

Efficacy of hemodialysis and other therapeutic measures in controlling hypocalcemia, hyperphosphatemia and elevated ALP in a group of patients with end-stage renal disease

Israa Nathir¹, Raid D. Hashim^{2*}, Omar Faridh Fawzi³

¹Al-Rasheed University College, Department of Pharmacy, Baghdad, Iraq

^{2,3}Al-Rasheed University College, Department of Dentistry, Baghdad, Iraq,

*Corresponding author:

Raid D. Hashim

vsd9@gmail.com

Abstract

Chronic kidney disease represents (CKD) a major global cause of morbidity and mortality. Its prevalence increased with the increased prevalence of hypertension and diabetes mellitus. CKD is associated with a wide range of metabolic disturbance including hypocalcemia and hyperphosphatemia which are usually associated with high activity of serum alkaline phosphatase (ALP). These disturbances require careful assessment and proper management as they are predictors of poor prognosis. Unfortunately, in many instances, the correction of these disturbances is relatively difficult. The current study aims to evaluate the serum levels of calcium, phosphorus, and ALP in a group of patients with CKD on hemodialysis. A total number of 160 patients with CKD on regular hemodialysis have been enrolled in the current study irrespective of the underlying cause of their CKD. These patients used to attend a hemodialysis center in Baghdad on a regular basis, usually twice weekly from the 13th of January to the 21st of February 2019. All participants were assessed for serum calcium, phosphorus, and ALP in addition to their routine laboratory tests. The results were statistically evaluated using SPSS software version 23. The results reflect the relative difficulty in controlling these metabolic disturbances. Hyperphosphatemia has been detected in 66% of participants, hypocalcemia in 41%, while 35% of participants have shown elevated serum ALP. Furthermore, most participants have more than a single disturbance where the combined hypocalcemia and hypophosphatemia represent the major form of combined disturbance (35%). Despite the progression in modalities of treatment of CKD, including hemodialysis, the correction of its associated metabolic disturbances remains a challenge especially hyperphosphatemia and to lesser extent hypocalcemia.

Keywords: Hemodialysis, hypocalcemia, hyperphosphatemia, ALP, CKD

How to cite this article: Nathir I, Hashim RD, Fawzi OF (2020: Efficacy of hemodialysis and other therapeutic measures in controlling hypocalcemia, hyperphosphatemia, and elevated ALP in a group of patients with end-stage renal disease, *Ann Trop Med & Public Health*; 23(S14): SP231427. DOI: <http://doi.org/10.36295/ASRO.2020.231427>

Introduction

Chronic kidney disease (CKD) is considered as one of the major causes of morbidity and mortality all over the world with increasing prevalence secondary to the universal increase in the prevalence and incidence of obesity, hypertension and diabetes⁽¹⁾. It is characterized by significant impairment in the normal physiological and metabolic function including anemia, vitamin D deficiency, insulin resistance, metabolic acidosis, dyslipidemia, malnutrition, decreased exercise tolerance, electrolyte disturbance with many other abnormalities⁽²⁾.

Diagnosis of CKD depends on the presence of decreased estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m² or one of the markers of renal damage for more than 3 months; these markers include histological abnormalities, abnormalities in urine sediment (granular, red cell or white blood cell casts, hematuria or the presence of renal tubular epithelial cells), structural abnormalities evident by imaging, history of renal transplantation, electrolyte abnormality secondary to tubular disorders or albuminuria (urinary albumin/creatinine ratio [ACR] \geq 30 mg/g)⁽³⁾. The burden of CKD on the health care system and the patient himself increases with the development of end-stage renal disease (ESRD) and the urgent need for renal replacement therapy making an early diagnosis of CKD and preventing its progression into ESRD of great importance. Specifically, hypocalcemia,

hyperphosphatemia, and increased ALP activity are of the most common metabolic derangement that accompanies CKD. These findings were observed to be associated with poor cardiovascular outcomes and a high mortality rate in patients with CKD on regular hemodialysis⁽⁴⁾.

Hypocalcemia during CKD is attributed to two main reasons, the hyperphosphatemia and the impaired activation of vitamin D. The elevated serum level of phosphorus is associated with increased precipitation of calcium in bone and other tissues while impaired activation of vitamin D is associated with decreased absorption of calcium in the intestine⁽⁵⁾. Furthermore, in patients with advanced CKD, the lower the basal serum calcium concentration the faster the progression of CKD⁽⁶⁾. Impaired renal excretion of inorganic phosphate is the major cause of hyperphosphatemia in patients with CKD despite the various compensatory mechanisms that are activated in response to this hyperphosphatemia which in turn leads to renal osteodystrophy, cardiovascular calcification and secondary hyperparathyroidism⁽⁷⁾.

