Prevalence of Renal Osteodystrophy and its Related Factors among End-stage Renal Disease Patients Undergoing Hemodialysis: Report from Imam Reza Referral Hospital of Medical University of Kermanshah, Iran

Abolhassan Seyedzadeh, Mohamad Reza Tohidi*, Sima Golmohamadi, Hamid Reza Omrani, Mohammad Saleh Seyedzadeh, Sara Amiri and Sara Hookari Department of Pediatrics, Pediatric Nephrology Division, Kermanshah University of Medical Sciences, Kermanshah, Iran

ARTICLE INFO *Article history:* Received: 24 July 2020 Accepted: 17 April 2021

Online:

DOI 10.5001/omj.2021.120

Keywords:

Cross-Sectional Studies; Chronic Kidney Disease-Mineral and Bone Disorder; Parathyroid Hormone; Renal Dialysis.

ABSTRACT

Objectives: We sought to determine the prevalence of renal osteodystrophy (ROD) and its related factors in a group consisting of end-stage renal disease (ESRD) patients undergoing maintenance hemodialysis. Methods: A total of 128 ESRD patients (52 men and 76 women) with a mean age of 59.3 years undergoing maintenance hemodialysis at Imam Reza Referral Hospital, Iran were included in this cross-sectional study. We measured serum parathyroid hormone (PTH) levels and determined 150 to 300 pg/mL as the desirable range for the values. Values lower or higher than this range were used to determine ROD. Furthermore, this study investigated the association of ROD with clinical and laboratory variables (age at the onset of renal failure, hemodialysis sessions per week, clinical symptoms associated with ROD, and serum calcium and phosphate levels). Results: ROD was diagnosed in 93 (72.7%) out of 128 patients studied. Of them, 53 (41.4%) patients had PTH levels above 300 pg/mL (high bone turnover, HTO group) and 40 patients (31.3%) had PTH levels below 150 pg/mL (low bone turnover, LTO group). No statistically significant difference was detected in terms of ROD-related clinical findings (p = 0.110), age at the time of ESRD diagnosis (p = 0.200), and the number of hemodialysis sessions per week (p = 0.200). Hyperphosphatemia was more prevalent in the ROD group (n = 52, 57.1%) compared with 11 patients (31.4%) included in the group without ROD (p = 0.004). *Conclusions:* The prevalence rate of ROD in this study was significant, and it was largely consistent with the rate reported in some Asian countries. Hyperphosphatemia were laboratory variables closely related to ROD.

enal osteodystrophy (ROD) refers to bone disorders resulting from or associated with chronic kidney disease (CKD) and its associated metabolic disorders. ROD initiates when the renal function starts to deteriorate.¹ The association between bone disorders and renal failure was firstly reported in the mid-19th century. Until the 1950s, it was believed that CKD was complicated by concomitant hyperparathyroidism.² CKD-mineral and bone disorder (CKD-MBD) is a broader clinical syndrome developing as a systemic abnormality of mineral and bone metabolism due to CKD. Accordingly, it is characterized by disturbance in bone and mineral metabolism and/or extraskeletal

