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Interactive effects of vitamin D and serum uric acid concentration on protein-energy wasting in maintenance hemodialysis patients

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ABSTRACT

This study aimed to explore the influence of the interaction between vitamin D level and blood uric acid level on protein-energy wasting (PEW) in patients with Maintenance hemodialysis (MHD), in order to provide a solution for disease prevention. For this aim, a total of 150 patients with maintenance hemodialysis aged 30-79 years in a hospital were included in the study. The logistic regression model was used to analyze the relationship between vitamin D level, blood uric acid level and PEW, and the additive interaction was evaluated by calculating the relative excess risk ratio (RERI) attributive ratio (AP) and synergy index (S) of the interaction. Finally, the ROC curve was drawn to evaluate the diagnostic value of vitamin D level and blood uric acid level for PEW. In this study, the detection rate of PEW was 68%, low vitamin D level was 57.33%, and high blood uric acid level was 64.67%. Compared with non-low vitamin D levels, the PEW risk was OR=16.794, 95%CI: 4.973-60.356; Compared with those without high uric acid levels, the PEW risk was OR=7.599, 95%CI: 2.460-23.468. However, there was no multiplicative interaction between the two on PEW risk (OR=0.345, 95%CI: 0.060-1.983, P=0.233). In the additive interaction analysis, the PEW risk OR=43.992,95%CI: 12.795-151.253, higher than those with only high uric acid levels or only low vitamin D levels, the combination of the two had a summative interaction with PEW risk, with a RERI of 20.599 (95%CI: -26.158-67.356) API was 0.468 (-0.159-1.095) and S was 1.920 (0.569-6.483). In conclusion, both vitamin D deficiency and high uric acid levels were associated with an increased risk of PEW in MHD patients, and low vitamin D and high uric acid levels had a summative interaction with protein-energy expenditure risk.

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Introduction

Maintenance hemodialysis (MHD) is the most common clinical method for end-stage renal disease. Due to chronic kidney disease, most MHD patients may have malnutrition in the early stage. The patients show obvious anorexia, fatigue, emaciation, and decreased physical strength, which seriously affect the quality of life of MHD patients. Once entering the dialysis stage, the catabolism of the patients is enhanced, the lean tissue is consumed in large quantities, and the protein synthesis is decreased, further aggravating the degree of malnutrition (1). In recent years, studies have shown that malnutrition in MHD patients (2) is not only related to insufficient protein-energy intake but also related to systemic inflammatory reaction, uremic toxins and other factors. In order to distinguish the concept of malnutrition caused by insufficient intake alone, and to detect and intervene in nutritional problems in dialysis patients earlier (3), Experts of the International Society of Nutrition and Metabolism of Kidney Disease have reached a consensus (4), naming the "malnutrition" state of reduced organic protein energy reserve and metabolic abnormalities in chronic kidney disease as protein-energy wasting (PEW), Studies (5) suggest that end-stage renal disease, The prevalence of PEW in ESRD patients with MHD is as high as 75%. The patients usually have significant emaciation, weakness and fatigue, poor living ability, susceptibility to co-infection or cardiovascular disease, decreased quality of life, increased mortality and other risk comorbidities. Therefore, it is particularly important to conduct in-depth research on the influencing factors of PEW in MHD patients. High blood uric acid levels and vitamin D deficiency are more common in MHD patients (6) and are risk factors for progression to end-stage renal disease in MHD patients. Both high blood uric acid and vitamin D deficiency are associated with PEW's risk of disease (7,8), so the two may interact with PEW's disease. At present, few studies have explored their interaction. This study investigated the interaction of vitamin D and uric acid levels on protein-energy expenditure in maintenance hemodialysis patients.

Materials and Methods

Research object

A total of 150 MHD patients admitted to a hospital from January 2021 to July 2022 were selected as research objects. General clinical data of patients were collected by questionnaire survey combined with laboratory testing.

