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Original

Assessment of chronic kidney disease-mineral and bone disorder in hemodialysis patients according to biomarkers value

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Abstract

Introduction: End-stage renal disease (ESRD) patients are complicated by various disorders including renal osteodystrophy. There are new guidelines for the management of chronic kidney disease-mineral and bone disorder (CKD–MBD).

Objectives: The aim of the study was to determine the frequency of CKD-MBD in hemodialysis patients in Lorestan province, Iran according to KDIGO.

Patients and Methods: This descriptive, cross-sectional study was carried out on all of the ESRD patients being managed in the hemodialysis centers of Lorestan University of Medical Sciences in 2017. Demographic data were prepared by a questionnaire, and laboratory values by fasting blood samples. Statistical analyses were done by SPSS software at a significance level of 0.05.

Results: Out of 110 patients, 42 (38.2%) were female. Sixty-one (55.5 %) of the patients had intact PTH (iPTH) values in the normal range. Patients' serum calcium values ranged between 5.86 to 11.06 mg/dL; 41(37.3%) of the subjects had serum calcium out of the normal range. The level of serum phosphorus was in normal range in 31 (28.2%) patients. The level of alkaline phosphatase ranged from 134 to 1578 mg/dL; while, 55 patients (50%) had normal values. Vitamin D as 25 (OH) Vit D was in normal range in 30 (27.3 %) patients.

Conclusion: The frequency of CKD-MBD is very considerable in our patients because about 100% of our patients have at least one of the biomarkers values to be abnormal. More than forty percent of our patients had iPTH values below or above KDIGO 2017 of target range. Low iPTH values were frequent in our study. We found strong positive correlation between Alp and PTH level, and Alp is a suitable substitute for PTH. Vitamin D values should be regularly checked in our patients because more than 70% of the patients had values below normal range. Modification in dietary regimen, quality of dialysis and regularity in taking drugs in our patients is necessary.

Keywords: End-stage renal disease, Renal osteodystrophy, iPTH, Calcium, Phosphorus, Alkaline phosphatase, Chronic kidney disease-mineral and bone disorder, glomerular filtration rate

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Introduction

End-stage renal disease (ESRD) is complicated by many disorders. Studies showed that the rates of ESRD are increasing in the world due to uncontrolled major risk factors, especially diabetes mellitus and hypertension. ESRD increasing rate is different between communities (1,2).

In Iran, the number of ESRD patients on renal replacement therapy (RRT) was near to 25 000 in 2006, and the increasing rate is about 12% per year (3).

Renal osteodystrophy (ROD) was a term used to describe the metabolic bone disease caused by abnormalities in mineral homeostasis resulting from kidney failure. In recent years, the recognition of a complex endocrine regulation of mineral and bone metabolism, and the association between abnormalities in mineral metabolism and increased morbidity and mortality in patients with kidney failure has led to suggestion of a new term, "chronic kidney disease–mineral and bone disorder" (CKD-MBD)(4).

The main biomarkers of CKD-MBD are the serum levels of calcium, phosphorous, parathyroid hormone (PTH) and 25(OH) vitamin D3. Like calcium, serum phosphorus levels remain in the normal range until late in the course of CKD, typically when glomerular filtration rate (GFR) is 30 to 40 mL/min/m^2. (5)

CKD-MBD is either one or a combination of the following events: 1. Abnormalities of calcium,

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Implication for health policy/practice/research/ medical education

In a study on 110 patients we found, the frequency of CKD-MBD is very considerable in our patients because about 100% of our patients have at least one of the biomarkers values to be abnormal.

phosphorus, PTH, or vitamin D metabolism, as measured by laboratory values; 2. Abnormalities in bone turnover, mineralization, volume, linear growth, or strength, as measured mainly by bone histology; 3. Vascular or other soft tissue calcifications.

The international study of ESRD patients reported that the lowest mortality was observed for calcium at 8.6 to 10.0 mg/dL, phosphorus at 3.6 to 5.0 mg/dL, and PTH between 100 and 300 pg/mL, with the highest mortality for calcium levels more than 10.0 mg/dL, phosphorus levels greater than 7.0 mg/dL, and PTH levels greater than 600 pg/mL. However, recent meta-analysis challenged the association between calcium and PTH levels and all-cause or cardiovascular mortality, whereas still strongly supporting the association between elevated levels of phosphorus and these outcomes. (6,7) The levels PTH are often increased in ESRD (5,8,9).

Objectives

There are some guidelines about diagnosis and management of CKD -MBD, which have some differences in target levels of biochemical markers. Because of the critical role of CKD-MBD in morbidity and mortality of patients under hemodialysis and new target ranges for biomarkers, we evaluated the biomarkers of CKD-BMD in all the patients undergoing hemodialysis in Lorestan province of Iran. Although by definition, any abnormality in the values of calcium, phosphorus, iPTH, or Vitamin D3 is considered to be CKD-MBD. In this study, the values of iPTH more than other biomarkers were considered.

