Evaluation of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Among Patients on twice weekly Hemodialysis in Khartoum Teaching Hospital, Sudan

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ABSTRACT

Background: Many predictors of morbidity and mortality in dialysis patients but bone metabolism remains one of the important factors. Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for bone metabolism and disease in chronic kidney disease (CKD) recommend that, in Stage 5 CKD, the target levels for calcium (Ca) (corrected for serum albumin), phosphate (P), calcium X phosphate (Ca X P) product and parathyroid hormone (PTH) levels should be maintained at 8.4-9.5 mg/dl, 3.5-5.5 mg/dl, < 55 mg2/dl2 and 150-300 pg /ml, respectively.

Objectives: To recognize the effectiveness of twice per week haemodialysis (8 hours per week dialysis) in achieving the control level of calcium, phosphorus, calcium phosphorus products according to K/DOQI guidelines.

Patients & Methods: A prospective observational cross-sectional hospital based study was conducted on 77 adult patients with End Stage Renal Disease (ESRD) who received complete two sessions of haemodialysis per week equivalent to eight hours/week hemodialysis.

Personal and demographic data was collected together with the data regarding calcium, phosphorus, calcium times phosphorus (ca X po4) product, PTH, Serum Albumin, information of the dialysis session, co-morbidities according to Davis score. Data was analysed using software program SPSS v 16. Correlation between control of mineral and bone disorder and co-morbidities was tested using Qui-Square test (α 0.05).

Results: The aetiology of ESRD was not recognized in 33.8% and thirty-two patients (41.6%) were hypertensive prior to initiation of hemodialysis Forty-two patients (54.5%) maintained residual renal function (RRF) as defined 24hours diuresis ≥ 100 ml. 84% of patient (n=65) had their HD sessions through arterio-venous (AVF.) About 88.2% of patients with AVF had mild Davies's score. While 20% and 75% of patients with jugular catheter either had moderate or severe score respectively, this relation found to be significant (p= 0.002).

The percentage of patients whose Ca, P, Ca X p product and PTH were within K/DOQI recommended ranges were 43%, 36%, 65% and 21% respectively. All the patients with target level of phosphorus had target level of ca x po4 product and 75% of patient with phosphorus level above the target had ca x po4 product above the target level also (P=0.0001). On the other hand serum calcium had no significant effect on the ca x po4 product (P= 0.24).

We found 85% of our study population used to take the fixed dose of 1500mg caco3 in 3 divided doses per day despite variation in their bone biochemical parameters. But on the other hand, 88.9% of patients with above target PTH level appropriately prescribed Vitamin D and 37.5% with target level of PTH did not take vitamin D (p=0.04).
Sixty out of the 77 patients in the study (78%) prescribed similar dose of Alfacalcidol (0.25ug/day) regardless of the level of PTH, in the other words this means 26 out of the 34 patients with low PTH (76.4%) were prescribing Alfacalcidol despite their lower level of PTH rendering them to in threat of developing dynamic bone disease.

Conclusion: Current clinical management of chronic kidney disease-metabolic bone disorder CKD-MBD is far from reaching the target set by K/DOQI guidelines not only because of twice weekly HD but also due to inappropriate phosphate binders and vitamin D prescriptions. Other approach rather than medical intervention such as well-planned parathyroidectomy need to be considered for management of uncontrolled secondary or tertiary hyperparathyroidism.

Keywords: Chronic kidney disease (CKD), Hemodialysis, End stage renal disease (ESRD), Kidney Disease Outcomes Quality Initiative (K/DOQI), Mineral and Bone Disorder

