c) level is very important in patients with diabetic kidney disease. Diabetic nephropathy brings changes in mineral metabolism. The changes in calcium and phosphorous level is a reason for increased morbidity or decreased quality of life in these patients. Conflicting reports are available on serum calcium level and decline in kidney function. This study is to analyse the changes in calcium and phosphorous level in different stages of diabetic nephropathy and its correlation with glycated haemoglobin.

Methods: A cross sectional study with 60 diabetic nephropathy patients admitted in MES Medical College for a period of 1.5 years. Patients with cardiac, liver, thyroid dysfunction, under dialysis were excluded from the study. Fasting blood sugar, HbA1c, calcium, phosphorous, creatinine were assessed by VITROS 5600 integrated system. The study population is divided into groups by two different means, according to HbA1c and estimated glomerular filtration rate (eGFR) value. Statistical analysis was performed by statistical package for the social sciences (SPSS) software. Level of significance calculated at 95%.

Results: eGFR value showed a highly significant correlation with age (p=0.016), creatinine (p≤0.00001), calcium (p≤0.00001), phosphorous (p≤0.00001) and HbA1c (p=0.00001). There was no significant difference in creatinine and eGFR between male and female subjects. Only eGFR (p=0.0396) showed a significant difference between poor and good glycaemic control groups.

Conclusions: This study shows highly significant correlation between the decreased eGFR hypocalcaemia, hyperphosphatemia, increased serum creatinine level and HbA1c. Strict glycemic control is crucial in maintenance of mineral homeostasis and prevention of blood calcium, phosphorous abnormalities.

Keywords: Glycated hemoglobins, Glomerular filtration rate, Diabetic nephropathy, Calcium

INTRODUCTION

Diabetic nephropathy (DN) is the major cause of chronic kidney disease and end-stage renal disease in people with type 2 diabetes mellitus (T2DM).1 According to data from the Indian Council of Medical Research (ICMR), the prevalence of diabetes in the adult population of India has increased to 7.1 percent.1 Importantly, as the incidence of T2DM has increased, so has the frequency of DN.1,2,3

Prevalence of disturbances in mineral metabolism is more in advanced stages of chronic kidney disease (CKD). Minimizing these derangements in mineral metabolism may be critical to delay progression of CKD.4 The whole body balance of calcium and phosphate is maintained by fine adjustments of urinary excretion to equal the net intake. Kidney regulate the homeostasis of calcium and phosphorous. Regulation occurs through different mechanism including glomerular filtration.5 The kidney disease: improving global outcomes (KDIGO) guidelines
recently identified aberrant bone mineral metabolism as CKD mineral and bone disease (CKD MBD), which contributes considerably to an increase in morbidity and mortality rates among patients with CKD. In Indian CKD patients, mineral metabolism abnormalities are more common, more severe, and emerge earlier in the course of CKD than in western populations. Monitoring for CKD-MBD should begin at early CKD stage. DN was the commonest cause for development of CKD.

Hemoglobin A1c (HbA1c) is a blood test that is used to track long-term glycemic control in persons with diabetes mellitus. HbA1c is linked to the risk of diabetic complications. Diabetes mellitus has a significant impact on calcium levels, and there is a strong negative link between glycemia management, as measured by a high HbA1c percentage, and a decrease in serum calcium levels, which is unaffected by gender or diabetes duration. Recent studies showed conflicting reports on the link between serum calcium level and decline in the kidney function.

This study is to find calcium and phosphorous balance in different stages of DN and its correlation with glycated hemoglobin.

**METHODS**

A cross-sectional study was done at MES Medical College, Kerala over a period of November 2019 to June 2021.

**Study design**

Study design was a cross-sectional study.

**Study place**

The study was conducted at the MES Medical College, Kerala.

**Study duration**

This study was conducted from November 2019 to June 2021.

**Inclusion and exclusion criteria**

This study conducted in DN patients with age 40-60 admitted in MES Medical College, Kerala. Patients with history of cardiac disorders, liver diseases, thyroid dysfunction, and those under dialysis were excluded from the study.

**Sample size**

Sample size is calculated using the equation for calculation of sample size from coefficient of correlation. A total of 60 DN patients were included as per the inclusion and exclusion criteria.