Patients and Methods

Study design

This descriptive, cross-sectional study was conducted on all ESRD hemodialysis patients in dialysis centers of Khorramabad city in Lorestan province of Iran, from January 2017 to September 2017.

We included patients with at least 3 months duration of hemodialysis in order to have a steadier state of bone mineral dynamics. Hence, subjects were included in the study without changing drug orders or drug discontinuation. Patients under supra-physiologic or therapeutic dosages of calcium or vitamin D products, or other drugs that may influence Ca-P- PTH (e.g. phosphate chelating agents etc) were excluded from this study.

Demographic data of all the patients were collected in a questionnaire, including the cause of kidney disease, age, gender, weight, occupation, location, literacy, Body mass index (BMI), and duration of dialysis.

Laboratory values for calcium, phosphorus, and PTH were calculated on fasting blood serum. Corrected calcium (in mg/dL) calculated as total calcium + (0.8 × (4.0 – albumin [in g/dL])). To decrease errors, all the samplings were performed in morning fasting time, before hemodialysis session by the same kit and the same person.

Because of accumulation of PTH fragments that are inactive and may be overestimate measurement of PTH level in patients with ESRD, intact PTH assay was measured. Intact PTH (iPTH) was measured by Elecsys technology ECL (ellectrochemiluminescence). Our device was Cobas E411 with iPTH kit LOT: 14325103.

Target range for calcium level was considered as 8.4-10.2 mg/dL, for phosphorous 2.7-4.6 mg/dL, and for ca × p product less than 55 mg^2/dL^2.

For 25(OH) vitamin D3 serums, deficient level was considered less than 50 nmol/L, insufficient level between 50-75 nmol/L and sufficient level between 75-250 nmol/L.

The 2017 Kidney Disease Improving Global Outcomes (KDIGO) guidelines and the 2010 Kidney Disease Outcomes Quality Initiative (KDOQI) US commentary suggest different target levels for CKD-MBD markers than previously recommended in the 2003 KDOQI guideline. The main change was a wide range for PTH levels, to 2–9 times the upper limit of normal (approximately 130–600 pg/mL). Older recommended range was between 150-300 pg/mL. These different recommended target ranges may have led to changes in management of CKD-BMD in dialysis centers (10,11).

Ethical issues

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The ethical committee of Lorestan University of Medical Sciences (ethical code: IR.LUMS.REC.1396.283) confirmed the study. The informed consent was taken from the patients. Besides, this study was extracted from the M.D, thesis of Marjan Hasani at this University (Grant # A-10-1419-3).

Statistical analysis

Collected data entered into SPSS version 18 and analyzed using descriptive statistics. Distribution of the data was analyzed using Kolmogorov-Smirnov test. Independent *t* test and Pearson's correlation coefficient tests were used for analysis. All statistically differences were considered significant at the level of *P* value lower than 0.05.

Results

Out of 110 subjects, 42 (38.2%) were female and 68 (61.8%) were male. The mean and standard deviation of age of the patients was 60.35±15.3 years, with a range from 15 to 95 years. The mean and standard deviation of dialysis duration of the patients was 32.47±30.78 months, ranging from 6 to 156 months. More than 95% of the patients were under hemodialysis for 3 sessions per week. Sixty-

four patients (58.2%) had normal BMI. Other important demographic data of the patients is summarized in Table 1.

The common underlying causes of ESRD in our study were hypertension, diabetes and nephrolithiasis, respectively (Table 1). In this study, intact PTH values were between 9.8 and 1716 pg/mL in the final evaluation of the data results. Sixty-one (55.5 %) of the patients had PTH concentration in the normal range (Table 2).

Patients' calcium values were between 5.86 to 11.06 mg/dL, with 41(37.3%) out of the normal range. Seventy-seven (71.3%) of the patients had phosphorus values above normal range and 31 (28.7%) of them had values within normal range. None had values below normal range.

25(OH) vitamin D3 levels were within the target range in only 30 (27.3%) patients. Patients with low vitamin D values, 58 (52.8%) of the patients had deficient level (less than 50 nmol/l) and 20 (18.2%) of the patients had inadequate level (50-75 nmol/L). Serum alkaline phosphatase values were between 134 to 1578 mg/dL (with mean level 392.27 mg/dL). Fifty-five patients (50%) had normal levels of ALP.

Table 3 shows the statistical correlation between various CKD-MBD biomarkers. iPTH has statistically significant positive correlation with ALP (Table 3 and Figure 1) and phosphorus, and negative correlation with calcium (Table 3 and Figure 2). There is a statistically significant relationship between iPTH and ALP (Table 3).