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INTRODUCTION

The national Centre for kidney disease and surgery was established in 1994 and the Sudan program for organ transplantation was launched in 2000, in 2005 the continuous peritoneal dialysis program became available for Sudanese patients[1]. In Sudan diabetes mellitus is one of the most important reasons of Chronic Kidney Disease (CKD) with higher percentage reach 50.3% in those with diabetes compared to nondiabetic patients[2]. Mineral metabolism has appeared as an important predictor of morbidity and mortality in dialysis patients. Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines for bone metabolism and disease in chronic kidney disease (CKD) recommend that, in Stage 5 CKD, the target levels for calcium (Ca) (corrected for serum albumin), phosphate (P), calcium x phosphate (Ca x P) product and parathyroid hormone (PTH) levels should be maintained at 8.4-9.5 mg/dl, 3.5-5.5 mg/dl, <55 mg2/ dl2 and 150-300 pg/ml, respectively[3]. Calcium carbonate (CaCO3) binds phosphorus efficiently but usually leads to higher calcium level, specifically in those with low turnover bone malady; a positive calcium balance leading to calcification in the vessels, valves, cardiac and distant calcification[4,5]. Recently some studies suggest to use lower calcium dialysate as treatment for patients with a dynamic bone disease can lead to improvement in bone density (1.0–1.25mmol/L)[6]. several assays are currently available that measure bone remodelling process either turn over (BTMs) or renewal. Such as measurement of the by products from collagen destruction or formation from bone cells[7,8]. The serum level of bone-specific alkaline phosphatase and osteocalcin reflect the cellular activity of osteoblasts[9,10]. The treatment of secondary hyperparathyroidism in chronic renal failure has evolved based upon new insights into the pathogenesis and clinical features of this disorder from a molecular standpoint, there are three major possible targets that regulate parathyroid gland function; G-protein-coupled calcium-sensing receptor (CaSR), Vitamin D receptor (VDR) and Putative extracellular phosphate sensor. Kidney failure disrupts systemic calcium and phosphate homeostasis and affects the bone, gut and parathyroid glands. This occurs because of decreased renal excretion of phosphate and diminished renal hydroxylation of 25-hydroxyvitamin D to calcitriol (1,25-dihydroxyvitamin D. Progressive kidney dysfunction results in hyperphosphatemia and calcitriol deficiency. The CaSR, which is highly expressed in the parathyroid glands, permits variations in the serum calcium concentration to be sensed by the parathyroid gland, leading to the desired changes in PTH secretion. The fall in serum calcium concentration with renal failure, as sensed by the CaSR, is a potent stimulus to the release of PTH. The net effect of low vitamin D levels is to directly increase PTH production due to removal of the normal suppressive effect of calcitriol on the parathyroid glands[11]. Increase in phosphate level is also an important factor for hyperparathyroidism, it may have a role in regulating parathyroid hormone secretion in end stage renal disease (ESRD)[12], by lowering the levels of ionized calcium and synthesis of 1,25-dihydroxyvitamin D, thereby resulting in increased PTH levels. Although frequently asymptomatic, this disorder can result in weakness, fractures, bone and muscle pain, and a vascular necrosis. These symptoms and signs do not generally occur until the patient is undergoing maintenance dialysis. There are several forms of renal osteodystrophy, including osteitis fibrosa cystica, a dynamic bone disease and osteomalacia. The 2003 K/ DOQI practice guidelines were formulated to help optimally manage secondary hyperparathyroidism and mineral metabolism abnormalities in patients with CKD[3].

To achieve adequate control of secondary hyperparathyroidism, the K/DOQI practice guidelines suggested that target plasma levels of intact PTH (second generation PTH assay) should be between 150 to 300 pg/mL for patients on dialysis or with an estimated GFR of less than 15 mL/min per 1.73 m2 (stage 5 chronic kidney disease) The 2009 KDIGO practice guidelines were developed to provide recommendations for the evaluation and management of chronic kidney disease-mineral and bone disorder (CKD-MBD)[13]. The term CKD-MBD was created to describe the syndrome associated with mineral, bone and calcific cardiovascular abnormalities. The guidelines were formulated in an attempt to minimize the morbidity and mortality associated with abnormal mineral metabolism, abnormal bone processes and extra skeletal calcification[13]. Numerous studies have demonstrated that the higher turnover bone disorders, osteitis fibrosa (and mixed uremic osteodystrophy), are associated with serum levels of intact PTH greater than 400 pg/mL. Suppression of PTH to normal values is also not desirable (below 150 pg/mL), since it is associated with a higher prevalence of a dynamic bone disease[13,14].

The principal rationale for this is based upon the consistent observation that hyperphosphatemia is associated with increased mortality in ESRD. Therefore, management consists of restricting dietary phosphate intake, calcium based and non-calcium-based phosphate binders to limit the absorption of dietary phosphate. calcium based may be associated with increased risk of vascular calcification and arterial disease and is associated with decreased serum PTH levels and increased serum calcium levels[15]. In dialysis patients with increased PTH levels, the use of calcitriol or vitamin D analogues or calcimimetics, or some combination to lower PTH levels is beneficial Active vitamin D analogue therapy should be administered in dialysis patients when the serum iPTH is above the target range (e.g., >300 pg/mL for the "intact assay"), corrected serum calcium is <9.5 mg/dL (<2.375 mmol/L) and serum phosphate is <5.5 mg/dL (<1.78 mmol/L)[3]. Up to one-half of patients with severe hyperparathyroidism show little or no decline in plasma PTH levels with calcitriol therapy[16-18].