calcification. It is alleged that the term ROD can be used solely to describe bone disorders associated with kidney disease.³ Thus, ROD can be considered as a part of the CKD-MBD.^{3,4} By considering the operation as the direct consequence of electrolyte abnormalities and endocrine disorders represented by high serum phosphate levels and low or normal serum calcium levels, ROD can lead to the elevated secretion of parathyroid hormone (PTH) by the parathyroid glands and of fibroblast growth factor 23 by osteoblast and osteocytes to normalize serum calcium and phosphate levels.^{1,5} ROD is associated with bone pain and the increased incidence of fractures and bone deformities, myopathy, muscle pain, and tendon rupture.^{3,4} The prevalence rate of ROD in developing countries ranges from 33.3% in Egypt to 81% in Brazil.⁶ This disorder can be divided into two categories of bone metabolic status. The high bone turnover (HTO) group is characterized by the increased serum PTH level, and the low bone turnover (LTO) group is characterized by normal or decreased serum PTH levels. HTO is osteitis fibrosa cystica, with clinical manifestations of pain and fragility of bones. On the other hand, LTO can be grouped into two categories, adynamic bone disease and osteomalacia.⁷ There is evidence that despite the decreased HTO type of ROD, LTO type of ROD (especially adynamic bone disease) follows an increasing trend. Correspondingly, this change in the epidemiology of ROD is hypothesized to be related to the newlyintroduced treatments and higher rates of access to hemodialysis worldwide.1 LTO is associated with reduced bone volume and mineralization, which can be engendered by suppressing PTH production, chronic inflammation, or both. PTH suppression can be caused by taking vitamin D supplements or excessive exposure to calcium in the form of calcium phosphate binders and high calcium hemodialysis solutions. Notably, adynamic bone disease complications are as follows: the increased incidence of bone fracture, bone pain, and having an association with the increased cardiovascular calcification.^{2,7} Although in a guideline entitled Kidney Disease Outcome Quality Initiative published by the National Kidney Foundation, the normal range of serum PTH level has been regarded from 150-300 pg/mL.8 There is still an unfortunate absence of multiple randomized controlled trials with the ability to determine an optimal PTH level for patients with CKD.⁴ Even though bone biopsy is considered the gold standard method for diagnosing ROD, it is an invasive procedure, so it cannot be routinely used to determine the prevalence of ROD. Serum PTH levels are regarded as an acceptable alternative to bone biopsy in diagnosing ROD and categorizing its subtypes, namely LTO and HTO.9 However, the novel recommendation in this regard is that the treatment should not be solely based on the elevated level of PTH.⁴ Since its development, ROD has played an effective role in the quality of life among CKD patients. The current research aimed to determine the prevalence of ROD among hemodialysis patients. Such a

prevalence is highly dependent on health care level and the adequacy of dialysis in a medical community.

Several studies have been previously performed to determine the prevalence of ROD in different parts of the world. Accordingly, the prevalence of ROD has been studied using various methods such as bone biopsy, radiography, and the measurement of chemical biomarkers. One of the most important reasons underpinning such a discrepancy in the prevalence of ROD is a wide variety of ROD diagnosis methodologies. The following part of this research mainly intended to determine the prevalence of ROD in a sample comprised of endstage renal disease (ESRD)-afflicted patients to investigate the relevant factors.

METHODS

In this cross-sectional research study, the study population was patients with ESRD who underwent maintenance hemodialysis at Imam Reza Referral Hospital of Kermanshah, Iran, in 2018. In addition, participants who the researchers could access their medical records were included in this study. This referral hospital provides tertiary-level medical services. The hospital also operates as the main hemodialysis center in Kermanshah province and fulfills the medical needs of at least two million people. The exclusion criteria included bone diseases before ESRD development, incomplete medical record information, irregular referrals of the patients for hemodialysis, and the patient's affliction with a dialysis duration of fewer than three months. Considering the study design and previous studies indicating a prevalence of 72% for ROD among the hemodialysis patients residing in Sanandaj province, Iran,¹⁰ and confidence level of 95% and accuracy of 8%, according to the formula, the required sample size (taking into account 10% dropout) was determined to be 133 patients. Finally, 128 patients from the study population who met inclusion criteria based on their medical records were selected using the available method and then entered the study, and their information was analyzed.

We used a data collection form designed by the researchers. This form included demographic information (age, gender, and weight at the last visit), clinical variables (underlying causes of ESRD including hypertension, diabetes mellitus, recurrent urinary tract infections, obstructive uropathy, congenital anomalies, and vesicoureteral reflux), duration of CKD, duration of hemodialysis, weekly hemodialysis sessions, age at the time of the onset of renal failure, age at the time of the onset of hemodialysis, calcium supplements, erythropoietin usage, and phosphate binder. Clinical symptoms related to ROD, including bone pain and sensory disturbances (paresthesia), were recorded.

