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Serum Calcium and Phosphorus Levels in Hemodialysis Patients: A Large Population-Based Multicenter Study

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Abstract

Background: Mineral bone disorder is one of the major factors affecting mortality and morbidity in dialysis patients, which is called chronic kidney disease-mineral and bone disorder (CKD-MBD).
Objectives: This study aimed to evaluate the laboratory parameters of mineral bone disorder in hemodialysis patients in Iran and their relationship with malnutrition and inflammation.
Methods: This multicenter observational study was conducted in 2016 in 58 dialysis centers in Iran. Data of a total number of 7191 chronic hemodialysis patients aged older than 18 years with a dialysis duration of > 3 months were collected. Idiopathic hypercalcemia and history of parathyroidectomy were considered as the exclusion criteria. The serum levels of calcium (Ca), phosphorus (P), and intact parathyroid hormone (iPTH) were measured over a period of three months, and the findings were compared with the K/DOQI (National Kidney Foundation Dialysis Outcomes Quality Initiative) guidelines. Moreover, the serum level of C-reactive protein (CRP) and nutritional status based on geriatric nutritional risk index (GNRI) were assessed.
Results: The percentage of the patients who had a serum iPTH level of < 150 pg/mL was 46% while that of patients with iPTH of > 300 pg/mL was 29.3%. Hypercalcemia and hyperphosphatemia were observed in 20.6% and 34.2% of the patients, respectively. Moreover, 51.7%, 61.3%, 24.7%, and 84.7% of the patients, respectively, reached the K/DOQI target range of Ca, P, iPTH, and Ca × P product. The percentages of mild-to-severe malnutrition based on GNRI in patients whose iPTH level was within, below, and above the recommended range of K/DOQI guidelines were 30.7%, 34.1%, and 25.9%, respectively ($P < 0.001$). Furthermore, the serum level of CRP was significantly higher in low-serum PTH patients than in the other two groups. In total, only could 8.3% of the patients reach the four KDOQI target levels of CKD-MBD.
Conclusions: The findings showed a significant percentage of patients had a low serum PTH level, which might be attributed to inflammatory and nutritional factors. Only had a small percentage of patients reached all the K/DOQI targets. Therefore, the effects of inflammatory and nutritional factors should also be considered, particularly in developing countries.

Keywords: Mineral, Bone, Calcium, Disorder, Hemodialysis, K/DOQI Guideline Phosphorus, PTH

1. Background

Nowadays, chronic kidney disease-mineral and bone disorder (CKD-MBD) is a common complication of chronic kidney disease (1). On the other hand, cardiovascular disease (CVD) and malnutrition are important causes of mortality in CKD patients (2, 3) and several studies have demonstrated a strong association between abnormal mineral metabolism and outcome in hemodialysis patients (4-6). Hyperphosphatemia is recognized to be independently associated with an excessive cardiovascular risk in CKD patients (7-9). However, it is important to note that both low (10) and high (11) serum parathyroid hormone (PTH) levels are associated with poor health outcomes in HD patients. A recent study found that the complex of biomarkers is more important than the status of a single biomarker of CKD-MBD in the survival of patients (12). Given the association between mineral and bone disorder and mortality in CKD patients, several guidelines have been developed for the management of CKD-MBD that emphasized the need to control calcium (Ca), phosphorus (P), and PTH in patients with CKD (13).

According to the National Kidney Foundation Dialysis

Outcomes Quality Initiative (K/DOQI) guidelines, the recommended serum levels of P, Ca, Ca × P product, and intact PTH (iPTH) in dialysis patients are 3.5 - 5.5 mg/dL, 8.4 - 9.5 mg/dL, < 55 mg^2/dL^2, and 150 - 30 Pg/mL, respectively (9).

2. Objectives

In this observational study, we aimed to assess the serum mineral levels, determine the degree of achieving the recommended levels based on the K/DOQI guideline, and evaluate the relationship between nutritional status and inflammation and CKD-MBD parameters.

3. Methods

3.1. Study Population

This multicenter observational study was conducted on 7191 patients in 58 dialysis centers in 20 provinces of Iran in 2015 - 2016. Patients aged ≥ 18 years who were under chronic maintenance hemodialysis for ≥ 3 months were enrolled in the study. Idiopathic hypercalcemia and history of parathyroidectomy were the exclusion criteria. The study was approved by the ethics committee of Nephrology Research Center of Shahid-Beheshti University of Iran (Ethical code: ir.unrc.1393.4). Prior to data collection, written informed consent was obtained from all participants.