Cinacalcet is indicated in all dialysis patients with PTH levels >300 pg/mL who have serum calcium levels >8.4 mg/dL (>2.1 mmol/L). Hyperphosphatemia is not a contraindication for starting cinacalcet, unlike vitamin D analogues. However, caution should be used in patients with seizure disorders and frequent monitoring of plasma calcium and PTH levels is needed, since hypocalcaemia may lead to seizures and QT prolongation[19]. The aim of the study was to recognize the effectiveness of twice per week hemodialysis (8 hours per week dialysis) in achievement the control level of calcium, phosphorus, calcium phosphorus products according to K/DOQI guideline.

PATIENTS AND METHODS

Study Design: Prospective observational cross sectional hospital base study.

Study Area and Time: The Specialized Centre for renal disease in Khartoum Teaching Hospital (KTH). The study was carried during the period from June2011 to December 2011.

Target Population: All adult patients with ESRD who attended the Specialized KTH center for regular hemodialysis and received twice session a week. This accounted for 182 patients.

Study Population: Adult patients with ESRD who received complete two sessions of hemodialysis per week equivalent to eight hours/ week hemodialysis. This accounted to 124 patients.

Inclusion Criteria

- Patients were eligible to be enrolled in the study if:
- No inclusion criteria were applied to age, gender, duration on dialysis, access to HD or etiology of ESRD.

- Patients with ESRD and on regular HD for more than 3 months.
- Patients received 8 hours HD, divided into two sessions per week.

Exclusion Criteria

- Patients with Acute kidney injury.
- HD schedule other than twice per week.
- Patients who had twice per week HD and their total dialysis dose is less than 8 hours per week [not adherent to dialysis schedule or interrupted HD session (hemodynamic instability or poor vascular access)].
- Patient underwent parathyroidectomy for tertiary or uncontrolled secondary hyperparathyroidism.

Study Sample & Sampling Technique

Sample size was obtained through the following formula:
$n= N/1+ N(d^2)$
where n= sample size. N= Population size (124patients).
d= The degree of accuracy (0.07) or ± 7% precision level where confidence level is 95% and p 5.
n= 124/1+ 124(0.0049)
n= 124/1.6076
n= **77 patients.** The patients were selected through systemic random sampling from sample frame of the 124 patients. First patient was selected randomly then ``the follow consecutive sample interval number (2).

Davies co morbidity score [36]: Seven co morbid domains were considered, including noncutaneous malignancy, ischemic heart disease (IHD), peripheral vascular disease (PVD; including cerebrovascular and renovascular disease), left ventricular dysfunction (LVD; moderate to severe hypokinesia on two-dimensional echocardiogram), diabetes (the current/previous need for oral anti-diabetics or insulin), systemic collagen vascular disease, and any other condition that is known to reduce life expectancy. The co morbidity score for each patient was defined as the number of these domains affected.
The co morbidity grade was then derived from the co morbidity score:
Score of 0 - 2: Mild co morbidity.
Score of 3 - 5: Moderate co morbidity.
Score of 6 &&: Sever co morbidity.

Target parameters according to the K/DOQI bone guidelines [4]:
S. ca =8.4–9.5 mg/dl
S. po4 =3.5–5.5 mg/dl
Ca X PO4 =<55 mg2/dl2 .
PTH =150–300 pg/ml.

All blood samples were tested in the same laboratory for S. albumin. S. ca, S. po4 and PTH.

Data Collection: Personal and demographic data from all patients was collected using designed questionnaire (attached) together with the data regarding calcium, phosphorus, ca X po4 product, PTH, Serum Albumin, dialysis session information (duration, frequency, compliance), co-morbidities according to Davies's score [36,37].

Data Processing: Collected Data from the questionnaire was entered into SPPS software program by the end of the study.

Data Analysis: Data was analysed using software program SPSS v 16. Correlation between control of mineral and bone disorder and co-morbidities was tested using Qui-Square test (significant if p value ≤ 0.05).

Ethical Consideration& Clearance

Research ethical committee- department of internal medicine/ Sudan medical specialization board (SMSB).

Ethical approval was obtained from the director of. Specialized CENTRE FOR RENAL DISEASE IN Khartoum Teaching Hospital (KTH).
Informed consent from the participants.