Table 1. Demographic and etiologic characteristics of ESRD patients

Variable	Categories	Number	Percent
Gender	Male	68	61.8
	Female	42	38.2
Education	Educated	44	40
	Uneducated	66	60
BMI (kg/m^2)	<18.5	8	7.2
	18.5-25	64	58.2
	25-30	21	19.1
	>30	17	15.5
Residency	Urban	88	80
	Rural	22	20
Occupation	Employed	27	24.5
	Unemployed	83	75.5
Cause of ESRD	Diabetes	33	31.7
	HTN	38	36.5
	Nephrolithiasis	13	12.5
	Glomerulonephritis	6	5.8
	Others	14	13.5

End-stage renal disease; BMI, Body mass index; HTN, Hypertension.

Discussion

Based on the results, the most common causes of ESRD in our centers were hypertensive nephropathy, diabetic nephropathy and nephrolithiasis, respectively.

In this study, CKD-MBD was more common in diabetic patients. It is known that the old age, female sex, diabetes, oxidative stress and inflammation, and the Caucasian race are predisposing factors for a dynamic bone disease (12).

Our study indicated that the majority of the diabetic patients had low PTH. There are some different study results about this finding, reporting majority with low PTH (13) or not (14).

No correlation was found between sex of the patients and renal osteodystrophy in this study, however, in the study by Gupta et al, gender was correlated with CKD-MBD (15). Perhaps race and sample size of the studies in various centers resulted in a different relationship between gender or etiologic causes of ESRD and renal osteodystrophy.

Such as some other studies, we found a statistically significant (Table 3) correlation between PTH level and the duration of hemodialysis; the more the duration, the more PTH level (16,17).

Theoretically, phosphorus influences the PTH level through a positive feedback pathway, so that hyperphosphatemia leads to hyperparathyroidism and increase in PTH. But as shown in Table 3, the correlation between phosphorous and PTH in this study is not significant, such as other studies (18,19).

Similar to other studies, our results showed strong positive correlation between alkaline phosphatase and

Table 2. Frequency (absolute and relative) of CKD-MBD in the hemodialysis patients according to KDIGO biomarkers target ranges

Biomarker	Abnormal				Normal		Target Range (KDIGO)	Mean ±SD
	Above normal		Below normal					
	No.	%	No.	%	No.	%		
iPTH (pg/mL)	21	19.1	28	25.5	61	55.4	150-600	393± 370
Ca (mg/dL)	7	6.5	20	18.5	81	75	8.4-10.2	8.9 ± 0.9
P (mg/dL)	77	71.3	0	0	31	28.7	2.7-4.6	5.4 ± 1.2
Vitamin D (nmol/L)	2	1.8	78	70.9	30	27.3	50-250	37.8 54.9±
ALP (mg/dL)	55	50	0	0	55	50	*	392.2278.7±

Note: In 8 patients (about 7.5%) of patients all recommended KDIGO biomarkers (iPTH, Ca, P, and Vit D) have abnormal values together.
Some data are missing for some biomarkers.
* Values more than 240 IU/L in females and more than 270 IU/L in males are considered abnormally high.

Table 3. Statistical correlation between various CKD-MBD biomarkers

Correlation	Number	Pearson coefficient	CI for Pearson coefficient	*P* value
iPTH & Ca	108	-0.265	-0.438 to -0.074	0.007
iPTH & P	108	0.148	-0.049 to 0.334	0.140
iPTH & ALP	108	0.375	0.194 to 0.531	0.000
iPTH & Vitamin D	108	-0.096	-0.285 to 0.099	0.332
iPTH & Duration of Dialysis	110	0.255	0.064 to 0.427	0.009
Ca & ALP	108	-0.291	-0.455 to -0.108	0.002
Ca & P	108	-0.143	-0.323 to 0.047	0.139
Ca & Vitamin D	105	0.401	-0.254 to 0.124	0.490
Vitamin D & ALP	105	-0.202	0.295 to 0.597	0.000
P & Vitamin D	105	-0.041	-0.172 to 0.208	0.852

PTH level (Table 3 and Figure 1) (20). Hence, ALP can be used as a surrogate for PTH.

Twenty-five percent and about 20% of the patients had low level and high level of PTH, respectively. These results are similar to other studies (13,21).

Results documented in DOPPS study showed that in Japan 58.6% and 19%, and in Europe 50.1% and 26.9% had lower and higher than normal PTH, respectively (22). The difference between their values and ours may be related to different target ranges.

