Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(2) 1–17

DOI: 10.1177/0300060519895844
journals.sagepub.com/home/imr
SAGE

Effect of CKD–MBD phenotype on health-related quality of life in patients receiving maintenance hemodialysis: A cross-sectional study

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Abstract

Objective: This study aimed to investigate the factors influencing health-related quality of life (HRQoL) in patients with different chronic kidney disease–mineral and bone disorder (CKD–MBD) phenotypes.

Methods: Patients undergoing maintenance hemodialysis (MHD) at our center from 1 July to 31 August 2017 were enrolled. Patients who received hemodialysis for less than 3 months or displayed poor compliance, or those with incomplete clinical data were excluded. QoL was evaluated using the Kidney Disease Quality of Life–Short Form (KDQOL-SF^{TM}) 1.3 scale. The influential factors were stratified based on different CKB–MBD phenotypes.

Results: There were 296 patients enrolled. The serum intact parathyroid hormone (iPTH) concentration was 436.40 ± 490.99 pg/mL, serum calcium (Ca) concentration was 2.14 ± 0.27 mmol/L, serum phosphorus (P) concentration was 1.81 ± 0.56 mmol/L, the kidney disease and dialysis-related QoL (KDTA) score was 57.07 ± 10.40, and the SF-36 score was 51.45 ± 17.62. Among patients with different CKD–MBD phenotypes, HRQoL was highest in the group with an iPTH concentration of 150 to 300 pg/mL, serum Ca concentration of <2.10 mmol/L, and serum P concentration of >1.78 mmol/L.

Conclusions: CKD−MBD phenotypes significantly affected HRQoL. Comprehensive management of serum iPTH, Ca, and P levels is important to improve QoL in patients receiving hemodialysis.

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Keywords
Hemodialysis, chronic kidney disease–mineral and bone disorder (CKD–MBD), calcium, parathyroid hormone, phosphate, quality of life

Date received: 3 September 2019; accepted: 27 November 2019

Introduction

For patients with end-stage renal disease (ESRD), maintenance hemodialysis (MHD) remains the main treatment strategy. The population receiving MHD is rapidly increasing in China,[1,2] and the health-related quality of life (HRQoL) in these patients is significantly worsening.[3,4] Chronic kidney disease–mineral and bone disorder (CKD–MBD) a complication of chronic kidney disease (CKD) that seriously affects the prognosis of hemodialysis patients, remarkably increasing the relative risks of all-cause mortality and cardiovascular mortality in these patients.[5,6] It is also considered to be an important factor affecting HRQoL. Based on cross-sectional studies of patients who are undergoing hemodialysis, serum phosphorus (P) and intact parathyroid hormone (iPTH) levels that are too high or too low are associated with a low HRQoL.[7–9] However, previous studies conducted on this topic have mainly focused on the effects of individual biochemical indicators of CKD–MBD on HRQoL, but these studies have not considered the combination of serum P, serum calcium (Ca), and iPTH levels when evaluating their association with HRQoL. There is a close intrinsic connection and interaction among these three factors.[10] Thus, separate analyses of these three parameters are associated with limitations. This study aimed to observe the relationships between different combinations of serum P, serum Ca, and iPTH levels and HRQoL in patients undergoing MHD and to explore the related factors affecting HRQoL in these patients.

Patients & methods

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. The Committee waived the requirement to obtain distinct written informed consent from the patients.

Study design and subjects

This retrospective study was performed at a single center using a cross-sectional design. Patients undergoing MHD at the Blood Purification Center of The First Affiliated Hospital of Nanchang University from 1 July 2017 to 31 August 2017 were selected for screening. The inclusion criteria were as follows: 1) patients undergoing MHD for more than 3 months; 2) patients who displayed good compliance and were able to cooperate with the investigation; 3) no limit for age and gender; and 4) the required laboratory test results were provided within 3 months before the investigation period. Exclusion criteria included patients who were unable to understand the questionnaire and those who had incomplete clinical data.

Study methods

The investigators in this study were all nursing staff. Before study initiation, the investigators were trained on the use of the Kidney Disease Quality of Life–Short Form (KDQOL)–SF^{TM} 1.3, which is a self-reporting and self-rating scale. The participants were assisted by trained personnel to complete the scale. Patients' demographic information, laboratory test results, and

hemodialysis-related information were collected from the Hospital Information System (HIS), Laboratory Information System (LIS), and Hemodialysis Center Information System (HCIS). The laboratory indicators used data within 3 months of the survey period, and data were collected before treatment on the day of dialysis. If there were multiple results within 3 months, the average value was used. The phenotype was divided into the following categories: intact parathyroid hormone (iPTH) levels of <150 pg/mL (low), 150 to 300 pg/mL (target), and >300 pg/mL (high); serum Ca levels of <2.10 mmol/L (low), 2.10 to 2.55 mmol/L (target), and >2.55 mmol/L (high); and serum P levels of <1.13 mmol/L (low), 1.13 to 1.78 mmol/L (target), and >1.78 mmol/L (high). Twenty-seven CKD–MBD phenotypes were obtained when the three sets of parameters were combined (Table 1).

Table 1. CKB–MBD phenotypes defined based on combinations of serum parameters.