RESULTS

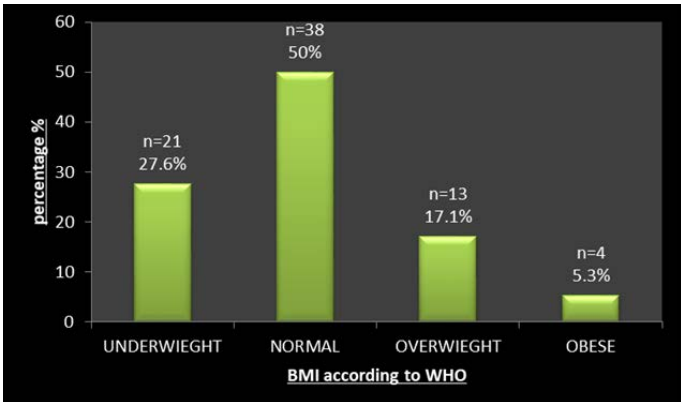
Data of 77 patients out of 124 according to inclusion criteria was analysed, the mean age of the study population was 48.7±16.6 years. Thirty-two patients (41.6%) were hypertensive prior to initiation of HD. The underline cause of ESRD was unknown in 33.8%. Male represented the majority of study population (63.6%) (Table 1).

Table 1: Etiology of ESRD among the study population

ETIOLOGY of ESRD	FREQUENCY	PECENTAGE (%)
Unknown	26	33.8
HTN	32	41.5
DM	5	6.5
GN	4	5.2
Obstructive Uoropathy	6	7.8
Polycystic Kidney Disease	1	1.3
Others	3	3.9
Total	**77**	**100.0**

ESRD: End Stage Renal Disease, HTN: Hypertension, DM: Diabetes Mellitus, GN: Glomerulonephritis.

According to World Health Organization (WHO) classification, 38 patients (50%) had normal BMI,21(27.6%) underweight, 13(7.8%) overweight and 4 (5.3%) were obese (Figure 1).



WHO=World Health Organization.
Figure 1: Body Mass Index (BMI) of HD patients in KTH according to WHO classification

Patients were classified to three group according to Davies's score of co morbidity; 68% had mild co morbidity (Davies's score 0 - 2), 5 % with moderate (Davies's score 3 - 5) and 4% had sever co morbidity (Davies's score 6 & 7).

Thirty-three patients (43%) had been on HD for 2 – 5 years, 38 % for less than two years and 19 % for more than 5 years (Table 2).

Table 2: Patients duration on HD among study population

Duration on HD	FREQUENCY	PECENTAGE (%)
< 2 years	29	38
2 – 5 years	33	43
> 5 years	15	19
Total	**77**	**100.0**

Forty-two patients (54.5%) maintained residual renal function (RRF) as defined 24 hours diuresis ≥ 100 ml.6 out of the 42 patients (7.8%) had 24 hours diuresis above 500 ml and the remaining 36 (46.8%) ranged between100 to 500ml. On the other hand 45.5% considered as having no RRF since the daily diuresis was less than 100 ml**.** None of the patients was on other modalities of RRT such as peritoneal dialysis or transplant. 65 (84.4%) of the patient received their HD sessions through AV fistula and 12 (15.6%) via jugular catheter [9 out of the 12 jugular catheters (75%) were permanent and 3(25%)were temporal]. There is significant correlation between degree of co morbidity according to Davies score and the HD access (P=0.002); 60 (88.2%) out of 68 patients who had mild co morbidity received their HD session through AV Fistula .There was no relationship between degree of co morbidity and duration on HD (P=0.2) or RRF (P=0.5).

Sixty-five, 43% and 36% of the patients achieve the target level of ca x po4 product and serum level of calcium and phosphorus respectively while only 21% had PTH within the recommended level and 44% had PTH below the target level. Those with PTH below the target level, 85% had mild Davies's score,12% had moderate and 3% had severe (Table 3). Calcium carbonate prescribed in a total daily dose of 1500 mg to the majority of patients (85.5%) in three divided doses, only one patient received total dose of 2 gram per day, On the other hand 78% of the patients were prescribed fixed dose of alfa-calciferol (0.25 ug per day) **(**Figure 2).