60 DN patients were sub grouped in two different ways according to HbA1c and estimated glomerular filtration rate (eGFR) values. The stages of diabetic kidney disease were defined according to the eGFR based on the guidelines of national kidney foundation. The different stages of DN determined by eGFR value, calculated using modification of diet in renal disease (MDRD) equation. Subjects were also grouped in to two, those with poor glycaemic control and good glycaemic control (HbA1c ≥7% and HbA1c <7%). Serum creatinine, fasting blood sugar, HbA1c, calcium and phosphorous were measured by the fully automated analyser, VITROS 5600 integrated system.

**Ethical approval**

Ethical approval for the study was obtained from research ethics board, scientific committee, MES Medical College (IEC/MES/07/2019). Informed consent was taken and confidentiality maintained.

**Statistical analysis**

Descriptive statistics like percentages, means was used for data summarization and presentation. The data were expressed as mean SD. Pearson correlation coefficient and unpaired t test were employed for inferential statistical analysis and a p<0.05 was considered as statistically significant. The significance of study parameters between different stages of DN has been measured by analysis of variance (ANOVA).

**RESULTS**

A total of 60 DN patients of age from 40-60 were enrolled in this study. Out of this 31 (52%) were males and 29 (48%) females (Figure 1). The study parameters are expressed as mean±standard deviation (SD). The eGFR showed a highly significant correlation with the parameters except fasting blood sugar level (Table 1). Hypocalcaemia and hyperphosphatemia were observed with decrease in eGFR.

![Figure 1: Gender distribution among the 60 participants.](image-url)
HbA1C variability is associated with progression of diabetic nephropathy. But other parameters showed no significant difference between the poor and good glycemic control groups (Table 2).

The subjects grouped in to 3 according to the eGFR value and distributed in stage 3-5 of diabetic nephropathy. 38% of the patients distributed in stage 3, 22% in stage 4 and 40% in stage 5 (Figure 2).

Analysis of variance (ANOVA) analysis showed a significant difference in creatinine, calcium and phosphorous between these 3 groups (Table 3). Decreased calcium, increased phosphorous and increased creatinine level were observed with a decline in eGFR value. Correlation between eGFR and other parameters is determined in each group (Table 4). A highly significant decrease in serum calcium with decrease in eGFR observed in stage 3. Creatinine showed a highly significant increase with decline in eGFR in stage 3, 4 and 5 of DN.

Table 1: Correlation of study parameters with eGFR.

| Parameters | Mean±SD | Correlation with eGFR | r   | P value |
|------------|---------|-----------------------|-----|---------|
| Age        | 57.4±7  | 0.308                 | 0.01666 |
| FBS        | 164.7±50.4 | -0.1632             | 0.21336 |
| Cr         | 4.07±3.51 | -0.7408              | <0.00001* |
| HbA1c      | 8.95±28.9 | -0.5315              | 0.00001* |
| Ca         | 8.4±0.54  | 0.7033                | <0.00001* |
| P          | 5.07±1.04 | -0.6771              | <0.00001* |

*Indicates highly significant; significance is measured at the level of p<0.05

Figure 2: Distribution of DN patients at different stages.

Table 2: Comparison of Ca and P in good and poor glycemic control group.

| Parameters | HbA1c <7 Mean±SD | HbA1c ≥7 Mean±SD | T value | P value |
|------------|------------------|------------------|--------|---------|
| Calcium    | 8.53±0.59        | 8.37±0.53        | 0.8365 | 0.2031  |
| Phosphorous| 4.62±0.81        | 5.17±1.07        | -1.5242 | 0.0664  |
| Creatinine | 2.61±1.9         | 4.41±3.7         | -1.4891 | 0.0709  |
| eGFR       | 34.7±7.12        | 22.96±17.3       | 1.96396 | 0.0272* |

*Indicates highly significant; significance is measured at the level of p<0.05

Table 3: Correlation of eGFR with other parameters in different stages of DN.

| Parameters | Stage 3 | Stage 4 | Stage 5 |
|------------|---------|---------|---------|
| Age        | Mean±SD | R value | P value | Mean±SD | R value | P value | Mean±SD | R value | P value |
| Age        | 59.5±6.7 | -0.048 | 0.828 | 59.1±6.8 | 0.389 | 0.189 | 54.4±6.4 | 0.212 | 0.319 |
| FBS        | 152.8±39.2 | 0.008 | 0.97 | 173.9±55.7 | -0.095 | 0.757 | 171.2±56.9 | 0.061 | 0.779 |
| Creatinine | 1.46±0.32 | -0.706 | 0.00016* | 2.73±0.59 | -0.760 | 0.002* | 7.29±3.45 | -0.706 | 0.0001* |
| HbA1c      | 8.04±2  | -0.369 | 0.0831 | 7.87±1.01 | -0.165 | 0.601 | 10.41±1.8 | 0.033 | 0.113 |
| Calcium    | 8.81±0.24 | 0.784 | <0.00001* | 8.32±0.47 | 0.111 | 0.718 | 8.04±0.5 | 0.439 | 0.032 |
| Phosphorus | 4.28±0.58 | -0.427 | 0.0421 | 5.18±0.6 | -0.017 | 0.956 | 5.8±1.06 | -0.304 | 0.149 |