This is why it is highly recommended to restrict dietary phosphate and take phosphate binders in patients with CKD⁽⁸⁾. The activity of serum ALP is expected to be high in patients with CKD due to the high bone turnover secondary to various metabolic dysfunction regarding parathyroid hormone and vitamin D. ALP has been correlated to the increased mortality rate and cardiovascular calcification in patients with CKD on dialysis⁽⁹⁾. The efficacy of various modalities of treatment, including dialysis, for these metabolic abnormalities, is variable and many studies have emphasized on this subject. The aim of the current study is to evaluate the ability of dialysis together with other modalities of treatment in the correction of hypocalcemia, hyperphosphatemia and elevated ALP activity in patients with CKD on regular hemodialysis.

Materials and methods

A total number of 160 adult patients were included in the current study, they represented the major portion of patients with CKD treated with hemodialysis twice weekly in a specialized hemodialysis center in Baghdad over the period from 13th of January to 21st of February 2019. Patients excluded from this study were those with acute kidney injury requiring hemodialysis, newly diagnosed with end-stage renal disease, pediatric age group and patients with any possible disorder of calcium and phosphorus other than CKD. Patients included in the current study have not been categorized according to the primary cause of CKD, or the presence of the expected complication of CKD, it has been emphasized on the duration of starting hemodialysis selecting patients with a relatively long history of CKD, attending dialysis center on regular basis. All participants were checked for their compliance with vitamin D and calcium supplements with phosphate binders.

In addition to the routine laboratory investigations, serum level of calcium (Ca), phosphorus (PO₄) and alkaline phosphatase (ALP) were measured for all participants. Other laboratory tests including complete blood count, liver function test, lipid profile, electrolytes, and other specific tests according to patient requirements have been assessed as well. Ca, PO₄, and ALP were measured using the Biolab auto-analyzer, daily quality control program has been applied and the results were evaluated before considering patients' results as dependable. The reference range of calcium is 8.4-10.4 mg/dl, the reference range of phosphorus is 2.5-4.5 mg/dl, while the reference range of ALP is 30-129 IU/l. The results were statistically evaluated using SPSS software version 23.

Results

A total number of 160 adult patients were involved in the current study, 91 were males while 69 were females. The mean age of the whole participants was 58 years (SD 12.6). The distribution of metabolic disturbance in serum Ca, PO₄ and ALP was variable. It is well known that the expected metabolic changes regarding parameters estimated in the current study are increased ALP activity, hypocalcemia and hyperphosphatemia, but the exact distribution of these changes is the real goal. Mean ALP activity of the studied patients was 130 IU/l (SD 67.4), the mean serum calcium level of the studied patients was 8.0 mg/dl (SD 1.65), while mean serum phosphorus level of the studied patients was 5.6 mg/dl (SD 2.1) as shown in table 1. Patients with increased activity of ALP were 56 patients (35%), patients with hypocalcemia were 66 patients (41%), and patients with hyperphosphatemia were 106 (66%), as shown in table 2.

It was noticed that only 31 patients (19%) of the total studied patients had no disturbance regarding ALP, calcium, or phosphorus. At the same time, only 27 patients (16%) had disturbances in all the previously mentioned laboratory tests. These findings clarify that most patients in the current study had a disturbance in one or two of the estimated laboratory tests. Accordingly, the distribution of a single metabolic disturbance was as follows: patients with

isolated increased ALP activity were only 6 (4%), patients with isolated hypocalcemia were only 4 (2%), while patients with isolated hyperphosphatemia were 27 (16%), as shown in table 3. Similarly, patients with combined metabolic disturbance were as follows: patients with combined high ALP and hypocalcemia were 33 (20%), patients with combined high ALP and hyperphosphatemia were 43 (27%), patients with combined hypocalcemia and hyperphosphatemia were 55 (34%), as shown in table 4.

Table 1: Mean serum level of calcium, phosphorus and ALP in the studied group.