Table 3: Correlation between PTH level and co-morbidity among the study population

		PTH Level			Total
		Below Target	**Within Target**	**Above Target**	
Davies comorbidity score	Mild (0 - 2)	29 85.3%	15 93.8%	24 88.9%	68 88.3%
	Moderate (3 - 5)	4 11.8%	1 6.2%	3 11.1%	8 10.4%
	Severe (6,7)	1 2.9%	0 0%	0 0%	1 1.3%
Total		**34 100%**	**16 100%**	**27 100%**	**77 100.0%**

P (Pearson Chi-Square) = 0.7

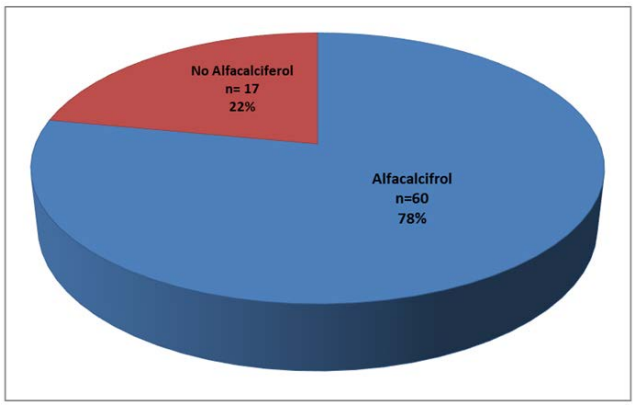


Figure 2: Variation in alfacalciferol prescription among study population

When we exclude patients with PTH below the recommended level from the analysis (n=34), we found a significant correlation between PTH and Alfacalcidol, (P=0.04) and this relation remain significant even when patients with low PTH were included (Table 4). Also, we found that serum calcium had no significant effect on the ca x po4 product (P= 0.24) unlike the serum phosphorus as all the patients with target level of phosphorus had target level of ca x po4 product and 75% of patient above the target level of phosphorus had ca x po4 product above the target level (P=0.0001) (Table 5).

Table 4: Correlation between parathyroid hormone(PTH) and alfacalcidol among patients with target/above target PTH results

		Alfacacifirol		Total
		No	**Yes (0.25 ug/ day)**	
Parathyroid Hormone	**Target level**	6 37.5%	10 62.5%	16 100%
	Above target level	3 11.1%	24 88.9%	27 100%
Total		9 20.9%	34 79.1%	43 100%

Chi-Square = 4 P = 0.039

Table 5: Correlation between serum phosphorus and calcium phosphorus product among patients with target/above target PTH level

		cAxPO4 product		Total
		Target Level	**Above The Target**	
Serum phosphorus (mg/dl)	**Target level**	19 100%	0 0%	19 100%
	Below target	12 100%	0 0%	12 100%
	Above target	3 25%	9 75%	12 100%
Total		34 79%	9 21%	43 100%

P (Pearson Chi-Square) = 0.0001

DISCUSSION

In Sudan, most patients are offered twice weekly HD free for economic reasons. But there are available private centres for those who can afford to make the third session out of the program. Earlier K-DOQI guidelines set thrice weekly sessions as the minimum frequency level of adequate HD. This standpoint changed in response to an important cross-sectional study from the USA that reported lower mortality risk (RR = 0.76, P = 0.02) for twice weekly HD compared to thrice weekly HD among prevalent patients. The authors attributed this survival advantage to patient selection and greater residual kidney function (RRF) among patients maintained on twice weekly HD[20].

Khartoum Teaching Hospital centre is one of the pioneers of Sudanese haemodialysis centres and we notice patients with prolonged duration of HD mostly due to many difficulties they face to have renal transplant that correlate to higher morbidity and mortality[21]. Of note most of the study population was of mild Davies's score 68% so we expect with close monitoring of modifiable factors as anaemia, bone profiles and nutrition we can improve the outcome and quality of life, Elamin S state that, patients with haemoglobin level < 10 g/dl had a significantly higher mortality than patients with haemoglobin level ≥10 g/dl (HR = 2.1, CI 1.4-3.1, P = 0.00)[22].

Although more than half of the patients (545%) maintained RRF most of them had daily diuresis between 100 to 500 ml (86%). Residual renal function (RRF) is important factor even after beginning of dialysis

in both peritoneal dialysis (PD) and haemodialysis (HD) patients, in whom it may improve survival[23,24], reduce HD sessions duration, give more flexibility regarding food and fluid restrictions and in PD it protect the residual renal function be better than HD[25].
The majority 84% of patient had their HD sessions through AVF and the majority 88.2% of them had mild Davies's score, while 20% and 75% of patients with jugular catheter either had moderate or severe score respectively, this relation found to be significant, and this may reflect unfitness for AVF operation or delay referral for vascular surgeon because of poor survival expectation. On the other hand, there was no relation between co-morbidity and duration on HD, similar study proved the vascular access significantly linked to comorbidities and the dialysis via a central venous catheter (CVC) carry double risk of one-year mortality compared to AVF[26].