Furthermore, serum biochemical variables documented in the medical records were gathered. These variables included levels of calcium after the correction based on serum albumin levels (normal range = 8.4-10.2 mg/dL), phosphate (normal range = 3.5-5.5 mg/dL), PTH, and alkaline phosphatase. Thereafter, to record the serum PTH level, the last recorded value in the medical records was extracted. The patients' serum PTH was measured every three months at the hemodialysis center of the study hospital. Given the date obtained from the last assessment of the serum PTH level, other biochemical variables measured concomitantly were extracted. Appropriate hormone levels for CKD patients were considered to be between 150-300 pg/mL. Serum PTH levels > 300 pg/mL were considered as HTO type of ROD, and values < 150 pg/mL were considered as LTO type of ROD.

This research was conducted in terms of the Declaration of Helsinki. The Ethics Committee of Kermanshah University of Medical Sciences approved the study. Moreover, the institutional ethical committee at Kermanshah University of Medical Sciences approved all the study's protocols (IR.KUMS. REC.1394.403). Accordingly, written informed consent was obtained from all the participants before the study, and data collection was then started. The present article was derived from an M.D thesis of Medical University of Kermanshah, Iran (Thesis#96035).

Frequency and percentage indices were used to report categorical variables. For continuous variables, mean and standard deviation were used. We used the chi-squared test to determine the association between the ROD and the laboratory and clinical variables. All statistical analyses were performed using SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). The statistical significance level was set at 0.050.

RESULTS

A total of 128 ESRD patients (52 men and 76 women) with a mean age of 59.3 ± 14.2 years (range = 23-87 years) and a mean weight of 66.3 ± 10.7 kg were included in the study. The mean age of ESRD diagnosis was 48.7 ± 16.7 years. Table 1 presents ESRD causes and ROD clinical findings in the 128 ESRD patients included in this study who were receiving maintenance hemodialysis. As observed, hypertension was the most common etiology for ESRD among these patients. In addition, bone pain was the most common symptom reported in about one-third of the patients.

Table 2 summarizes the laboratory findings of the studied population. Hypocalcemia was more common than hypercalcemia, and hyperphosphatemia

Characteristics	Category	Frequency, n	Percentage, %
ESRD causes	Hypertension	67	52.3
	Diabetes mellitus	16	12.5
	Diabetes mellitus + hypertension	17	13.3
	Congenital urinary tract abnormalities ^a	9	7.0
	Autoimmune disorders	6	4.7
	Acute renal injury	8	6.3
	Obstructive uropathy	5	3.9
ROD symptoms/signs	Bone pain	41	32.0
	Paresthesia	9	7.0
	Numbness	3	2.3
	Combination of clinical findings	58	45.3
	None	17	13.3

Table 1: Clinical and laboratory characteristic	s of 128 end-stage renal disease (ESRD) patients.	

"These abnormalities included vesicoureteral reflux, polycystic kidney disease, and renal dysplasia. ROD: renal osteodystrophy.



Characteristics	Category	Frequency, n	Percentage, %
Corrected calcium levels	Hypocalcemia (< 8.4 mg/dL)	48	37.5
	Normocalcemia (8.4–10.2 mg/dL)	72	56.3
	Hypercalcemia (> 10.2 mg/dL)	8	6.3
Phosphate	Hypophosphatemia (< 3.5 mg/dL)	9	7.0
	Normal (3.5–5.5 mg/dL)	54	42.2
	Hyperphosphatemia (> 5.5 mg/dL)	63	49.2
	Missing	2	1.6
Alkaline phosphatase	> 92	122	95.3
	Missing	6	4.7
Albumin	< 3.5	10	7.8
	3.5–5.5	114	89.1
	> 5.5	3	2.3
	Missing	1	0.8
Renal osteodystrophy	No	35	27.3
	LTO	40	31.3
	HTO	53	41.4

Table 2: Laboratory findings in 128 end-stage renal disease patients
--

LTO: low bone turnover; HTO: high bone turnover.

was more common than hypophosphatemia. Furthermore, all the patients whose alkaline phosphate level was measured, regardless of their PTH level, had high alkaline phosphate levels.