Laboratory test	Mean	SD
ALP	130	67.4
Calcium	8.0	1.65
Phosphorus	5.6	2.1

Table 2: Distribution of metabolic disorders among participants

Metabolic disturbance	Number of patients	Percentage
Elevated ALP	56	35
Hypocalcemia	66	41
Hyperphosphatemia	106	66

Table 3: Distribution of isolated metabolic disturbance among participants

Metabolic disturbance	Number of patients	Percentage
Isolated high ALP	6	4
Isolated hypocalcemia	4	2
Isolated hyperphosphatemia	27	16

Table 4: Distribution of combined metabolic disturbance among participants

Metabolic disturbance	Number of patients	Percentage
Combined high ALP and hypocalcemia	33	20
Combined high ALP and hyperphosphatemia	43	27
Combined hypocalcemia and hyperphosphatemia	55	34

Discussion

Metabolic abnormalities in patients with CKD are quite common, and despite the development in the modalities of treatment and the increasing availability of renal replacement therapy, these abnormalities remain a difficult challenge for physicians and carry a high risk of developing morbidity & mortality in such patients. Hypocalcemia is a well-known associated metabolic disorder in patients with advanced stages of CKD, even in those whom renal replacement therapy is not yet indicated. The prevalence of hypocalcemia was so prominent in the current study where 41% of the participants had hypocalcemia of variable severity despite their regular supplement of both calcium and vitamin D. Many other similar studies have shown variable severity of hypocalcemia in patients with CKD on hemodialysis.

Ying-Ping sun has observed that 34% of studied patients had hypocalcemia and the mean serum calcium level was 8.9 mg/dl which are nearly comparable to the results of the current study⁽¹⁰⁾, while a similar study performed in India has shown a much less prevalence of hypocalcemia reaching 15.6%⁽¹¹⁾. In Nepal, Rajbhandari A and his colleagues have shown a significantly higher prevalence reaching 75% of the studied patients with stage 5 CKD in the predialysis state, where mean serum calcium level was 8.0 mg/dl⁽¹²⁾. These studies and many others highlight the relative difficulties in controlling hypocalcemia in patients with CKD on hemodialysis despite daily supplement of both vitamin D and calcium which necessitate more aggressive therapy although infrequent studies have shown a

much better result with normal mean serum calcium or very low prevalence of hypocalcemia among the studied patients^(6,13).

Ying-Ping sun has observed that 34% of studied patients had hypocalcemia and the mean serum calcium level was 8.9 mg/dl which are nearly comparable to the results of the current study⁽¹⁰⁾, while a similar study performed in India has shown a much less prevalence of hypocalcemia reaching 15.6%⁽¹¹⁾. In Nepal, Rajbhandari A and his colleagues have shown a significantly higher prevalence reaching 75% of the studied patients with stage 5 CKD in predialysis state, where mean serum calcium level was 8.0 mg/dl⁽¹²⁾. These studies and many others highlight the relative difficulties in controlling hypocalcemia in patients with CKD on hemodialysis despite daily supplement of both vitamin D and calcium which necessitate more aggressive therapy although infrequent studies have shown a much better result with normal mean serum calcium or very low prevalence of hypocalcemia among the studied patients^(6,13).

All these findings and many others are indicators for the more required attention regarding hyperphosphatemia in patients with CKD especially with more evidence about the role of hyperphosphatemia in increased morbidity and mortality in such patients. Elevated activity ALP is an expected finding in many medical conditions of hepatic or bony source, although it might be elevated in physiological conditions as well as in children & during pregnancy. The current study has shown that the mean activity of ALP was 130 IU/L and the prevalence of high ALP activity was 35% of the participants. These results were comparable to results obtained by other similar studies performed in the USA (32.8%) and Italy (32.9%) although much less prevalence of elevated ALP in patients with stage 5 CKD has been shown in other similar studies as in a study in South Korea where the prevalence was 10.4%⁽¹⁷⁾ while it was 18.7% in a similar study in Taiwan^(18, 19).

It is obvious that the severity and prevalence of hypocalcemia, hyperphosphatemia, and elevated ALP are highly variable among studies, even in the same country. This can be explained by many factors including the availability of treatment including hemodialysis, compliance of the patient with both to diet and drug therapy. In conclusion, the prevalence of hypocalcemia & hyperphosphatemia and elevated ALP activity is relatively high among patients with CKD on stage 5. These metabolic disorders seem to be difficult to be corrected even with proper follow-up and treatment. Hyperphosphatemia represents the most prevalent and most difficult disorder to be treated compared to hypocalcemia & elevated ALP activity and it requires more attention.

Compliance with ethical standards

Funding: This study was funded by the three authors of it; Raid D. Hashim, Israa Nathir and Omar Faridh Fawzi.