3.2. Data Collection

We enrolled 7390 patients, of whom 199 were excluded. The patients were observed over three months. A questionnaire was used to assess the demographic data of participants (age, sex, BMI, and weight) and clinical data (cause of ESRD, dialysis vintage, adequacy of dialysis (Kt/V), and frequency of HD). The data were recorded by nurses or physicians. Before the hemodialysis sessions, laboratory data such as serum Ca, P, and iPTH, hemoglobin, serum albumin, blood glucose, serum creatinine, serum ferritin, lipid profile, and CRP were measured at the central laboratory of each center. Serum Ca and P levels were measured by the spectrophotometry assay and iPTH by the immunoradiometric assay. All of the centers performed the laboratory tests monthly. Accordingly, the mean value of the laboratory parameters was calculated. Albumin-corrected calcium was calculated as [4-serum albumin (g/dL)] × 0.8 + total serum Ca (mg/dL)]. The Ca × P product was also calculated.

The nutritional status was assessed base on the geriatric nutritional risk index (GNRI). The GNRI formula used in this study was as follows (14):

GNRI = [1.489 × albumin (g/dL)] + [41.7 × body weight/ideal body weight]

The Robinson formula was used to assess the ideal body weight (15).

Bouillanne et al. defined four levels of nutrition-related risk: major risk (GNRI < 82), moderate risk (GNRI: 82 to < 92), low risk (GNRI: 92 to ≤ 98), and no risk (GNRI: > 98) (14).

The sample size formula was as follows:

$$n = \frac{\left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2 \times \left(P_1\left(1-P_1\right) + P_2\left(1-P_2\right)\right)}{\left(P_1 - P_2\right)^2}$$

where $\alpha = 0.05$, $\beta = 0.8$, and P_1 and P_2 are the expected sample proportions of the two groups. Considering a 50% achievement in one group, in order to detect only a 5% difference, at least 1562 individuals required to be enrolled in each group. For sampling, three levels of dialysis centers were identified to cluster 58 centers and a proportional sample was taken from each center based on its annual admission rate. The governmental hemodialysis centers were included, too.

3.3. Statistical Analysis

IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, N.Y., USA) was used for data analysis. Continuous data were presented as means ± standard deviation, and categorical variables were presented as frequencies and percentages. The one-way analysis of variance (ANOVA) test was used to compare the continuous variables between the three levels of iPTH. The Chi-square test and Pearson correlation coefficient test were used to evaluate the associations between categorical and continuous variables, respectively. Logistic regression analysis was used to determine the independent factors associated with hyperphosphatemia. A P value of less than 0.05 was considered statistically significant.

4. Results

Of a total number of 7191 patients, 4200 patients (58%) were male and 2991 patients (42%) were female. The range and mean (SD) age of the patients, respectively, were 18 - 85 years and 57 ± 15 years. The most common causes of ESRD were diabetes and high blood pressure, which were observed in 2648 patients (37%) and 2067 patients (29%), respectively. Table 1 presents the clinical characteristics and dialysis status of the patients.

The levels of corrected Ca, P, Ca × P product, and iPTH in 51.7%, 61.3%, 84.7%, and 24.7% of the patients were within the target ranges recommended by the K/DOQI

Table 1. The Clinical Characteristics and Status of Dialysis Patients

Variable	Values[a]
Weight, kg	66 ± 11
BMI, kg/m^2	24.1 ± 3.5
ESRD cause	
Diabetes	2648 (37)
Hypertension	2067 (29)
Glomerulonephritis	464 (7)
PCKD	253 (4)
Urologic Causes	325 (5)
Other causes	429 (6)
Unknown	1003 (14)
Dialysis duration, months	40 ± 35
Dialysis sessions/week, median (IQR)	3 (3-3)
Dialysis session duration, hour/week	3.9 ± 0.3
Kt/V	1.3 ± 0.2

Abbreviations: IQR, interquartile range; PCKD, polycystic kidney disease.
[a] Values are expressed as mean ± SD or No. (%).

guideline (Figure 1). The percentage of patients with adynamic bone disease was higher than the percentage of patients with hyperparathyroidism. In 9.3% of the patients, e iPTH level was higher than 600 pg/mL. Of all CKD-BMD tests, only could 8.3% achieve the targets recommended by the K/DOQI guidelines. We compared diabetic and non-diabetic groups in terms of the degree of achieving the targets. The results showed the percentage of people who met two or more target ranges recommended by the K/DOQI guideline was higher in the diabetic group (2126 persons; 80.3%) than in the non-diabetic group (3450 persons; 75.9 %) ($P < 0.001$ from Chi-square test).