The mean hemodialysis duration was 6.2 ± 7.5 years (range = 0.3-7.5 years). The mean weekly

hemodialysis session was 2.9 ± 0.3 sessions (range = 1-3 sessions). The mean age at the hemodialysis onset was 53.6 ± 15.4 years (range = 12-84 years). Of 128 patients included in this study, ROD was diagnosed in 93 patients (72.7%). In this category, 53 patients (41.4%) had serum PTH levels > 300

Table 3: Comparison of the studied variables between two groups of 128 end-stage renal disease (ESRD)
patients with and without renal osteodystrophy (ROD).	

Variables	Category	ESRD with ROD n (%)	ESRD without ROD, n (%)	Total N	χ^2	<i>p</i> -value
Age at ESRD diagnosis, years	< 20	10 (10.8)	1 (2.9)	11	4.65	0.200
	21-40	18 (19.4)	5 (14.3)	23		
	41-60	47 (50.5)	17 (48.6)	64		
	61-80	18 (19.4)	12 (34.3)	30		
Hemodialysis sessions, per week	≤ 2	7 (7.5)	5 (14.3)	12	1.37	0.200
-		86 (92.5)	30 (85.7)	116		
ROD symptoms/signs	No	13 (14.0)	4 (11.4)	17	11.62	0.110
	Yes ^a	80 (86.0)	31 (88.6)	111		
Corrected calcium levels, mg/dL	< 8.4	40 (43.0)	8 (22.9)	48	4.75	0.093
C	8.4-10.2	47 (50.5)	25 (71.4)	72		
	> 10.2	6 (6.5)	2 (5.7)	8		
Serum phosphate, mg/dL	< 3.5	3 (3.3)	6 (17.1)	9	10.96	0.004
	3.5-5.5	36 (39.6)	18 (51.4)	54		
	> 5.5	52 (57.1)	11 (31.4)	63		
Age, year	20-40	14 (15.1)	4 (11.4)	18	3.64	0.161
-	41-60	38 (40.9)	9 (25.7)	47		
	> 60	41 (44.1)	22 (62.9)	63		

"Symptoms of ROD comprised bone pain, paresthesia, and numbness alone or in combination. Percentages are presented vertically.

Variables	Category	HTO ROD n (%)	LTO ROD n (%)	Total N	χ^2	p-value
Age at ESRD diagnosis, year	< 20	6 (11.3)	4 (10.0)	10	1.89	0.590
	21-40	8 (15.1)	10 (25.0)	18		
	41-60	27 (50.9)	20 (50.0)	47		
	61-80	12 (22.6)	6 (15.0)	18		
Hemodialysis sessions, per week	≤ 2	2 (3.8)	5 (12.5)	7	2.50	0.120
	3	51 (96.2)	35 (87.5)	86		
Corrected calcium levels, mg/dL	< 8.4	29 (54.7)	11 (27.5)	40	12.55	0.002
c	8.4-10.2	24 (45.3)	23 (57.5)	47		
	> 10.2	0 (0.0)	6 (15.0)	6		
Serum phosphate, mg/dL	< 3.5	1 (1.9)	2 (5.1)	3	2.30	0.320
-	3.5-5.5	18 (34.6)	18 (46.2)	36		
	> 5.5	33 (63.5)	19 (48.7)	52		
Age, year	20-40	8 (15.1)	6 (15.0)	14	0.02	0.987
	41-60	22 (41.5)	16 (40.0)	38		
	> 60	23 (43.4)	18 (45.0)	41		

Table 4: Comparison of the studied variables between two groups of 93 end-stage renal disease (ESRD) patients with high bone turnover (HTO) and low bone turnover (LTO) renal osteodystrophy (ROD).

Percentages are presented vertically.

pg/mL (HTO type of ROD), and 40 patients (31.3%) had serum PTH levels < 150 pg/mL (LTO type of ROD). Notably, serum PTH levels were desirable (i.e., 150–300 pg/mL) in 35 patients (27.3%).

Table 3 compares variables between the two patient groups, namely with and without ROD. As shown, no statistically significant difference was observed in terms of ROD-related clinical findings (p = 0.110), age at the time of ESRD diagnosis (p =0.200), number of hemodialysis sessions per week (p = 0.200), and the patients' ages (p = 0.161). However, a statistically significant difference was found regarding serum phosphate levels between the two groups. It was observed that hyperphosphatemia (52 patients, 57.1%) was more prevalent in the ROD group compared with 11 patients (31.4%) in the group without ROD (p = 0.004). Accordingly, this means that the prevalence of hyperphosphatemia among patients with ROD was > 1.5-times higher than in the patients without ROD.