Groups	iPTH	Ca	P
1	high	high	high
2	high	high	target
3	high	high	low
4	high	target	high
5	high	target	target
6	high	target	low
7	high	low	high
8	high	low	target
9	high	low	low
10	target	high	high
11	target	high	target
12	target	high	low
13	target	target	high
14	target	target	target
15	target	target	low
16	target	low	high
17	target	low	target
18	target	low	low
19	low	high	high
20	low	high	target
21	low	high	low
22	low	target	high
23	low	target	target
24	low	target	low
25	low	low	high
26	low	low	target
27	low	low	low

iPTH, intact parathyroid hormone; Ca, calcium; P, phosphorus.

Assessment of HRQoL

The KDQOL-SF™ 1.3 scale comprised a general HRQoL (SF-36) assessment, which included analyses of physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH), and a kidney disease, dialysis-related quality of life (KDTA) field, which included a symptoms/discomfort list (SPL), effects of kidney disease (EKD), burden of kidney disease (BKD), work status (WS), cognitive function (CF), quality of social interaction (QSI), sexual function (SeF), sleep, social support (SoS), dialysis staff encouragement (DSE), and patient satisfaction (PS). In accordance with the scoring criteria developed by Hays et al.,[11] a 100-point system (minimum, 0 points; maximum, 100 points) was implemented to score each field, in which the higher scores indicated a better quality of life in patients.

Statistical methods

SPSS 24.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The measurement data are reported as the mean ± standard deviation (mean ± SD), and the count data are presented as the number and percentage (n, %). An independent sample *t*-test was used to compare the mean values for measurement data with a normal distribution between the two groups, and the Mann–Whitney U test, which is a nonparametric test, was used to compare the mean values for measurement data with a non-normal distribution.

One-way analysis of variance (ANOVA) was used to compare the means among multiple groups. Among the CKD–MBD phenotype groups, the groups that included more than ten patients were treated as dummy variables, and the differences in HRQoL between the groups were compared using a linear regression analysis. A linear regression analysis was conducted to analyze the linear relationship between HRQoL and continuous variables. The multivariate linear regression model used HRQoL as a dependent variable, CKD–MBD phenotype group as an independent variable, and age, single-pool urea clearance index ($spKt/V_{BUN}$), dialysis duration albumin (ALB) level, serum creatinine (Scr) level, serum urea nitrogen (BUN) level, urinalysis (UA), and blood flow as covariates, and these were treated in a stepwise manner. The nonlinear relationship between HRQoL and continuous variables was estimated by curve fitting. $P < 0.05$ was considered to be statistically significant.

Results

Survey completion

During the survey, 435 patients underwent MHD at our center, and 418 of them were screened for this study. Among these patients, 52 had received MHD for less than 3 months, 22 lacked laboratory results in the past 3 months, and two patients exhibited poor compliance. Three hundred forty-two patients met the inclusion criteria, but 15 patients were unable to understand the survey content. Three hundred twenty-seven patients completed the survey, and 296 patients had complete data available and were included in this analysis (Figure 1).

Demographic information and clinical characteristics

Two hundred ninety-six patients were included in this analysis, comprising 178 men and 118 women. The mean age of the patients was 59.27 ± 14.47 (range, 26–90) years, and most (76%) of the population resided in an urban location. The duration of dialysis was less than 10 years, and it accounted for 95.3% of the total population. Additionally, 29.4% of patients took P binders, 32.8% of patients took calcitriol, and 19.9% of patients took a calcimimetic. The primary diseases were chronic glomerulonephritis, diabetic nephropathy, and hypertensive nephropathy. As shown in Table 2, the $spKt/V_{BUN}$ was 1.47 ± 0.28, the mean iPTH level was 436.40 ± 490.99 pg/mL, the mean Ca level was 2.14 ± 0.27 mmol/L, and the mean P level was 1.81 ± 0.56 mmol/L.

Distribution of patients with each CKD–MBD phenotype

The 27 CKD–MBD phenotypes were distributed among the 296 patients included in the analysis. Among these patients, phenotypes 3, 12, 20, and 21 were not observed. Group 7 had the most patients ($n = 42$), while group 19 had the fewest patients ($n = 19$) (Figure 2).

Quality of life score and its relationship to the CKD–MBD phenotype

The total KDTA–SF score was 57.07 ± 10.40, and the total SF-36 score was 51.45 ± 17.62. Ten phenotype groups with at least ten patients were statistically analyzed. Two hundred forty-seven patients were included in this analysis, which accounted for 83.45% of the total number of patients (Table 3).

The highest KDTA and SF-36 scores were in group 16, with a serum iPTH level of 150 to 300 pg/mL, serum Ca level of <2.10 mmol/L, and serum P level of >1.78 mmol/L. The CKD–MBD phenotype group was considered to be a dummy variable. The KDOQI CKD–MBD guidelines[12]