Table 2 compares the mean values of Ca, P, and Ca × P product at different iPTH levels. In patients with higher levels of iPTH, the levels of Ca × P product and P were significantly higher while the level of Ca was significantly lower.

Table 3 shows the correlation of serum iPTH, P, and CRP level with other variables. The mean serum level of iPTH had a positive correlation with the mean serum P level and a negative correlation with the mean serum Ca level. The mean serum P level had a negative correlation with the mean serum corrected Ca level, too. Patients who had been under dialysis for longer periods had higher iPTH and lower Ca and P. Moreover, in patients with higher CRP, the levels of serum P and iPTH were lower, which may indicate the effect of inflammation on the serum P and iPTH levels.

Table 4 shows the nutrition status based on GNRI. The percentage of mild-to-severe malnutrition based on GNRI was significantly higher in patients with PTH level of < 150 pg/mL than in patients meeting the target PTH range or having a PTH level of > 300 pg/mL (34.1%, 30.7%, 25.9%, respectively, $P < 0.001$).

The logistic regression analysis was performed to investigate the relationship between hyperphosphatemia and different parameters. The results showed that after adjustment for sex, the levels of hemoglobin, albumin, and hyperphosphatemia still had an independent negative correlation with age (OR = -0.989, 95% CI = (-0.986) - (-0.992)), duration of the disease (OR = -0.997, 95% CI = (-0.995) - (-0.998)), and CRP (OR = -0.995, 95% CI = (-0.992) - (-0.998)).

Table 5 shows the levels of serum corrected calcium, phosphorus, and intact parathyroid hormone (iPTH) classified by the ranges recommended by the K/DOQI guidelines in each province. In addition, Figure 2 shows the status of each province concerning the national target range.

5. Discussion

The results of the study showed that only could a small percentage of hemodialysis patients reach all the target ranges of Ca, P, serum iPTH, and Ca × P product. Overall, about 51.7%, 61.3%, and 24.7% of the patients reached the target ranges of Ca, P, and iPTH recommended by K/DOQI. In DOPPS 4 study, 55.8%, 54.2%, and 31.8% of the patients met the target ranges of Ca, P, and iPTH recommended by K/DOQI (Table 6) (16). The results of a multicenter study conducted in Korea showed that 58.7%, 51%, and 30.8% of the patients met the target ranges of Ca, P, and iPTH (17). In comparison with the two mentioned studies, our findings indicated that the target range of P is better met in Iran; however, the Ca and iPTH levels in our study were slightly lower than the levels observed in the other two studies. Our results are largely in line with the results of DOPPS 2011 study in the USA and Canada (53.7% and 63.1% for Ca, 52.6% and 55.3% for P, and 31.4% and 22.1% for iPTH, respectively) (16).

In this study, the majority of patients with iPTH levels outside the K/DOQI target ranges had a PTH level of < 150 pg/mL which is comparable with the results of studies in Turkey and Korea (48.6% and 42.7%, respectively) (17, 18). However, in DOPPS 4 study, a higher percentage of patients with iPTH levels outside the target range had developed hyperparathyroidism (16). The observed biochemical changes are in line with the histologic spectrum of bone diseases in hemodialysis patients reported in a study conducted over the past decade (19).