Although no significant relationship was observed between serum calcium levels and ROD, almost half of the patients with ROD (47 patients, 50.5%) had normal calcium levels (p = 0.093).

Table 4 compares the variables between the two groups of the ROD patients (HTO vs. LTO groups). Hypocalcemia was more common (29 patients, 54.7%) in the HTO group compared to the LTO group (11 patients, 27.5%); p = 0.002.

Variables	Category	Hemodialysis sessions, ≤ 2 per week n (%)	Hemodialysis sessions, ≥ 3 per week n (%)	Total N	χ²	<i>p</i> -value
Corrected calcium levels, mg/dL	< 8.4	3 (25.0)	45 (38.8)	48	16.59	< 0.001
	8.4-10.2	5 (41.7)	67 (57.8)	72		
	> 10.2	4 (33.3)	4 (3.4)	8		
Serum phosphate, mg/dL	< 3.5	1 (8.3)	8 (7.0)	9	0.03	0.985
c	3.5-5.5	5 (41.7)	49 (43.0)	54		
	> 5.5	6 (50.0)	57 (50.0)	63		

Table 5: Comparison of the number of dialysis sessions of patients with their calcium and phosphate levels.

Percentages are presented vertically.



Variables	Category	Serum PTH 150 mg/dL n (%)	Serum PTH 150–300 mg/dL n (%)	Serum PTH > 300 mg/dL n (%)	Total N	χ²	p-value
Corrected calcium levels, mg/dL	< 8.4	10 (25.0)	8 (22.9)	30 (56.6)	48	20.14	< 0.001
-	8.4-10.2	24 (60.0)	25 (71.4)	23 (43.4)	72		
	> 10.2	6 (15.0)	2 (5.7)	0 (0.0)	8		
Serum phosphate, mg/ dL	< 3.5	2 (5.1)	6 (17.1)	1 (1.9)	9	14.26	0.007
	3.5-5.5	19 (48.7)	18 (51.4)	17 (32.7)	54		
	> 5.5	18 (46.2)	11 (31.4)	34 (65.4)	63		
ROD	ESRD with ROD ESRD without ROD	40 (100) 0 (0.0)	0 (0.0) 35 (100)	53 (100) 0 (0.0)	93 35	128.00	< 0.001

Table 6: Comparison of the level of	PTH of patients with their c	alcium and phosphate levels.
-------------------------------------	------------------------------	------------------------------

PTH: parathyroid bormone; ROD: renal osteodystrophy; ESRD: end-stage renal disease. Percentages are presented vertically.

Additionally, the results of the association between the patients' dialysis sessions number and their calcium and phosphate levels showed that there was a statistically significant relationship between the number of dialysis sessions and the patients' blood calcium levels. More than half of the patients with dialysis sessions performed three or more times per week have normal blood calcium [Table 5].

Table 6 shows the association among the level of PTH, the serum calcium and phosphate levels, and the patients' involvement with ROD. Accordingly, a statistically significant relationship was found between phosphate and calcium levels and PTH levels. This means that the patients' blood phosphate and ROD increase with PTH level increasing, but this relationship has been reported reversely for calcium levels.

DISCUSSION

ROD as a constellation of metabolic bone abnormalities in chronic kidney disease is accompanied by the alternation in serum levels of PTH, calcium, phosphorus, and vitamin D, which consequently lead to bone turnover impairment.^{11,12} Since the low prevalence of ROD is an aftermath of the standard medical care level and adequacy of dialysis, and given that its high prevalence negatively affects patient's quality of life, the current research intended to determine the prevalence of ROD among the patients undergoing hemodialysis in Imam Reza Referral Hospital of Kermanshah, Iran. Moreover, this study aimed to compare the obtained rate with similar studies. We found hypertension as the most common cause of ESRD. Although the prevalence rate of ROD was 72.7% (HTO 41.4%), the impact of the factors, including etiology of renal failure, demographic factors, quality of treatment and hemodialysis frequency, and laboratory factors and nutrition, led to significant discrepancies in prevalence, type, and nature of ROD in various studies.^{7,11} In a 2015 systematic review, the approximate prevalence rate of secondary hyperparathyroidism (SHPT) (PTH > 300 mg/dL) was reported to be 30-50%, while the prevalence of SHPT in CKD patients across Europe and Australia ranged from 30-49%. In addition, the prevalence rate among North American patients (Canada and US) was estimated to be 54%. In Asia, the SHPT prevalence rate was 28% in India and 11.5% in Japan.¹¹