Inclusion criteria

(I) Diagnosis of kidney disease according to Clinical Practice Guidelines for Chronic Kidney Disease and Dialysis II (9); (II) Dialysis age over 3 months, hemodialysis

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2-3 times a week, each lasting 4h; (III) Age ≥ 18 years old, ≤ 79 years old; (IV) This study was approved by the Medical Ethics Committee of our hospital. All patients were aware of the purpose of this study and actively signed informed consent;

Exclusion criteria

(I) malignant tumor, surgical trauma; (II) other serious organ diseases affecting blood uric acid level; (III) serious cardiovascular and cerebrovascular accidents occurred in the last three months; (IV) History of taking drugs that affect uric acid metabolism and uric acid lowering drugs in the past six months.

Data collection

(I) Clinical data were collected and investigated during admission, including age, income level, dialysis age, body mass index (BMI), middle upper arm muscle circumference (MAMC), triceps skin fold thickness (TSF), and grip strength (HGS). (II) Serum albumin, human cell mass, urea nitrogen, potassium, sodium, magnesium, blood calcium, serum 25 hydroxyvitamin D[25(OH)D], and blood uric acid level (SUA) of the patients were tested by blood, and serum 25(OH)D was measured by electrochemiluminescence (10). (III) The PEW incidence rate of patients was evaluated according to the PEW criteria (11): ① serum albumin < < 38g/L, total cholesterol < 2.59mmol/L, proalbumin < 300 mg/L; ② Standardized protein metabolic rate < 0.8g/kg·d); (IV) BMI< 22 kg/m2; (V) Muscle mass and muscle circumference of middle upper arm were decreased in 3 months > 5% or 6 months' reduction > 10%: At least 3 of these conditions can be met to confirm the diagnosis of PEW. Patients were divided into the non-Pew group and the PEW group.

Observation index

(I) Vitamin D evaluation criteria Vitamin D deficiency and deficiency: < 30ng/ml; (II) High uric acid level: fasting uric acid level was higher than 420μmol/L in males and 360μmol/L in females twice on different days, which was called hyperuricemia; (III) BMI= weight (Kg)/height (m^2); (IV) The basic and clinical data of the two groups were compared; (V) The body composition levels of the two groups were compared; (VI) Correlation analysis was conducted to discuss the effects of vitamin D level, blood uric acid level and protein-energy consumption.

Statistical analyses

Using SPSS 23.0 software analysis, normal distribution of measurement data using ($\bar{x}\pm s$) said, using independent sample t-test, rank and inspection compared between groups. Statistical data were expressed as (%), and the chi-square test was used for comparison between groups. Binary Logistic regression was used to analyze the interaction between vitamin D level and blood uric acid level on PEW in maintenance hemodialysis patients. Calculate the attributable proportion of interaction (API), relative excess risk of interaction, RERI), and the Synergy index (S). Take P< 0.05 was considered statistically significant. ROC curve was drawn to evaluate the diagnostic value of vitamin D level and blood uric acid level for PEW.

Results

Univariate analysis of protein-energy consumption in maintenance hemodialysis patients

A total of 150 maintenance hemodialysis patients were investigated, including 102 patients in PEW, with a prevalence rate of 68.00% in the PEW group. 48 patients did not have PEW, with no prevalence rate of 32.00%, including the non-Pew group. The mean age of the non-Pew group was (54.83±16.55) years old, with 28 males (58.33%) and 20 females (41.67%). The mean age of the PEW group was (51.23±17.94) years old, with 50 males (49.02%) and 52 females (50.98%). Non-pew patients and PEW patients had statistical differences in BMI, MAMC, albumin, human cell mass, grip strength, urea nitrogen, high blood uric acid levels, and low vitamin D levels (P< 0.001) (Tables 1 and 2).