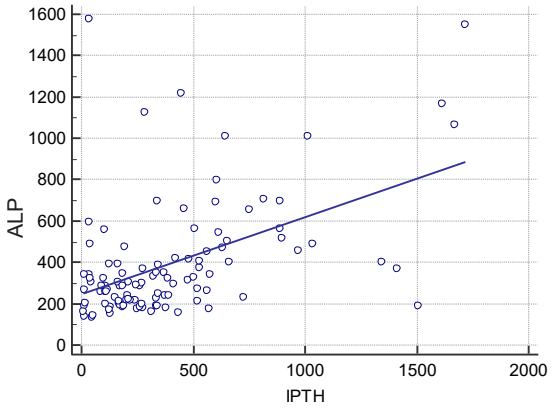

Figure 1. Scatter plot of serum iPTH and alkaline phosphatase

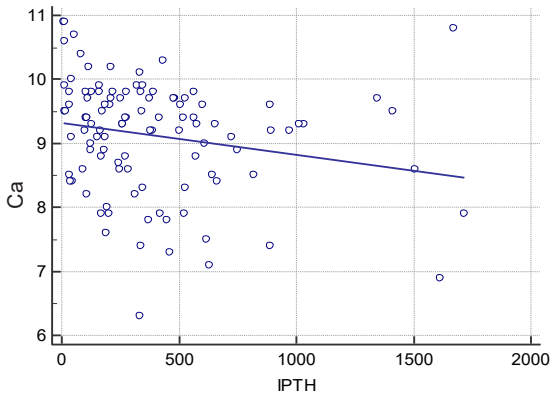

Figure 2. Scatter plot of serum iPTH and calcium

Some studies in Iran reported that according to PTH values more than half of the hemodialysis patients had renal osteodystrophy (23,24). Although no statistically significant correlation was seen between vitamin D and iPTH values in this study ($P=0.171$), because of the suppression of PTH, we should consider the prescription of vitamin D supplements to our patients.

Relative vitamin D depletion is an independent risk factor for secondary hyperparathyroidism in hemodialysis patients (25). Low 25-D (25-hydroxycholecalciferol) level in our patients may be due to dietary regimen and insufficient sunlight exposure (26).

Based on the results, about 71% of our patients had hyperphosphatemia. No patients had hypophosphatemia. In the study by Mahdavi et al, 41% of the patients had high phosphorous level (24). Dietary regimens of patients, quality of dialysis, and regular using of phosphate binders are influencing factors for phosphorous levels.

Similar to other studies, about 7.2% of our patients had hypercalcemia (13,16,24).

In this study, calcium-phosphorous product was more than 55 mg^2/dL^2 in 28 (25.5%) of the patients. There are other studies reporting 82% and 25% (similar to our finding) of the patients to have high (more than 55 mg^2/dL^2) values, respectively (16,24). Calcium-phosphorous products correlate with mortality of patients (27). This marker is the main target in the management of patients and has direct relationship with cardiovascular mortality in CKD patients.

Our analysis of CKD-MBD biomarkers, particularly PTH, was based on KDIGO 2017 target levels. Our analysis of CKD-MBD biomarkers, specifically PTH, was based on KDIGO 2017 target levels. For being comparable with other studies, we also analyzed PTH values based on KDOQI 2003 guideline target levels. According to KDOQI, 82 (74%) of the patients had PTH values out of ranges: 28 (25.5%) of the patients had low PTH and 54 (49%) had PTH more than 300 pg/mL. These results are more similar to other studies (16,28).

The main reasons of the differences among the results of the studies may be different target levels of biomarkers, different mean duration of dialysis which may affect the value of PTH, different methods for PTH measurement, and differences in quality of hemodialysis, drugs used and dietary regimens in different centers.

Overall, our study indicates that according to iPTH, 44.6%, according to calcium, 25%, according to phosphorus, 71.3%, according to Vitamin D, 72.7%, and according to ALP, 55% of the patients have CKD-MBD. In about 7.5% of our patients, all KDIGO 2017 recommended biomarkers (iPTH, Ca, P, and vitamin D) have abnormal values. However, if we define CKD-MBD as abnormality of only one of the biomarkers, all the studied patients have CKD-MBD.

Conclusion

CKD-MBD biomarkers are not well controlled in our centers. With regards to correlation analysis results, disorder of any of the biomarkers should be considered as an important alarming indicator of CKD-MBD and all patients being continuously monitored for mineral and bone disorder with all biomarkers recommended by KDIGO. Dietary regimen of our patients, quality of hemodialysis and drug prescription and adherence are some of the contributing factors that need to be improved. We suggest that, at least in centers with no suitable equipment for PTH assays, alkaline phosphatase be used as a suitable surrogate for it.

Limitations of the study

There were not biopsy samplings and radiological evaluations for renal osteodystrophy in hemodialysis patients.

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Authors' contribution

BH participated in the design and conduct of the study and also preparing the manuscript. AZM participated in describing the methodology of the study and statistical analysis of the data and amending the manuscript draft of the article. AH participated in the statistical analysis and preparing the manuscript draft. MH prepared the draft of the proposal and participated in conduct of the study (data collection, enter data to software). All authors read and approved the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

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