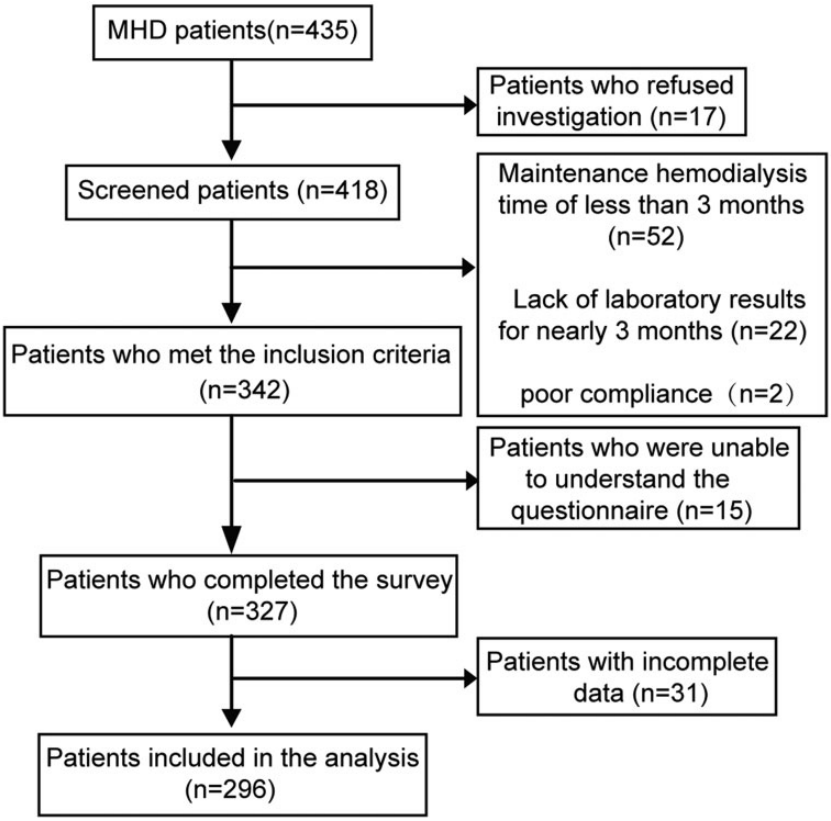

Figure 1. Flow chart of patient selection and inclusion.

recommended the use of serum iPTH, Ca, and P levels based on a control group in a linear regression analysis, which showed the following ranges: iPTH, 150 to 300 pg/mL; serum Ca, 2.10 to 2.55 mmol/L; and serum P, 1.13 to 1.78 mmol/L (Group 14). The KDTA and SF-36 scores in group 16 were significantly higher compared with group 14 ($P < 0.05$). After adjusting for age, primary disease, P binders, calcitriol, and calcimimetics, there was still a significant difference ($P < 0.05$; Tables 4 and 5).

Among the ten groups that were included in this analysis, there was no significant difference in the proportion of patients taking P binders and calcitriol in each group. The proportion of patients taking a calcimimetic agent was positively correlated with the iPTH level in each group. iPTH and serum Ca levels were different in groups of the same division. The KDTA and SF-36 score that was recorded by the group had high serum P levels that were higher compared with the group with low serum P levels. For example, the KDTA and SF-36 score in group 4 was higher compared with group 5, the score in group 7 was higher compared with group 8, the score in group 22 was higher compared with group 23, and the SF-36 score in group 13 was higher compared with group 14. In addition, the serum creatinine levels in the groups with high serum P levels were always higher compared with the groups with low serum P levels. All P values showed significant differences ($P < 0.05$, Table 3). SPSS software was

Table 2. Demographic information and clinical characteristics.

Item	Statistics
Number of patients	296
Men/women (n = 296)	178/118
Age (years) (n = 296)	59.27 ± 14.47 (26–90)
Married/unmarried (n = 296)	295/1
Primary disease (n = 296)	
Chronic glomerulonephritis	122 (41.2%)
Diabetic nephropathy	83 (28.0%)
Hypertensive nephropathy	57 (19.3%)
Other	34 (11.5%)
Area of residence (n = 296)	
City	225 (76%)
Town	22 (7.4%)
Rural area	49 (16.6)
Dialysis duration (n = 296)	
<1 year	73 (24.7%)
1–5 years	145 (49.0%)
5–10 years	64 (21.6%)
>10 years	14 (4.7%)
Nature of job (n = 296)	
Mental worker	89 (30.1%)
Manual worker	201 (69.9%)
Educational level (n = 296)	
College and above	30 (10.1%)
High school	91 (30.7%)
Middle school	91 (30.7%)
Elementary school and below	84 (28.4%)
Annual income (n = 296)	
>150,000 RMB Yuan	26 (8.8%)
100,000–150,000 RMB Yuan	66 (22.3%)
<100,000 RMB Yuan	204 (68.9%)
spKt/V_{BUN} (n = 296)	1.47 ± 0.28
Hb (g/L) (n = 296)	96.70 ± 20.13
TP (g/L) (n = 286)	66.50 ± 6.76
ALB (g/L) (n = 287)	39.47 ± 4.85
TG (mmol/L) (n = 279)	1.77 ± 1.16
TC (mmol/L) (n = 279)	4.27 ± 2.69
LDL (mmol/L) (n = 279)	2.31 ± 0.83
Scr (μmol/L) (n = 296)	882.85 ± 310.51
BUN (mmol/L) (n = 296)	22.09 ± 7.50
UA (μmol/L) (n = 296)	402.08 ± 120.99
Ca (mmol/L) (n = 296)	2.14 ± 0.27
P (mmol/L) (n = 296)	1.81 ± 0.56
iPTH (pg/mL) (n = 296)	436.40 ± 490.99
FER (μg/L) (n = 220)	147.24 ± 208.68
The proportion of taking phosphorus binder (n = 296)	29.4%
The proportion of taking calcitriol (n = 296)	32.8%

(continued)