Table 1. Basic data differences between non-PEW group and PEW group

Variate		Non-PEW group (n=48)	PEW group (n=102)	x^2\t-value\Z-value	P-value
Gender	Male	28(58.33)	50(49.02)	1.127	0.288
	Female	20(41.67)	52(50.98)		
Age		54.83 ± 16.55	51.23 ≤ 17.94	1.174	0.242
Duration of dialysis	≤ 6 months	23(47.92)	53(51.96)		
	6 to 10 months	21(43.75)	26(25.49)	0.085	0.771
	＜10 months	4(10.93)	23(22.55)		
Income level	＜3500 yuan	21(43.75)	59(57.84)		
	3500 yuan~7000 yuan	23(47.92)	37(36.27)	2.536	0.111
	＜7000 yuan	4(10.93)	6(5.88)		
BMI	＜18.4	2(4.16)	23(22.55)		
	＜18.5~23.9	14(29.17)	73(71.57)		
	＜23.9~26.9	17(35.42)	4(3.92)	63.191	＜0.001
	＜26.9~35	15(31.25)	2(1.96)		
MAMC(cm)		24.5＜21	20.3＜2.1	12.322	＜0.001
TSF(mm)		19.31 ± 4.32	18.67 ± 4.53	1.102	0.272
Grip strength (kg)		35.3 ± 6.8	30.8 ± 9.6	2.878	0.005

Table 2. Biochemical differences between non-PEW and PEW groups.

Variate		Non-PEW group (n=48)	PEW group (n=102)	x^2\t-value\Z-value	*P*-value
Grip strength (g/L)		37.3 ± 2.9	28.4 ± 4.3	12.057	± 0.001
Human cell mass (kg)		23.6 ± 2.4	20.2 < 3.4	5.691	< 0.001
Urea nitrogen (mmol/L)		25.29 ± 4.60	20.27 ± 4.93	5.852	± 0.001
Hemoglobin (g/L)		112.30 17.20	108.01 17.17	1.651	0.101
Potassium (mmol/L)		4.82 ± 0.73	4.80 ± 0.52	0.433	0.666
Sodium (mmol/L)		2.27 ± 0.19	2.21 ± 0.17	2.229	0.027
Magnesium (mmol/L)		1.01 ± 0.14	0.94 ± 0.13	0.735	0.002
Blood calcium (mmol/L)		2.27 ± 0.19	2.19 ± 0.17	-0.321	0.707
Hyperuric acid	No	28(58.33)	26(25.49)	-7.142	< 0.001
	Yes	20(41.67)	76(75.51)		
Vitamin D deficiency	No	28(58.33)	28(27.45)	-5.187	< 0.001
	Yes	20(41.67)	74(72.55)		

Comparison of vitamin D levels and blood uric acid levels between the two groups

In the non-Pew group, there were 20 patients with high uric acid levels and 28 patients without high uric acid levels. In the PEW group, 76 cases showed high uric acid levels, while 26 cases did not, as shown in Figure 1. The number of patients with high uric acid levels in the non-Pew group was less than that of patients without high uric acid levels (58.33% vs. 41.67%). The number of patients with high uric acid levels in the PEW group was much higher than that of patients without high uric acid levels (75.51% vs. 25.49%).

In the non-Pew group, there were 20 patients with low vitamin D levels and 28 patients without low vitamin D levels. In the PEW group, 74 patients had low vitamin D levels and 28 patients had no low vitamin D levels, as shown in Figure 2. The number of patients with low vitamin D levels in the non-Pew group was less than that of patients without low vitamin D levels (58.33% vs. 41.67%). The number of patients with low vitamin D levels in the PEW group was much higher than that of patients without low vitamin D levels (72.55% vs. 27.45%).

In MHD patients, the results of the two groups of clinical data can be preliminarily concluded that PEW occurrence is correlated with blood uric acid level and vitamin D level, and the P value between the two groups. 0.01; It is necessary to further analyze whether there is multiplication and addition interaction between the two levels.

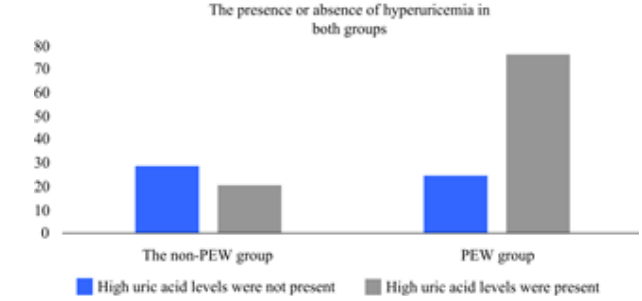

Figure 1. The presence or absence of high uric acid levels in both groups.