In another study conducted in Pakistan in 2016, 89% of the studied patients had ROD, and the most common type was SHPT in 32% of the patients, followed by the mixed type of ROD in 27% of the patients, as well as a dynamic bone disease in 23%. More importantly, the results of the above-mentioned research were almost inconsistent with our findings.¹²

In studying ROD among the patients afflicted with CKD, it is important to measure the 25-OH vitamin D level, which was not available in our study.^{12,13} Due to the same absence, it was impossible to distinguish adynamic bone disease from osteomalacia in the LTO group of ROD. Herein, serum PTH measurement was performed for ROD diagnosis. However, there was a debate in the literature regarding the accuracy of this measurement in the diagnosis of ROD.⁴ Herberth et al,¹⁴ in 2009 referred to the inability of PTH measurements to reliably diagnose bone turnover and then suggested performing more measurements of some other markers reflecting the effects of bone turnover, rather than measuring PTH as a single effector. They also represented that the common clinical practice of measuring alkaline phosphatase does not increase the predictive value of the classification rule for diagnosing bone turnover abnormalities in CKD patients. For instance, in a previous study performed in Libya, 103 patients on hemodialysis were included, and intact PTH (iPTH) was used to categorize the enrolled patients.¹³ As a result, ROD was diagnosed in about half of the patients (55.3%). In this research, adynamic bone disease (diagnosed by iPTH levels < 60 pg/mL) was reported in 28 cases, and hyperparathyroid bone disease was found in 29 cases. Since the diagnosis of ROD in the study mentioned above was done based on the iPTH levels, and because PTH is more accurate than iPTH levels,¹⁵ the lower prevalence of ROD in this study can be partially justified.

In another study from India¹⁶ on 462 patients with CKD-MBD, SHPT was found among 82.7% of the patients using iPTH.

In a multicenter study in 2002,¹⁷ 683 patients with a mean age of 61 years and a mean duration of dialysis of 72 months were selected from 29 dialysis centers in southern Italy. Overall, 25.4% of patients had hyperparathyroidism (iPTH > 400 pg/mL) and only 19.5% had iPTH levels within the normal range (i.e., 100–250 pg/mL). In addition, both oversupression of the parathyroid gland and hyperparathyroidism were common among the patients, albeit the first one was more common.

In this study, hypocalcemia (37.5%) was found to be more common than hypercalcemia (6.3%), and hyperphosphatemia (49.2%) was more common than hypophosphatemia (7.0%). This finding is consistent with the nature of CKD and the result of an Indonesian study that reported hypocalcemia in 61% of patients.¹⁸ The development of ROD begins too early during CKD. The three important pathogenic mechanisms include reduced calciferol production (glomerular filtration rate (GFR) < 90 mL/min/1.73 m²), hyperphosphatemia (GFR < 35–30 mL/min/1.73 m²), and hypocalcemia occurring relatively early during CKD.^{9,19} In recent years, due to the extensive consumption of calciumcontaining agents in patients, the pathogenic role of hypocalcemia in the development of ROD has remained in the background.¹⁹

A study investigating the relationship between the studied variables with ROD in the current article indicated an important relationship between phosphate levels and ROD. Although we found no association between calcium levels and ROD, about half of the patients with ROD reported normal serum calcium. Accordingly, this may indicate a weaker link between calcium levels' disorders and renal ROD, contrary to previous reports. However, our results may have been influenced by medications or hemodialysis. Contrary to what was explored regarding calcium, the statistical relationship between ROD prevalence and blood phosphate level was strongly important, and the prevalence of hyperphosphatemia among the patients with ROD was > 1.5-times that of those patients without ROD. It can be concluded that hypocalcemia was more common (29 patients, 54.7%) in the HTO group compared to the LTO group (11 patients, 27.5%). Buargub et al,¹³ in their study reported higher serum calcium levels in LTO patients.