Table 2. Continued

Item	Statistics
The proportion of taking calcimimetics (n = 296)	19.9%
Blood flow (mL/min) (n = 296)	235.54 ± 23.87
IWG/DW (n = 296)	0.039 ± 0.016
Number of weekly dialysis sessions (n = 296)	2.64 ± 0.44
KDTA score (n = 296)	61.34 ± 10.74
SF-36 score (n = 296)	51.42 ± 16.96

spKt/V_{BUN}: single-pool urea removal index; Hb, hemoglobin; ALB, albumin; TG, triglycerides; TC, total cholesterol; LDL, low-density lipoprotein; Scr, serum creatinine; BUN, blood nitrogen urea; UA, urinalysis; Ca, calcium; P, phosphorus; iPTH, intact parathyroid hormone; KDTA, kidney disease and dialysis-related quality of life; IWG/DW, interdialysis weight gain/dry weight; TP, total plasma protein; FER, serum ferritin.

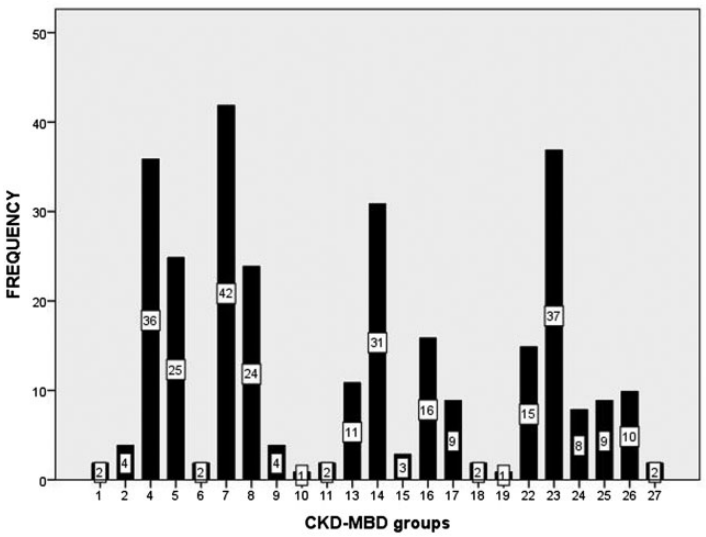

Figure 2. Distribution of CKD–MBD phenotypes.

used to construct scatter plots of serum P, serum Ca, Ca×P products, and iPTH levels compared with KDTA scores, and SF-36 scores were plotted for curve estimation. Inverse "U" type correlations were observed between serum P levels, Ca×P products, and KDTA and SF-36 scores ($P < 0.05$). There was still statistical significance after correction of P binders, calcitriol, and calcimimetics. No significant correlations were observed between serum Ca levels, iPTH levels, and quality of life scores (Figures 3, 4, 5, and 6).

The one-way ANOVA was performed for demographic information, clinical characteristics, and laboratory examinations for groups that were stratified based on CKD–MBD phenotype. The results revealed that age, spKt/V_{BUN}, dialysis duration, ALB levels, Scr levels, BUN levels, urinalysis (UA), calcimimetics, and blood flow demonstrated statistically significant differences. No significant differences were found in gender, marital status, residence, nature of work, education, income level, lipid level, and ultrafiltration. A multivariate linear

Table 3. Main parameters and quality of life scores of each group of CKD–MBD phenotypes included in the analysis.

Group	n	P (mmol/L)	Ca (mmol/L)	Ca×P (mg^2/dL^2)	iPTH (pg/mL)	Scr (μmol/L)	KDTA score	SF-36 score
4	36	2.29 ± 0.39	2.27 ± 0.11	64.48 ± 1.85	943.46 ± 701.36	1119.54 ± 275.33*	64.76 ± 12.34	56.68 ± 12.34
5	25	1.55 ± 0.16	2.25 ± 0.08	43.32 ± 0.98	735.57 ± 533.93	831.17 ± 239.70*	58.82 ± 8.00	54.72 ± 15.26
7	42	2.23 ± 0.38	1.88 ± 0.16	51.72 ± 1.30	559.88 ± 332.64	1090.43 ± 307.28#	61.50 ± 8.94	55.52 ± 14.25
8	24	1.55 ± 0.18	1.91 ± 0.12	36.79 ± 0.83	637.94 ± 485.08	946.89 ± 237.34#	59.11 ± 12.28	50.63 ± 16.53
13	11	2.21 ± 0.38	2.21 ± 0.08	60.83 ± 3.33	245.48 ± 36.58	932.92 ± 228.63&	58.55 ± 8.99	50.64 ± 14.20
14	31	1.47 ± 0.17	2.24 ± 0.10	40.87 ± 0.85	224.78 ± 41.89	718.10 ± 255.56&	59.36 ± 11.35	45.94 ± 14.40
16	16	2.34 ± 0.66	1.85 ± 0.20	53.26 ± 3.80	252.48 ± 42.76	1115.95 ± 275.57	65.89 ± 11.51	57.57 ± 16.88
22	15	2.34 ± 0.37	2.29 ± 0.12	63.55 ± 3.04	112.37 ± 70.46	865.29 ± 287.25Δ	65.73 ± 9.17	53.97 ± 16.23
23	37	1.46 ± 0.18	2.29 ± 0.10	41.30 ± 0.77	94.92 ± 35.26	624.01 ± 249.79Δ	61.49 ± 11.10	51.06 ± 20.55
26	10	1.52 ± 0.14	1.99 ± 0.11	37.48 ± 1.00	132.96 ± 67.69	629.16 ± 164.70	60.12 ± 12.11	42.04 ± 16.22

*$P < 0.001$; #$P = 0.04$; &$P = 0.02$; Δ$P = 0.004$.