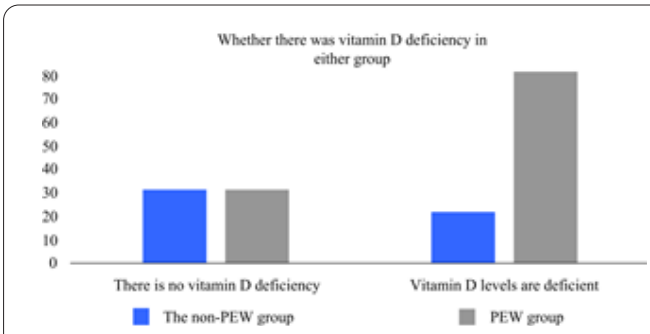

Figure 2. The presence or absence of vitamin D deficiency in both groups.

Interaction between vitamin D levels and blood uric acid levels

With PEW as the dependent variable and low vitamin D level and high blood uric acid level as independent variables, binary Logistic regression analysis was conducted, and the analysis results are shown in Table 3. The results of the regression model suggested that patients with low vitamin D levels and high blood uric acid levels had a higher risk of PEW than those with normal vitamin D levels and normal uric acid levels, with OR values of 16.800 (95%CI: 4.673-60.395) and 7.600 (95%CI: 2.460-23.479). There was no multiplicative interaction between low vitamin D levels and high blood uric acid levels OR=0.345 (95%CI: 0.060-1.983).

Additive interaction analysis of risk factors for protein-energy expenditure in maintenance hemodialysis patients

The control group had no low vitamin D levels and high uric acid levels. The results showed that when

Table 3. Multiplicative interaction between vitamin D level and serum uric acid level.

Variate	*β*-value	S	Wald x^2-value	P-value	OR(95%CI)value
Low vitamin D levels	2.821	0.653	18.678	0.000	16.800(4.673-60.395)
High blood uric acid level	2.028	0.576	12.420	0.000	7.600(2.460-23.479)
Low vitamin D level and high blood uric acid level	-1.065	0.893	1.424	0.233	0.345(0.060-1.983)

Table 4. Additive interaction analysis of risk factors for PEW in MHD patients.

Low vitamin D levels	High blood uric acid level	Non-PEW group (n=48)	PEW group (n=102)	OR(95%CI)
no	no	28(58.33)	7(6.86)	1.00
no	yes	5(10.42)	21(20.59)	16.794(4.973-60.356)
yes	no	10(20.83)	19(18.63)	7.599(2.460-23.468)
yes	yes	5(10.42)	55(53.92)	43.992(12.795-151.253)

Table 5. Additive interaction between vitamin D level and high serum uric acid level.

Index	Estimated value	(95%CI) Value
RERI	20.599	-26.158-67.356
API	0.468	-0.159-1.095
S	1.920	0.569-6.483

Table 6. Diagnostic value of high serum uric acid level versus low vitamin D level for PEW in MHD patients.

Element	AUC	Sensitivity	Specificity	95%CI	P value
High blood uric acid level	0.768	0.745	0.208	0.686-0.851	< 0.001
Low vitamin D levels	0.706	0.725	0.313	0.615-0.798	< 0.001

low vitamin D levels were present alone, the PEW risk OR=16.794, 95%CI:4.973-60.356; When high blood uric acid levels were present alone, the PEW risk OR=7.599, 95%CI:2.460-23.468; When both are present, the PEW risk for patients with this type of MHD OR=43.992, 95%CI:12.795-151.253 (Table 4).

Quantitative analysis of additive interaction

The results showed an additive interaction between low vitamin D levels and high blood uric acid levels in MHD patients with PEW. The RERI was 20.599 (95%CI: -26.158-67.356), the API was 0.468 (-0.159-1.095), and the S was 1.920 (0.569-6.483). See Table 5 for details.

Predictive value of ROC curve

The diagnostic value of ROC curve showed that the AUC of high blood uric acid level was 0.768 (95%CI: 0.686-0.85), P&lt. 0.001, the sensitivity was 76.80%, the specificity was 20.80%; The AUC of low vitamin D level under ROC curve was 0.706 (95%CI: 0.615-0.798), P< 0.001, sensitivity was 72.25%, specificity was 31.30% (Table 6, Figure 3).