Conflict of interest: Author Raid D. Hashim, author Israa Nathir, and author Omar Faridh Fawzi declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies involving animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participant included in the study.

References

1. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736–88.
2. Slee AD. Exploring metabolic dysfunction in chronic kidney disease. *Nutr Metab*. 2012;9:1–16.
3. Fraser SD, Blakeman T. Chronic kidney disease: identification and management in primary care. *Pragmatic Obs Res [Internet]*. 2016 [cited 2019 Oct 15];7:21–32.
4. Liu C Te, Lin YC, Lin YC, Kao CC, Chen HH, Hsu CC, et al. Roles of serum calcium, phosphorus, PTH and ALP on mortality in peritoneal dialysis patients: A nationwide, population-based longitudinal study using TWRDS 2005–2012. Vol. 7, *Scientific Reports*. Nature Publishing Group; 2017.
5. Langman CB, Cannata-Andía JB. Calcium in chronic kidney disease: Myths and realities. *Clinical Journal of the American Society of Nephrology*. 2010;5(SUPPL. 1).

6. 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 Dec 1;8(1).
7. Shaman AM, Kowalski SR. Hyperphosphatemia Management in Patients with Chronic Kidney Disease. Vol. 24, *Saudi Pharmaceutical Journal*. Elsevier B.V.; 2016. p. 494–505.
8. Andrea C, Ospina G, Cielo Holguín M, Cáceres Escobar D, Restrepo Valencia CA. (No Title). *Rev Colomb Nefrol* [Internet]. 2017 [cited 2019 Nov 21];4(1):24–41.
9. Kovesy CP, Ureche V, Lu JL, Kalantar-Zadeh K. Outcome predictability of serum alkaline phosphatase in men with pre-dialysis CKD. *Nephrol Dial Transplant* [Internet]. 2010Sep1[cited2019Nov21];25(9):3003–11.
10. Sun YP, Yang WJ, Li SH, Han YY, Liu J. Clinical epidemiology of mineral bone disorder markers in prevalent hemodialysis patients in the Xinjiang uyghur autonomous region in China. *Biomed Res Int*. 2017;2017.
11. Vikrant S, Parashar 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 Endocrinol Metab* [Internet]. 2016 [cited 2019 Nov 23];20(4):460.
12. Rajbhandari A, Agrawal RK, Baral A, Pokhrel A, Shrestha D, Hada R. Estimation of Serum Vitamin D, Calcium and Phosphorus in Chronic Kidney Disease. *Med J Shree Birendra Hosp*. 2017 Aug 21;16(1):30–6.
13. 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 Heal Sci*. 2016;5(3):49–56.
14. Afifi A, El-Sayed H, El-Setouhi M, Ahmed H, Khalifa N. Hyperphosphatemia among end-stage renal disease patients in developing countries: A forgotten issue? *Hemodial Int*. 2005 Oct;9(4):409–15.
15. Okoye JU, Arodiwe EB, Ulasi II, Ijoma CK, Onodugo OD. Prevalence of CKD-MBD in pre-dialysis patients using biochemical markers in enugu, south-east Nigeria. *Afr Health Sci*. 2015;15(3):941–8.
16. Blayney MJ, Pisoni RL, Bragg-Gresham JL, Bommer J, Piera L, Saito A, et al. High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. *Kidney Int*. 2008 Sep;74(5):655–63.
17. Jin K, Ban TH, Jung JY, Kim AJ, Kim Y, Lee SY, et al. Stabilization of serum alkaline phosphatase in hemodialysis patients by implementation of local chronic kidney disease-mineral bone disorder management strategy: A quality improvement study. *Kidney Res Clin Pract*. 2018;37(2):157–66.
18. Zhu J-G, Cheng B-C, Lee W-C, Li L-C, Lee C-H, Long G, et al. Serum Alkaline Phosphatase Levels are Not Associated with Increased Death Risk in Prevalent Hemodialysis Patients: 5-Year Experience in a Single Hemodialysis Center. *Kidney Blood Press Res* [Internet]. 2016 [cited 2019 Nov 28];41(4):498–506.
19. Sahib, A.H.A., Al-Shareefi, E. and Hameed, I.H., 2019. *Harpagophytum procumbens* and *Cordia myxa*: In vitro Antibacterial Activity and Bioactive Compounds of Methanolic Fruit Extract Using Fourier-Transform Infrared Spectroscopic Technique. *Indian Journal of Public Health Research & Development*, 10(1), pp.981-987.