P, phosphorus; Ca, calcium; iPTH, intact parathyroid hormone; KDTA, kidney disease and dialysis-related quality of life; Scr, serum creatinine.

Table 4. Results of the linear regression analysis of KDTA scores from CKD–MBD phenotype groups.

Coefficient[a]					
	Unstandardized coefficient		Standardized coefficient		
Model	B	Standard error	Beta	t	Significance
1					
(Constant)	59.359	1.927		30.802	<0.001
Group 16	6.534	3.303	0.149	1.978	0.049
2					
(Constant)	66.478	3.522		18.876	<0.001
Group 16	6.506	3.252	0.149	2.001	0.047
Age	−0.134	0.051	−0.177	−2.634	0.009
Primary disease	0.068	0.471	0.009	0.145	0.885
Phosphorus binder	−0.896	1.517	−0.039	−0.590	0.555
Calcitriol	−3.604	1.468	−0.158	−2.455	0.015
Calcimimetics	0.509	1.782	0.020	0.286	0.775

[a]Dependent variable: total KDTA score; models in which the total KDTA score was a dependent variable used group 14 as the control.

KDTA, kidney disease and dialysis-related quality of life.

regression analysis was performed for indicators with significant differences, and the SF-36 score showed a negative correlation with age, but a positive correlation with Scr levels, blood flow, and ALB levels. The KDTA score was positively correlated with blood flow (Table 6). P binders, calcitriols, and calcimimetics showed no correlation with SF-36 and KDAT scores.

Statistical analysis of serum ALB level and serum P concentration in the included patients revealed a linear correlation between the two parameters ($P < 0.05$; Table 7).

Table 5. Results of linear regression analysis of SF-36 scores of CKD–MBD phenotype groups.

Coefficient[a]					
	Unstandardized coefficient		Standardized coefficient		
Model	B	Standard error	Beta	t	Significance
1					
(Constant)	45.941	2.990		15.364	<0.001
Group 16	11.626	5.125	0.170	2.268	0.024
2					
(Constant)	60.544	5.360		11.296	<0.001
Group 16	11.632	5.004	0.171	2.325	0.021
Age	−0.288	0.079	−0.243	−3.669	<0.001
Primary disease	1.127	0.725	0.100	1.555	0.121
Phosphorus binder	−1.327	2.335	−0.037	−0.568	0.570
Calcitriol	0.977	2.596	0.027	0.433	0.666
Calcimimetics	2.519	2.743	0.062	0.918	0.359

[a]Dependent variable: total SF-36 score; models in which the total SF-36 score was the dependent variable SF-36 used group 14 as the control.
CKD–MBD, chronic kidney disease–mineral and bone disorder; KDTA, kidney disease and dialysis-related quality of life.

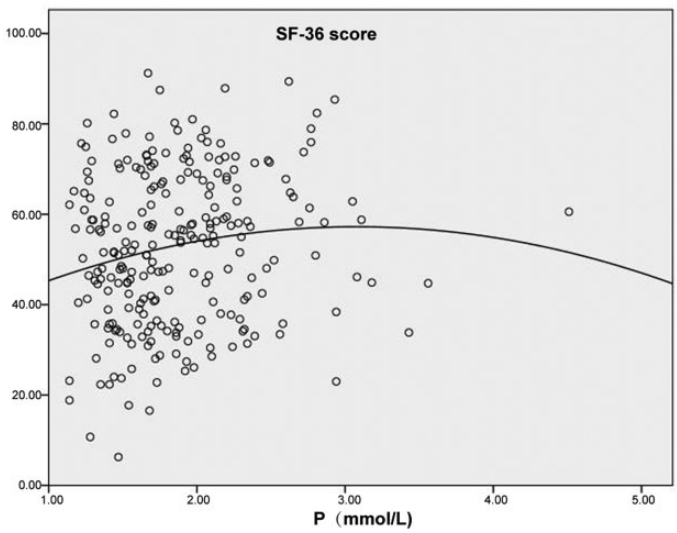

Figure 3. Correlation between serum phosphorus levels and SF-36 scores.

Discussion

For the 296 included patients, the total KDTA score was 57.07 ± 10.40, and the total SF-36 score was 51.45 ± 17.62, and these were consistent with those results of a recent study by Homaierad.[13] The low HRQoL scores in CKD patients were

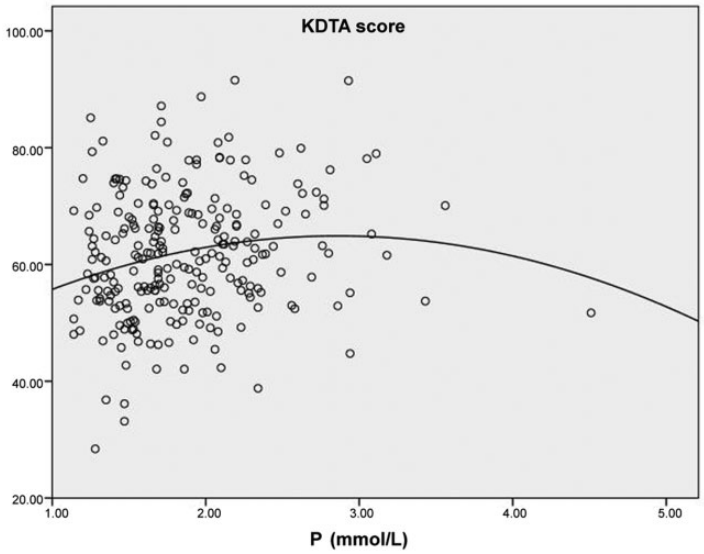

Figure 4. Correlation between serum phosphorus levels and KDTA scores.