Difficulty in achieving plasma po4 and PTH with reference to K/DOQI targets has been reported in Spanish ESRD patients[27]. Our percentages of controlled parameters were also below the recommended target by K/DOQI and previous reports, but the difference here was the fact that our patients received twice HD session (8 weeks) per week because of financial and economic barriers. we need to think about other ways than increasing the dialysis dose to improve and pushed these percentages it towards the targets.

Medical Intervention can be achieved through individualizing the calcium carbonate dose (the most available phosphate binder in Sudan) and active vitamin D derivative according to biochemical bone metabolism parameters; Most dialysis patients have elevated po4 that adversely affect patients survival[28]. The role of phosphate retention in the pathogenesis of secondary Hyperparathyroidism has been established[29], Secondary hyperparathyroidism causes bone resorption and subsequent calcifications in tissues, a condition known as renal osteodystrophy[30].

It is well known that high and lower PTH levels than K/DOQI guidelines are associated with increased mortality by causing renal osteodystrophy and a dynamic bone disease respectively[31]. In this study 44% of patients had low target parathyroid hormone in spite that it had no significant relation with previous comorbidities as assessed through Davies's score. This relation may affect by the fact that we exclude patients with less than three-month duration on HD which reflect the low percentage of patients with severe Davies's score of comorbidities among our study population.

Apart from dietary restriction, appropriate phosphate binders' dose is required for achieving Ca and P close to K/DOQI guideline. It will also help in prevention and management of renal osteodystrophy and cardiovascular complications in ESRD patients.

Every patient should be managed separately according to his/her bone biochemical parameters toward achievement of K/DOQI guidelines goals to reduce morbidity, mortality and improve the quality of dialysis care in our country. We found 85% of our study population used to take the fixed dose of 1500mg calcium carbonate in 3 divided doses per day despite variation in their biochemical parameters. But on the other hand, 88.9% of patients with above target PTH level appropriately prescribed Vitamin D and 37.5% with target level of PTH did not take vitamin D (p=0.04).

There is thoughtful other point of view regarding the above-mentioned result, Sixty out of the 77 patients in the study (78%) prescribed similar dose of Alfacalcidol (0.25ug/day) regardless the level of PTH. This very serious because patients with high PTH usually need higher dose of vitamin D and intermediate regimen may be better than daily continuous one. But the more serious is the fact that 26 out of the 34 patients with low PTH (76.4%) were prescribing Alfacalcidol despite their lower level of PTH rendering them to in threat of developing dynamic bone disease.

Increase the awareness of surgical correction of hyperparathyroidism through well planned Parathyroidectomy. The severity of hyperparathyroidism was associated with a lower likelihood of achieving the targets for calcium and phosphorus, whereas patients with a history of parathyroidectomy were more likely to achieve these targets as compared with those who had not undergone surgery despite high PTH levels[32].

The Japanese Society for Dialysis Therapy (JSDT) guideline, released in 2006, recommends target ranges for serum levels of calcium (8.4-10.0 mg/dl), phosphorus (3.5-6.0 mg/dl), and intact PTH (60-180 pg/ml)[33]. This guideline is characterized by a lower target range for intact PTH compared with that of the KDOQI guidelines (150-300 pg/ml). The threshold beyond which surgical parathyroidectomy is indicated in the Japanese Society for Dialysis Therapy guideline is intact PTH 1500 pg/ml, which is also lower than that of the K/DOQI guidelines (intact PTH 1800 pg/ml). Hence, collaboration with surgery for parathyroidectomy seem to be of cost effective and reduce morbidity and mortality[33].

CONCLUSION

Improving aspects of dietary control and use of modern phosphate binders help in achieving Calcium and Phosphorus close to K/DOQI guideline targets in patients on dialysis in Sudan. It is also to individualize the dose of drugs according to biochemical parameters to achieve these targets. Well-planned parathyroidectomy need to be considered for management of uncontrolled secondary or tertiary hyperparathyroidism.

RECOMMENDATION

Updating awareness of the guidelines in management of the metabolic bone disease in dialysis centres. The importance of early and appropriate treatment of secondary hyperparathyroidism either medically or surgically. To work with surgical team for getting proper vascular access.as there is significantly increased morbidity in patients undergoing dialysis through a central catheter rather than arterio-venous fistula. With further studies recommended in improving the aspect of metabolic bone disease management in Sudan.

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Potential Conflict of Interest: None

Competing Interest: None

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