Some studies have focused on the relationship between low serum iPTH and calcium homeostasis and increased risk of mortality in hemodialysis patients (20-23). There are several reasons for the reduction of iPTH levels in the patients among which, we may note the follow-

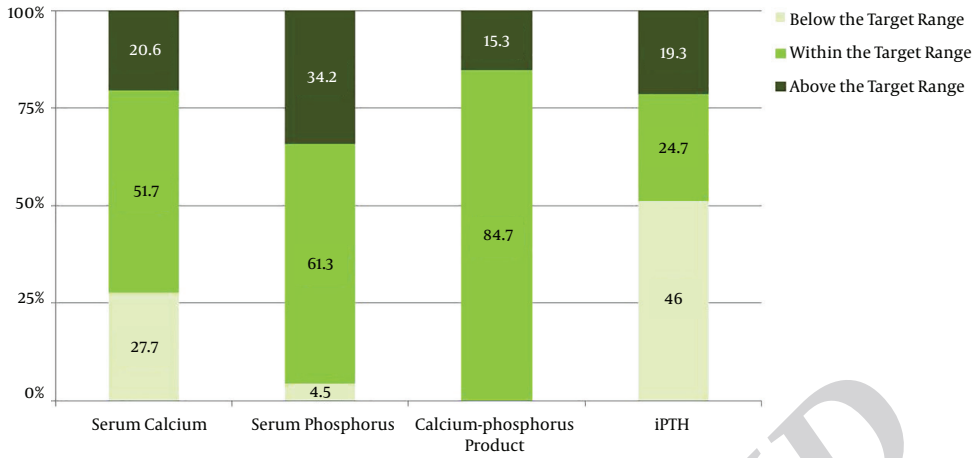

Figure 1. Distribution of the national value of serum corrected calcium, phosphorus, calcium-phosphorus product, and intact parathyroid hormone (iPTH) levels, classified by the ranges recommended in the K/DOQI guidelines

Table 2. Comparison of Mean Values of Ca, P, and Ca × P Product at Different iPTH Levels

Variable	iPTH Level, pg/mL			P Value[a]
	< 150	150 - 300	> 300	
Corrected Ca, mg/dL	8.99 ± 0.88	8.81 ± 0.86	8.70 ± 0.81	< 0.001
P, mg/dL	4.99 ± 1.06	5.15 ± 1.09	5.24 ± 1.08	< 0.001
Ca × P product, mg^2/dL^2	44.21 ± 9.78	44.90 ± 9.86	45.60 ± 9.92	< 0.001

[a] One-way ANOVA, there was a significant difference between groups in all tests.

ing: parathyroidectomy, taking calcimimetics, increasing intake of Ca and vitamin D and hypercalcemia (24, 25), dialysate Ca concentration (26), inflammatory syndrome, malnutrition (1, 27, 28), and long-term inactivity (29).

In this study, PTH and serum P levels had a positive correlation with albumin, creatinine, triglycerides, and Kt/V. This finding is consistent with the results of previous studies (30-32). In addition, a cohort study in Japan reported a relationship between the low level of serum albumin and low PTH (33). In our study, serum P and PTH had a negative correlation with age; this finding was similarly reported by previous studies, as well (34).

Consistent with previous studies (35, 36), malnutrition was observed more significantly in patients with iPTH of < 150 pg/mL than in the other two groups and there was a negative correlation between serum iPTH and P, and CRP. The inflammatory-malnutrition syndrome was associated with low iPTH and adverse prognosis (37). Given the relationship between inflammatory and nutritional factors and low iPTH levels in our study that has been suggested by other studies, as well (38, 39), it is necessary to pay special attention to the nutritional status and inflammatory factors to treat PTH disorders (40). Unfortunately, nutrition screening is not performed routinely in CKD patients in a large number of kidney care centers (41).

Since the high intake of vitamin D analogs increases the risk of adynamic bone disease and reduces serum PTH (42), it is necessary to consider the use of vitamin D receptor agonists for the treatment of this group of patients. In the DOPPS study, 43% of patients with PTH of < 150 pg/mL were treated with vitamin D analogs (16). Moreover, in a multicenter study that was recently conducted in Iran, 70% of the hemodialysis patients had been receiving this group of drugs (43). In our study, 9.3% of the patients had PTH of > 600 pg/mL; the low cost and high intake of vitamin D analogs could explain this low percentage.

Dialysate Ca concentration is the other factor that plays a role in the reduction of the iPTH level (26). Since Iranian dialysis centers use a dialysate Ca concentration of 2.5 mEq/L which is lower than those used in many other countries (dialysate Ca concentration of 3 mEq/L), this factor cannot explain the high percentage of patients with high PTH.