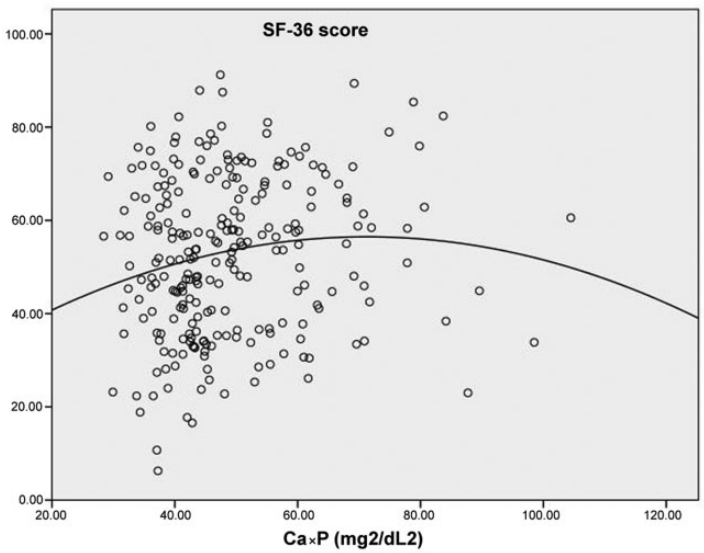

Figure 5. Correlation between the levels of calcium–phosphorus product and SF-36 scores.

considered to be an independent risk factor for cardiovascular events and death.[14] The HRQoL score can predict the prognosis of patients with ESRD, and patients receiving hemodialysis with high physiology scores have a low risk of all-cause mortality.[15] Analysis of factors affecting the HRQoL score has important clinical value. Many studies have examined the individual effects of serum iPTH, Ca, and P levels on

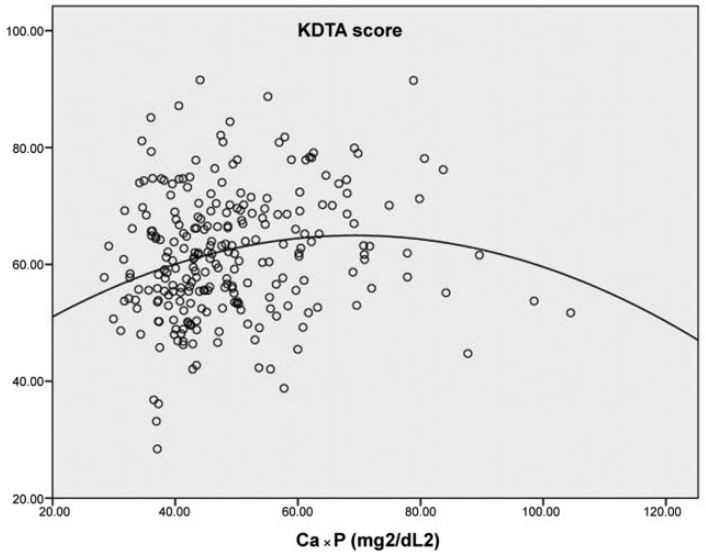

Figure 6. Correlation between calcium–phosphorus product and KDTA scores.

Table 6. Results of multivariate linear regression analysis of SF-36 and KDTA scores.

Item	Unstandardized coefficient	Constant	F value	*P*
SF-36				
Blood flow	0.124	7.524	10.21	0.04
KDTA				
Age	−0.177	7.524	10.21	0.023
ALB	0.501	7.524		0.032
Scr	0.007	7.524		0.043
Blood flow	0.133	30.447		<0.01

KDTA, kidney disease and dialysis-related quality of life; ALB, albumin; Scr, serum creatinine.

Table 7. Analysis of linear correlation between plasma albumin and blood phosphorus.

Coefficient[a]					
	Unstandardized coefficient		Standardized coefficient		
Model	B	Standard error	Beta	t	Significance
1					
(Constant)	36.435	1.167		31.212	<0.001
P (mmol/L)	1.668	0.607	0.176	2.750	0.006

[a]Dependent variable: Alb (g/L).
P, phosphorus.

HRQoL, but only a few studies have investigated the effect of different CKD–MBD phenotypes on HRQoL.

In this study, the effect of CKD–MBD phenotypes on HRQoL was examined. The iPTH, serum Ca, and serum P levels were classified and combined to form 27 phenotypes. Several groups were not observed in the patients, which may be related to the treatment mode and the patients' condition. Because of medical insurance payments, some patients could only receive two MHD treatments per week, and most patients were not able to receive regular hemodiafiltration HDF or hemoperfusion (HP) treatments. Typically, not enough P is removed. In addition, because of the lack of full-time nutrition guidance, P control in the diet is not sufficient, and there are more patients with high blood P and fewer patients with hypophosphatemia. This may be the main reason Groups 3, 12, and 21 were not observed in the patients and Group 20 was not included because of the small number of patients. The CKD–MBD phenotypes that were represented by more than ten enrolled patients were compared and then analyzed. The group with iPTH levels of 150 to 300 pg/mL, serum Ca levels of <2.10 mmol/L, and serum P levels of >1.78 mmol/L (e.g. group 16) showed the highest score. Compared with the control group, both the KDTA and SF-36 scores in group 14 showed significant differences, and these differences persisted after adjusting for age, primary disease, and prescribed medications (Tables 4 and 5).