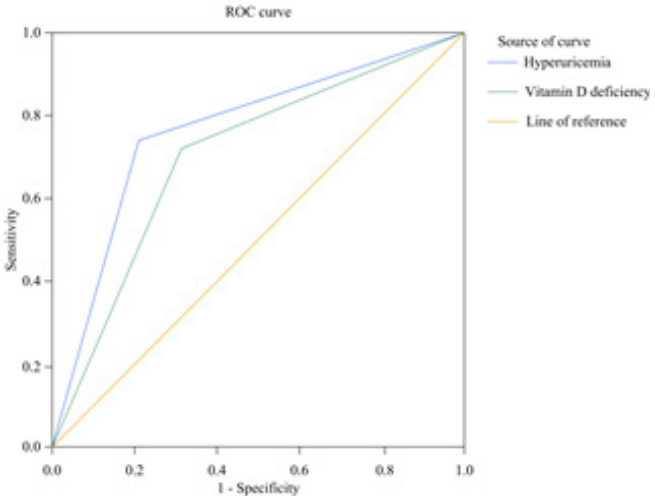

Figure 3. ROC curves of low vitamin D levels and high serum uric acid levels for the diagnosis of PEW in MHD patients

Discussion

Protein-energy expenditure (PEW) is one of the most common complications in patients with MHD, and its impact on patients' quality of life and prognosis is increasingly significant as the disease progresses. In recent years, the number of PEW studies has been increasing, and this phenomenon has been paid more and more attention by academic and clinical research (12,13). PEW's reasons involve a variety of aspects, such as insufficient nutritional intake, dialysis-related factors and other factors, which influence each other and synergistically increase the risk of patients with diseases (14). In addition, PEW can also cause problems such as hypocalcemia and hyperphosphatemia, which is also a cause of a range of symptoms in patients and is more common in MHD patients. 25(OH) D is an important indicator reflecting the body's vitamin D level. Therefore, the detection of 25(OH)D can help us better understand whether the vitamin D level in patients is normal, and further explore the relationship between vitamin D level and PEW (15). Studies have shown that vitamin D plays a role in immune regulation, inflammation mediating and insulin resistance in the body (16). The microinflammatory state is one of the important causes of PEW. Long-term dialysis results in a large loss of protein and other nutrients in the body, and the inflammatory response also induces a large decomposition of protein in the body, and at the same time, the patient's appetite is decreased and protein intake is insufficient. Vitamin D directly affects the inflammatory state in the body and indirectly leads to PEW (17-19).

Insulin resistance is one of the main mechanisms leading to protein energy consumption, which will lead to the degradation of muscle protein and affect the wasting of skeletal muscle (20), thus leading to the appearance of PEW symptoms in the body. Multiple studies (21-24) have reported a close relationship between hyperuricemia and insulin resistance. Hyperuricemia will directly cause insulin resistance. It will cause a large amount of uric acid concentration to accumulate in the body through renal tubule cells, thus affecting the insulin function of the pa-

tient's body and resulting in insulin resistance (25). Insulin resistance is also the mechanism of PEW, and high blood uric acid level indirectly leads to PEW in MHD patients. In this study, with normal vitamin D levels and normal uric acid levels as the reference group, MHD patients with low vitamin D levels and high blood uric acid levels had a PEW risk of 43.992, and the RERI of their interaction was 20.599 (95%CI: -26.158-67.356) API is 0.468 (-0.159-1.095) S is 1.920 (0.569-6.483), indicating that there is additive interaction and synergistic effect between the two. ROC curve analysis showed that low vitamin D levels and high blood uric acid levels were of diagnostic value to PEW's risk of disease.

In summary, the results of this study found that low vitamin D levels and high blood uric acid levels have a synergistic effect on the PEW risk of MHD patients. Vitamin D supplements should be taken during the treatment of MHD patients. Patients should exercise more in daily life to make the body sweat so that uric acid and other garbage in the body can be excreted as soon as possible with sweat and urine. Strictly limit foods high in purines. The innovation of this study is that there are few previous studies on the PEW correlation between vitamin D level and blood uric acid level in MHD patients, and the limitation is that only 150 MHD patients in our hospital are targeted, with a small sample size.

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