Since the association between PTH and ROD has been established in previous studies, the results show a strong statistically significant relationship between PTH levels and calcium and phosphate levels. Similar to the findings of our study, a significant relationship was also found between blood phosphorus levels and iPTH in another study.¹⁶

Additionally, the results of our study underline that there is no significant relationship between age, the number of hemodialysis sessions per week, and the prevalence of ROD, LTO, and HTO.

Despite the inability to find a relationship between phosphate levels and the number of dialysis sessions per week, the current research explored the normal calcium levels in 57.8% of the patient with more frequent hemodialysis sessions per week (\geq 3 times per week). While this finding is reasonable, a more important point is that almost 38.8% of patients with more frequent hemodialysis sessions per week were afflicted with hypocalcemia. However, to improve this situation, we need to



comply with effective nursing considerations within the dialysis process to optimize hemodialysis machines using a high-efficiency dialyzer, proper phosphate binder, and nutritional advice, for better controlling phosphate.

Contrary to our study, Daugirdas et al,²⁰ found that blood phosphorus levels were significantly lower in patients undergoing six hemodialysis sessions per week than those undergoing three sessions per week.

Pain is a multidimensional sensation with psychological and physical components associated with significant activity limitations in work and psychological problems. In this regard, ROD is a painful syndrome with multifactorial etiology; one of the most common complications is musculoskeletal pain.^{9,21}

Bone pain was the most common complaint of the patients in this study (32.0%). This finding is consistent with other studies. In research performed on 95 hemodialysis patients in Turkey, 51.6% of cases experienced moderate to severe bone pain. Chronic bone pain was found to be significantly associated with PTH levels.²¹ In another Turkish study conducted on 100 hemodialysis patients with at least three months of dialysis initiation, 51% of patients complained of chronic bone pain. Likewise, this study found a relationship between chronic bone pain and PTH levels.²² The discrepancy between these results and those of our study may be due to the differences in bone pain assessment methods used.

In our study, to perform the pain assessment, patients were asked whether they felt any pain or not, and no standard pain classification scale was used regarding the pain duration and severity. This can be regarded as another limitation of the present research.

Although bone fractures, especially hip fractures, had been reported more commonly among hemodialysis patients with ROD,⁵ the incidence of fractures was not assessed in the current study as it has a cross-sectional design.

Our study has some limitations. Most importantly, we did not perform a bone biopsy to demonstrate the type of ROD histologically in our patients. Secondly, we did not measure serum vitamin 25-OH vitamin D to rule out pure osteomalacia from the patients with ROD (LTO). In addition, the pain detection method can be considered as another limitation.

CONCLUSION

The prevalence of ROD among patients undergoing maintenance hemodialysis in our study was somewhat close to similar studies with similar reference serum PTH levels, patients' mean age, and hemodialysis mean duration, especially in other regions of Iran. Accordingly, the results clearly showed that the prevalence of ROD was high at our referral hospital. Correspondingly, this high rate highlights the fact that patients need to be more closely monitored by physicians and informed of the side effects of osteodystrophy as well as its impact on their quality of life. As it is necessary to differentiate two types of ROD, particularly LTO, it is advised to measure vitamin D levels regularly along with other laboratory variables that are extensively applicable for patient monitoring.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