Cross-sectional studies of the predialysis population revealed an association between MBD and HRQoL, and patients with MBD had even lower scores of GH, BKD, PF, and WS.[16] Cross-sectional studies of the hemodialysis population showed that serum P levels <1.13 mmol/L or >1.78 mmol/L and the use of phosphate-lowering drugs showed an association with even lower HRQoL compared with patients with normal serum P level.[7,8] Another case-control study divided patients undergoing hemodialysis into groups with iPTH levels >300 pg/mL and <300 pg/mL, and the results revealed that patients in the iPTH >300 pg/mL group had lower HRQoL scores.[9] The conclusions of these studies regarding the correlation between iPTH levels and HRQoL were consistent with those of the present study. Moreover, no significant effect of serum Ca levels on HRQoL was observed. However, conclusions about the effect of serum P levels on HRQoL in the previous studies differed from those of the present study, but there were only a few studies that investigated this issue. Randomized controlled trials (RCTs) that investigated the effect of serum P levels on all-cause mortality and cardiovascular mortality in patients undergoing hemodialysis demonstrated a "U"-type relationship between serum P levels and the risk of death because excessively low and high serum P levels increased the risk of death. However, the range of serum P levels with a low risk of death showed inconsistent results among different studies. One study showed that the serum P level <0.71 mmol/L or >1.98 mmol/L significantly increased the risk of death, while another study found that a serum P level >2.25 mmol/L significantly increased this risk.[5,6] Thus, the appropriate serum P level should be confirmed in further studies.

The studies described above did not examine the correlations among serum iPTH, serum Ca, and serum P levels. In 2016, Block et al.[17] used the data from 26,211 patients who receiving MHD from DaVita, Inc. and were included in the US Renal Data System (USRDS). Patients were divided into four groups based the following iPTH levels: <150 pg/mL, 150 to 300 pg/mL, 300 to 600 pg/mL, or >600 pg/mL; into three groups based on the following serum Ca levels: <2.10 mmol/L, 2.10 to 2.55 mmol/L, or >2.55 mmol/L; and into three groups

based on the following serum P levels: <1.13 mmol/L, 1.13 to 1.78 mmol/L, or >1.78 mmol/L. These three parameters were combined to generate 36 CKD–MBD phenotypes, which in turn were used to observe the effects of different CKD–MBD phenotypes on all-cause mortality and cardiovascular hospitalization or mortality rates. The CKD–MBD phenotype with an iPTH level of 150 to 300 pg/mL, serum Ca level of 2.10 to 2.55 mmol/L, and serum P level of 1.13 to 1.78 mmol/L reached the target control range in the guidelines, and the lowest all-cause mortality, cardiovascular hospitalization, and mortality rates were observed in this group. Among all phenotypes, the CKD–MBD phenotype with an iPTH level of 150 to 300 pg/mL, serum Ca level of <2.10 mmol/L, and serum P level of >1.78 mmol/L was the only type with all-cause mortality and cardiovascular hospitalization or mortality rates that were lower compared with the phenotype in which all three indicators were in the standard range. These results are similar to those reported in the present study.

Hyperphosphatemia showed a strong correlation with mortality in patients who were undergoing MHD. Different studies suggested different targets for serum phosphate control.[18–20] Two large-scale RCTs have been conducted on this topic. Floege et al.[5] collected data from 7970 patients who were undergoing MHD at the Fresenius Hemodialysis Center in Europe. The results showed the correlations among iPTH, serum Ca, and serum P levels with the relative risk of mortality, which revealed that the baseline serum P levels increased the risk of mortality, except for the group with levels of 1.13 to 1.78 mmol/L. The correlation between serum P levels and the risk of mortality was analyzed over time. The risk of mortality showed a significant increase when the serum P level was >2.25 mmol/L. Fouque et al.[6] studied the correlations between iPTH, serum Ca, and serum P levels with the relative risk of mortality among 8377 patients undergoing MHD, and a significantly increased risk of mortality was observed among patients with a serum P level <0.71 mmol/L or >1.98 mmol/L. Based on the pathophysiology, an increase in serum P levels in patients with CKD within a certain range is shown to be a compensatory mechanism for disease.[10] When the disease progresses to decompensation, the increase in serum P levels exceeds a certain threshold before affecting the patient prognosis. Moreover, this threshold may vary in patients with different iPHT and serum Ca levels. The 2017 update of the Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD guidelines also recommended the initiation of phosphate-lowering therapy in patients with severe and persistent elevation of serum P concentrations.[21] Plasma ALB levels in the high-score group were also higher compared with the low-score group, which suggested that the plasma ALB level showed a positive correlation with SF-36 score (Table 6). The plasma ALB level is considered to be a strong linear prognostic factor for nutritional status and the survival rate of patients undergoing MHD,[22,23] and the serum P level is also considered to be a marker of malnutrition.[24] Statistical analysis of serum P and plasma ALB levels in the included patients revealed a positive correlation (Table 7). In addition, serum creatinine levels were higher in the group with higher serum P. The K/DOQI Nutrition Clinical Practice Guidelines also indicate that serum creatinine levels are too low and nutritional status needs to be assessed.[25] Thus, a better nutritional status might be an explanation for high HRQoL in the high serum P group.