*Indicates highly significant; significance is measured at the level of p<0.05

DISCUSSION

In the present study, we investigated the correlation of eGFR with fasting blood sugar, serum creatinine, calcium, phosphorous and HbA1c. The result showed a highly significant negative correlation with creatinine, phosphorous, HbA1c and a highly significant positive correlation with serum calcium level. Similar to this, Freethi et al reported a significant increase in serum phosphorous level in cases compared with control.15 Floege et al also reported hyperphosphatemia as the
disease progresses and concluded it as a risk factor for increased mortality rate in CKD.\textsuperscript{16} Haglin et al, Park et al and Pawar et al showed the negative correlation between serum phosphate levels and fasting blood sugar levels.\textsuperscript{17-19} Hus et al revealed a significant decrease in calcium among these patients and agrees with the study reported in Iraq.\textsuperscript{20,21} Lupica et al reported unexpected hypercalcemia in diabetic kidney disease without any microangiopathic alterations.\textsuperscript{22}

In our study we observed a significant difference in serum calcium, phosphorous and creatinine in different stages of diabetic nephropathy. Correlation between eGFR and other parameters in 3 stages of DN showed a highly significant decrease in serum calcium in stage 3 of diabetic nephropathy. Janmaat et al demonstrated that lower baseline serum calcium, but within the normal reference range, is associated with a subsequent more rapid eGFR decline in individuals with CKD stages 3b-5.\textsuperscript{23} Lim et al reported low serum calcium to be associated with a faster kidney function decline in a pooled cohort of CKD stage 3–4 patients.\textsuperscript{24} Schwarz et al found no association between calcium and CKD progression in CKD stage 1–5 patients.\textsuperscript{12}

Limitations

Present study was single centred with small sample size.

CONCLUSION

This study showed a highly significant correlation between the decreased eGFR hypocalcaemia, hyperphosphatemia, increased serum creatinine level and HbA1c. Analysing the correlation in different stages of diabetic nephropathy, lowered calcium level highly correlated with declined kidney function strict glycemic control is crucial in maintenance of mineral homeostasis and prevention of blood calcium, phosphorous abnormalities.