In this study, 8.3% of the patients reached the four tar-

Table 3. Correlation of Serum iPTH, P, and CRP Levels with Other Variables

Variable	iPTH		P		Corrected Ca		CRP	
	r	P Value	r	P Value	r	P Value	r	P Value
iPTH	-	-	0.119[a]	< 0.001	-0.128[a]	< 0.001	-0.071[a]	< 0.001
P	0.119[a]	< 0.001	-	-	-0.165[a]	< 0.001	-0.078[a]	< 0.001
Corrected Ca	-0.128[a]	< 0.001	-0.165[a]	< 0.001			0.165a	< 0.001
Age	-0.042[a]	< 0.001	-0.107[a]	< 0.001	0.130[a]	< 0.001	0.007	0.577
BMI	0.040[a]	0.001	0.061[a]	< 0.001	-0.016	0.168	0.019	0.111
ESRD duration	0.140[a]	< 0.001	-0.049[a]	< 0.001	-0.042[a]	< 0.001	-0.028[b]	0.017
Creatinine	0.155[a]	< 0.001	0.287[a]	< 0.001	-0.120[a]	< 0.001	-0.002	0.851
Albumin	0.122[a]	< 0.001	0.097[a]	< 0.001	-0.425[a]	< 0.001	-0.186[a]	< 0.001
Hemoglobin	0.009	0.443	0.007	0.544	0.081[a]	< 0.001	-0.052[a]	< 0.001
Triglyceride	0.031[a]	0.009	0.043[a]	< 0.001	-0.021	0.075	0.019	0.116
Cholesterol	-0.020	0.085	0.030[b]	0.012	0.043[a]	< 0.001	0.042[a]	< 0.001
CRP	-0.071[a]	< 0.001	-0.078[a]	< 0.001	0.165[a]	< 0.001	-	-
Ferritin	0.027[b]	0.024	0.067[a]	< 0.001	0.032[a]	0.007	-0.043[a]	< 0.001
Kt/V	0.069[a]	< 0.001	0.041[a]	< 0.001	-0.020	0.085	-0.018	0.130

Abbreviations: BMI, body mass index; Ca, calcium; CRP, C-reactive protein; ESRD, end-stage renal disease; iPTH, intact parathyroid hormone; Kt/V, adequacy of dialysis; P, phosphorus; r, Pearson correlation coefficient.
[a] Correlation is significant at the 0.01 level.
[b] Correlation is significant at the 0.05 level.

Table 4. Comparison of Mean Values of Ca, P, and Ca × P Product at Different iPTH Levels[a]

GNRI	iPTH Level, pg/mL			P Value[b]
	< 150	150 - 300	> 300	
No risk	2179 (65.9)	1233 (69.3)	1561 (74.1)	< 0.001
Mild risk	691 (20.9)	342 (19.2)	360 (17.1)	
Moderate risk	351 (10.6)	180 (10.2)	157 (7.5)	
Severe risk	85 (2.6)	24 (1.3)	28 (1.3)	

Abbreviation: GNRI, Geriatric nutritional risk index.
[a] Values are expressed as No. (%).
[b] Chi-square test.

get ranges recommended by K/DOQI that is higher than 1.8% reported by a previous study in Iran in 2007 (44). However, there was no significant difference between the two studies in terms of reaching the target ranges of Ca, P, and iPTH. There was only a small improvement in achieving the target range of P. Non-calcemic phosphate binders and calcimimetic drugs have recently been covered by insurance schemes; thus, so far there has been no significant difference in their consumption because of the changes in availability and insurance coverage; hence, it seems natural not to see a change in the target ranges. However, the improvements in the P target range may be associated with increased use of high flux dialyzers in recent years.

As one of the limitations of this study, the laboratory tests were performed at various centers, not in the same laboratory. In addition, we did not evaluate other factors affecting CKD-MBD including diet, dietary phosphorus, residual renal function, and the use of drugs effective in CKD-MBD. In addition, our study used a cross-sectional design. However, this multi-center study was conducted with a large sample size that could provide a good picture of the status of different parameters of mineral bone disorder in Iranian hemodialysis patients and showed a relationship between malnutrition and inflammation and CKD-MBD parameters. This study may be the first one with a large sample size and wide distribution of sample to assess malnutrition.