The present study showed that the serum Ca level in the group 16 phenotype with a high score was lower compared with that of the group 14 phenotype, and the three

parameters met the target. With the issuance of the KDIGO CKD–MBD guidelines in 2009, new epidemiological evidence suggested that the high serum calcium level increases the mortality rate in patients with CKD.[6,26] With the introduction of calcimimetics, the incidence of hypocalcemia has increased, but the mild degree of hypocalcemia does not increase the mortality rate.[27,28] Floege et al.[5] showed that mild hypocalcemia did not increase the risk of death. In the present study, statistical analysis of patients with serum Ca levels that were below the target range showed that the mean serum calcium level was 1.90 ± 0.16 mmol/L, which was significantly higher compared with the cut-off value of <1.59 mmol/L for a significantly increased risk of death that was reported by Fouque et al.[6] Therefore, mild hypocalcemia showed no reduction in the quality of life scores.

The Ca×P product showed a consistent association with vascular and soft tissue calcification in patients undergoing MHD.[29,30] When the Ca×P product was approximately $50\,mg^2/dL^2$, the risk of organ calcification remained low.[31] As shown by Block et al.,[32] the risk of death remained low when the concentration of the Ca×P product was 42 to $52\,mg^2/dL^2$. The K/DOQI guidelines also indicated that the Ca×P product should be maintained at levels less than 55 mg^2/dL^2.[12] The Ca×P product and quality of life score showed an inverse "U"-shaped correlation in our study (Figures 5 and 6). Thus, the quality of life was decreased when the concentration of the Ca×P product was too high or too low. When 50 to $55\,mg^2/dL^2$ was used as the target range for the Ca×P product, the CKD–MBD phenotype was 150 to 300 pg/mL for iPTH, <2.10 mmol/L for serum Ca, and >1.78 mmol/L for serum P; group 16 was closest to this range (Figure 7). Based on these results, mild hyperphosphatemia and hypocalcemia are associated with high quality of life scores if the Ca×P product meets the target, and a possible explanation for this is that there is a low risk of developing tissue and organ calcification.

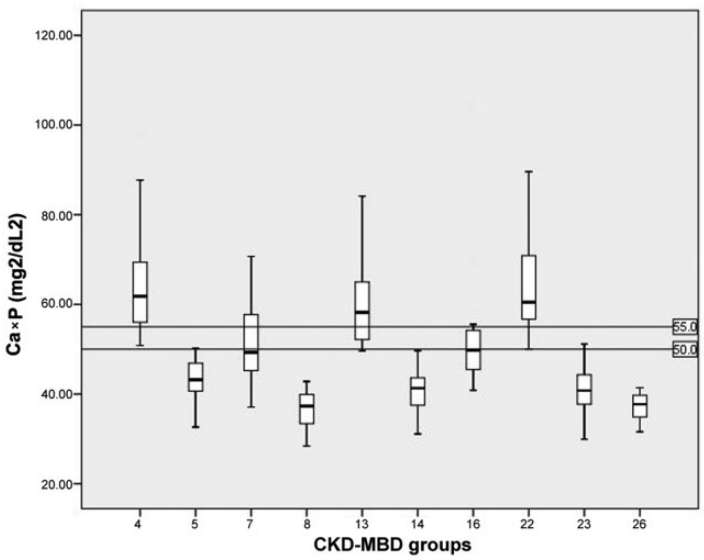

Figure 7. Distribution of the levels of calcium–phosphorus product in various CKD–MBD phenotypes.

This study also has some limitations. Because this is a single-center, cross-sectional study, some bias might exist in the baseline data, which showed no effects of CKD–MBD-related parameters on HRQoL over time. The laboratory data included in this study should be obtained less than 3 months before the investigation to reduce the impact of these limitations on the results. The investigators were uniformly trained to reduce the bias associated with collecting the baseline data. Moreover, only phenotype groups with more than ten patients were included in this study, which improved the reliability of our results. In the future, the effects of different CKD–MBD phenotypes on HRQoL in patients who are undergoing hemodialysis over time, as well as the effects of CKD–MBD-related treatments on HRQoL will be investigated in large, multicenter studies.

Conclusion

This study suggests that different CKD–MBD phenotypes exerted significant effects on the patients' quality of life. When the recommended iPTH levels are attained, patients with mild low serum Ca and mild high serum P have better quality of life scores, which may be because these patients have better nutritional status and a lower risk of tissue and organ calcification. Comprehensive assessment of serum iPTH, Ca, and P levels is necessary to improve the quality of life of patients receiving hemodialysis. Active control of serum iPTH, Ca, and P levels during clinical treatment might improve the disease prognosis. Currently, relevant studies are rare, and the results of different studies varied significantly, especially regarding the close interactions of iPTH, Ca, and P levels. A study with a rigorous design and efficient organization and implementation strategies is needed to combine the three parameters to determine their effects on HRQoL in a large-sample, multicenter, and long-term observational study.

Acknowledgements

Not applicable

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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