ACKNOWLEDGEMENTS

Authors would like to extend heartfelt thanks to Dr. Sheela P. Haveri, Professor and HOD, and Dr. Kanniyan Binub, Associate professor, Department of Community Medicine for the statistical support. They would want to thank Dr. Raju A. Gopal, Associate Professor, endocrinologist and diabetologist, MES Medical College for the clinical support and Ms. Linimol Paul, lab-in-charge, central laboratory for the technical support at the beginning of their study. Also they would like to thank Dr. Sethupathi S., Dr. Santha K., Dr. Inmozhi Sivagamasundhari and Dr. Bhaskaran, Department of Biochemistry, Rajah Muthiah Medical College, Annamalai University for their support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Zhang XX, Kong J, Yun K. Prevalence of Diabetic Nephropathy among Patients with Type 2 Diabetes Mellitus in China: A Meta-Analysis of Observational Studies. J Diabet Res. 2020;1:1-11.
2. Varma PP. Prevalence of chronic kidney disease in India - Where are we heading? Indian J Nephrol. 2015;25(3):133-5.
3. Wu AYT, Kong NCT, de Leon FA, Pan CY, Yeung VTF, Rouillon A, Weir MR. An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetic patients: The Micro Albuminuria Prevalence (MAP) study. Diabetologia. 2005;48(1):17-26.
4. Ting IW, Yeh HC, Huang HC, Chiang HY, Chu PL, Kuo CC. Joint Longitudinal Low Calcium High Phosphorus Trajectory Associates with Accelerated Progression, Acute Coronary Syndrome and Mortality in Chronic Kidney Disease. Nature. 2020;10:9682.
5. Blaine J, Chonchol M, Levi M. Renal Control of Calcium, Phosphate, and Magnesium Homeostasis. Clin J Am Soc Nephrol. 2015;10:1257-72.
6. Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olaard K. Definition, evaluation, and classification of renal osteodystrophy: A position statement from kidney disease: Improving global outcomes (KDIGO). Kidney Int. 2006;69:1945-53.
7. Russo D, Corrao S, Battaglia Y, Andreucci M, Caiazza A, Carlmagno A, et al. Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis. Kidney Int. 2011;80:112 8.
8. Vikrant S, Parasher A. Prevalence and severity of disordered mineral metabolism in patients with chronic kidney disease: A study from a tertiary care hospital in India. Indian J Endocr Metab. 2016;20:460-7.
9. Rajapurkar MM, John GT, Kirpalani AL, Abraham G, Agarwal SK, Almeida AF, et al. What do we know about chronic kidney disease in India: first report of the Indian CKD registry? BMC Nephrology. 2012;13:10.
10. Randie R, William LA. Review of Variant Hemoglobins Interfering with Hemoglobin Alc Measurement. J Diabet Sci Tech. 2009;3:446-50.
11. Hassan ABE, Elsheikh WAR, Rahman NIA, Elbagir NM. Serum Calcium Levels in Correlation with Glycated Hemoglobin in Type 2 Diabetic Sudanese Patients. Adv Diabet Metabol. 2016;4(4):59-64.
12. 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;1:825-31.
13. Bargman JM, Skorecki K. Chronic kidney disease. In Braunwald E, Fauci AS. Harrison’s Principles of Internal Medicine. 18th edition. New York: Mc Graw Hill International Publication. 2011:2:2308.
14. Sharma AP, Yasin A. Diagnostic accuracy of creatinine based eGFR Equations at different GFR
levels in children. Clin J Am Soc Nephrol. 2011;6:1599-608.
15. Freethi R, Raj AV, Ponniraivan K, Khan MR, Sundhararajan A, Venkatesan. Study of serum levels of calcium, phosphorus and alkaline phosphatase in chronic kidney disease. Int J Med Res Health Sci. 2016;5(3):49-56.
16. Sirgrist MK, Taal MW, Bungay P, McIntyre CW. Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney diseases. Clin J Am Soc Nephrol. 2007;1241-8.
17. Haglin L, Lindblad A, Bygren LO. Hypophosphataemia in the metabolic syndrome. Gender differences in body weight and blood glucose. Eur J Clin Nutr. 2001;55(6):493-8.
18. Park W, Kim BS, Lee JE, Huh JK, Kim BJ, Sung KC, et al. Serum phosphate levels and the risk of cardiovascular disease and metabolic syndrome; a double-edged sword. Diabetes Res Clin Pract. 2009;83(1):119-25.
19. Pawar A, Prasad S, Kumar R, Sharma P, Manhas S, Bhutani K, Kumar M. Effects of diabetic nephropathy on phosphorous homeostasis. Int Educ Res J. 2019;5(1):1-9.
20. Hus AI, Tahleel B, Hasan AEI, Albagir EH, Mohammad MA, Salah S, Elmahdi SA. Serum Calcium Level in Type 2 Diabetes Mellitus in Khartoum State. Clin Microbiol. 2019;8:332.
21. Dabelea D, Stafford JM, Mayer-Davis EJ, Dolan L, Linder B, et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA. 2017;317:825-35.
22. Lupica R, Buemi M, Campenni A, Trimboli D, Canale V, Cernaro V, Santoro D. Unexpected hypercalcemia in a diabetic patient with kidney disease. World J Nephrol. 2015;4(3):438-43.
23. Janmaat C, Diepen MV, Gasparini A, Evans M, Qureshi AR, Arnlov J, et al. Lower serum calcium is independently associated with CKD progression. Scientific Rep. 2018;8:5148.
24. Lim LM, Kuo HT, Kuo MC, Chiu YW, Lee JJ, Hwang HJ, Tsai JC, Hung CC, Chen HC. Low serum calcium is associated with poor renal outcomes in chronic kidney disease stages 3-4 patients. BMC Nephrol. 2014;15:183.

Cite this article as: Kavuparambil L, Pammi AK, Kattil JT, Kollathodi S. Serum calcium and phosphorous balance in diabetic nephropathy and its correlation with glycated hemoglobin. Int J Adv Med 2021;8:xxx-xx.