5.1. Conclusions

The results of this multicenter study showed that only a small percentage of hemodialysis patients met all the K/DOQI targets. On the other hand, adynamic bone disease is a more significant problem than hyperparathyroidism. In our study, there was a relationship between iPTH and P abnormalities and inflammation and malnutrition. Moreover, although the newer drugs are more easily accessible in developed countries, there is no clear distinction between our country and other developed countries in terms of the achievement of the K/DOQI targets. Thus, paying

Table 5. Value of Serum Corrected Calcium, Phosphorus, and Intact Parathyroid Hormone (iPTH) Levels, Classified by the Ranges Recommended in the K/DOQI Guidelines in Each Province

Province	Corrected Ca Level, mg/dL			P Level, mg/dL			iPTH Level, pg/mL		
	< 8.4	8.4 - 9.5	> 9.5	< 3.5	3.5 - 5.5	> 5.5	< 150	150 - 300	> 300
Khuzestan	18.4	31.2	50.4	3.6	68.4	28	54	33.2	12.8
Zanjan	0	40	60	5.7	51.4	42.9	62.9	15.2	21.9
Markazi	7.1	45.8	47.1	16.1	56.2	27.7	47.1	25.8	27.1
Chahar Mahal and Bakhtiari	28.1	61.2	10.7	4.1	81.4	14.5	16.9	23.2	59.9
Mazandaran	44.2	43	12.8	3.3	63.2	33.5	47.2	30.2	22.6
Azerbaijan, West	15.1	46	38.9	6.2	54	39.8	48.5	21.6	29.9
Ilam	12.5	87.5	0	0	50	50	45.8	27.1	27.1
Semnan	11.5	65.4	23.1	7.7	80.8	11.5	34.6	23.1	42.3
Khorasan, Razavi	27	52.5	20.5	5.9	57.6	36.5	46.5	20.5	33
Khorasan, South	10.6	70.2	19.2	5.8	50	44.2	77.9	17.3	4.8
Golestan	25.6	63.9	10.5	2.3	68.9	28.8	49.3	22.8	27.9
Hamadan	15.4	60.1	24.5	9.1	81.8	9.1	54.3	28.4	17.3
Isfahan	28.1	55.5	16.4	1.5	74.2	24.3	37.8	26.2	36
Alborz	42.3	46.2	11.5	0	46.2	53.8	26.9	28.9	44.2
Kerman	38.9	53.1	8	0.6	36.7	62.7	31.9	28.9	39.2
Kermanshah	34.4	50	15.6	2.5	73.7	23.8	63.1	25.4	11.5
Kohkiloyeh and Boyer-Ahmad	45.1	36.7	18.2	0.8	55.3	43.9	30.4	21.9	47.7
Fars	13.2	40.8	46	2.6	64.5	32.9	52.6	23.7	23.7
Gilan	16.7	73.3	10	6.7	56.6	36.7	26.7	13.3	60
Tehran	28.9	53.2	17.9	4.7	60.5	34.8	49.9	25.2	24.9
National value	27.7	51.7	20.6	4.5	61.3	34.2	46	24.7	29.3

Table 6. Comparison of CKD-MBD Tests Based on K/DOQI Guidelines Between This Study and DOPPS4[a,b]

Test	Current Study	DOPPS4
Corrected Ca, mg/dL		
< 8.4	1994 (27.7)	1046 (12.4)
8.4 - 9.5	3720 (51.7)	4675 (55.8)
> 9.5	1994 (20.6)	2662 (31.8)
P, mg/dL		
< 3.5	324 (4.5)	1116 (12.1)
3.5 - 5.5	4407 (61.3)	4978 (54.2)
> 5.5	2460 (34.2)	3085 (33.6)
iPTH, pg/mL		
< 150	3306 (46)	2726 (33)
150 - 300	1779 (24.7)	2628 (31.8)
300 - 600	2106 (29.3)	2918 (35.2)

[a] Dialysis Outcomes and Practice study (DOPPS4, 2010) includes data from US, NZ, UK, France, Belgium, Canada, Germany, Italy, Japan, Spain, and Sweden (1).
[b] Values are expressed as No. (%).

more attention to nutrition and inflammatory factors may provide new chances for controlling CKD-MBD disorders, particularly in developing countries, and reduce mortality and improve disease outcomes.

Footnotes

Conflict of Interests: The authors declare that there is no conflict of interest among them.