REFERENCES

- 1. El-Kishawi AM, El-Nahas AM. Renal osteodystrophy: review of the disease and its treatment. Saudi J Kidney Dis Transpl 2006;17(3):373-382.
- Ott SM. Renal osteodystrophy-time for common nomenclature. Curr Osteoporos Rep 2017 Jun;15(3):187-193.
- Moe S, Drüeke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al; Kidney Disease: Improving Global Outcomes (KDIGO). Definition, evaluation, and classification of renal osteodystrophy: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int 2006 Jun;69(11):1945-1953.
- Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. Kidney Int 2017 Jul;92(1):26-36.
- Cejka D. Renale osteodystrophie. Wien Med Wochenschr 2013 Sep;163(17-18):403-408.
- 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):409-415.
- Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J. Harrison's principles of internal medicine. 19th ed. New York: McGraw-Hill. Medical Publishing Division 2015;21(6):1663-1668.
- Arenas MD, Alvarez-Ude F, Gil MT, Soriano A, Egea JJ, Millán I, et al. Application of NKF-K/DOQI clinical practice guidelines for bone metabolism and disease: changes of clinical practices and their effects on outcomes and quality standards in three haemodialysis units. Nephrol Dial Transplant 2006 Jun;21(6):1663-1668.
- Martin KJ, Olgaard K, Coburn JW, Coen GM, Fukagawa M, Langman C, et al; Bone Turnover Work Group. Diagnosis, assessment, and treatment of bone turnover abnormalities in renal osteodystrophy. Am J Kidney Dis 2004 Mar;43(3):558-565.
- 10. Sedighi-Gourabi V, Afkhamzadeh A, Nikkhu B, Rahimi-

Rastgoo B, Habibi S, Moradinia Gh. Investigation of renal osteodystrophy among hemodialysis patients referring to Towhid Hospital, Sanandaj, Iran. Chron Dis J 2014;2(1):41-45.

- Hdgeman E, Lipworth L, Lowe K, Saran R, Do T, Fryzek J. International burden of chronic kidney disease and secondary hyperparathyroidism: a systematic review of the literature and available data. IJN 2015;2015.
- Jat JA, Mal P, Kumar D. Renal osteodystrophy in end stage renal failure patients on maintenance haemodialysis. J Clin Exp Nephrol 2016;1(4):25.
- 13. Buargub MA, Nabulsi MF, Shafeh TA. Prevalence and pattern of renal osteodystrophy in chronic hemodialysis patients: a cross sectional study of 103 patients. Saudi J Kidney Dis Transpl 2006;17(3):401-407.
- Herberth J, Monier-Faugere M-C, Mawad H, Branscum A, Herberth Z, Wang G, et al. The five most commonly used intact parathyroid hormone assays are useful for screening but not for diagnosing bone turnover abnormalities in CKD-5 patients. Clin Nephrol 2009;72(1):5-14.
- Taniguchi M, Tanaka M, Hamano T, Nakanishi S, Fujii H, Kato H, et al. Comparison between whole and intact parathyroid hormone assays. Ther Apher Dial 2011 Jun;15(1)(Suppl 1):42-49.
- 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 2016 Jul-Aug;20(4):460-467.

- Gallieni M, Cucciniello E, D'Amaro E, Fatuzzo P, Gaggiotti A, Maringhini S, et al; Collaborating nephrologists of the CARDIALISI Study Group. Calcium, phosphate, and PTH levels in the hemodialysis population: a multicenter study. J Nephrol 2002 Mar-Apr;15(2):165-170.
- Santoso D, Yogiantoro M, Tomino Y. Osteodystrophy in Indonesian haemodialysis patients. Nephrology (Carlton) 2003 Oct;8(5):261-265.
- Grozeva V, Kundurzhiev A. Calcium-phosphate metabolism disorder in patients with renal failure clinical significance, diagnosis and treatment. Acta Medica Bulgarica 2019;46(1):50-56.
- Daugirdas JT, Chertow GM, Larive B, Pierratos A, Greene T, Ayus JC, et al; Frequent Hemodialysis Network (FHN) Trial Group. Effects of frequent hemodialysis on measures of CKD mineral and bone disorder. J Am Soc Nephrol 2012 Apr;23(4):727-738.
- 21. Elsurer R, Afsar B, Mercanoglu E. Bone pain assessment and relationship with parathyroid hormone and health-related quality of life in hemodialysis. Ren Fail 2013;35(5):667-672.
- Golan E, Haggiag I, Os P, Bernheim J. Calcium, parathyroid hormone, and vitamin D: major determinants of chronic pain in hemodialysis patients. Clin J Am Soc Nephrol 2009 Aug;4(8):1374-1380.