Ethical Considerations: The study was approved by the ethics committee of Nephrology Research Center of Shahid-Beheshti University of Medical Sciences (Ethical code: ir.unrc.1393.4). Prior to data collection, written informed consent was obtained from all participants.

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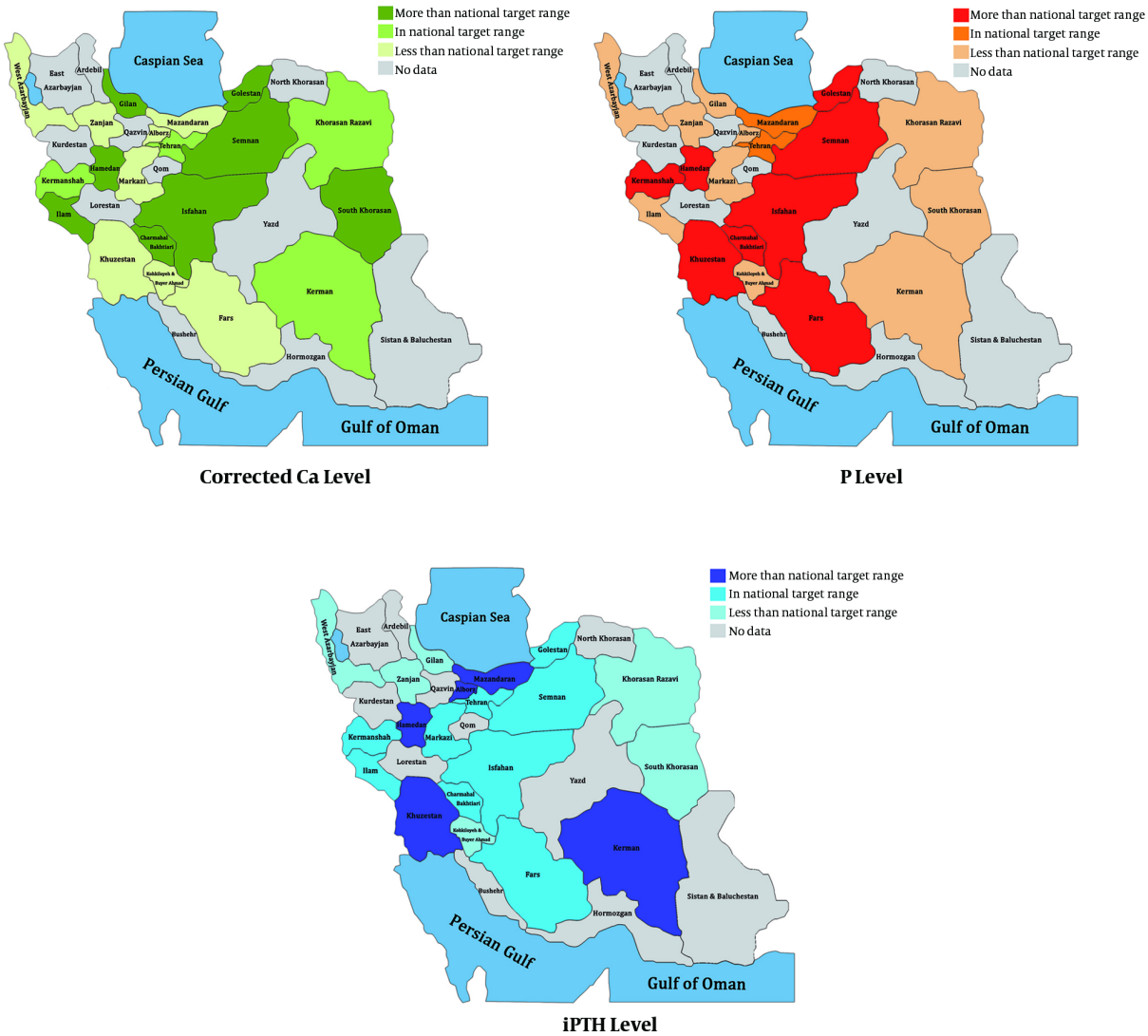

Figure 2. Comparison of the target range of serum corrected calcium, phosphorus, calcium-phosphorus product, and intact parathyroid hormone (iPTH) levels of each province with the national target range

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