THE TCM SYNDROMES OF PATIENTS WITH CKD-MBD IN STAGE 5D AND THEIR RELATIONSHIP WITH KLOTHO AND FGF23 LEVELS

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ABSTRACT

Objective*: To analyze Traditional Chinese Medicine (TCM) syndromes in dialysis patients with Chronic Kidney Disease-Mineral and Bone Disorder in stage 5 (CKD-MBD stage 5D) and their relationship with FGF23 levels and Klotho protein.*

Methods: *A total of 154 patients eligible for inclusion were collected, and a survey was conducted to observe laboratory indexes, including FGF23, Klotho, calcium, and phosphorus, as well as to analyze the characteristics of TCM syndrome types and their relationship with FGF23 and Klotho.*

Results: *(A) In this study, 154 patients with CKD-MBD stage 5D showed a higher percentage in symptoms of liver-and-kidney-yin-deficiency syndrome, spleen-and-kidney-qi-deficiency syndrome, spleen-and-kidney-yang deficiency and blood stasis. Furthermore, liver-and-kidney-yin-deficiency syndrome and blood stasis were the TCM syndrome types most commonly seen; (B) Compared with the healthy control group, the serum FGF23 level and FGF23/Klotho ratio of all patients significantly increased, while the Klotho level decreased (P<0.05); and (C) The level of serum FGF23 and FGF23/Klotho ratio of patients in the spleen-and-kidney-qi-deficiency group and the damp heat group was higher than that of other groups, while the Klotho level was lower than that of the other groups (P<0.05).*

Conclusion: *In patients with CKD-MBD stage 5D, syndromological syndromes that are most commonly seen include liver-and-kidney-yin-deficiency, spleen-and-kidney-qi-deficiency and spleen-and-kidney-yang-deficiency. Additionally, symptomatic syndrome is mostly manifested as blood stasis syndrome, while an increase in FGF23 and decrease in serum Klotho protein have a close connection with spleen-and-kidney-qi-deficiency and damp heat syndrome.*

Keywords: *Chronic kidney disease and mineral and bone disorder, TCM syndrome, fibroblast growth factor 23, Klotho.*

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Introduction

Mineral and bone disorder (MBD) is a common clinical complication in patients with chronic kidney disease (CKD)[1]. CKD-MBD will not only induce malnutrition, refractory anemia, cardiovascular disease and other complications, but also seriously affect the quality of life and prognosis of patients[2, 3]. Researches on CKD-MBD in TCM in recent years were mainly focused on the treatment of TCM. However, there was little research on TCM syndrome type, especially in dialysis patients with CKD-MBD stage 5 (CKD-MBD stage 5D), which prevents the involvement of TCM treatment and reduces the accuracy of TCM syndrome differentiation and medication. Studies have shown that fibroblast growth factor-23 (FGF23) and Klotho proteins are closely related to the occurrence and development of CKD-MBD. Currently, it is accepted that abnormal FGF23-Klotho axis is an important indicator to CKD-MBD, and the regulation of FGF23 and Klotho levels is of great significance for the prevention and treatment of CKD-MBD[4, 5]. Hence, this study collected the clinical data of patients with CKD-MBD stage 5D for TCM syndrome differentiation, examined the relationship between TCM syndrome type and FGF23 and Klotho protein level, and analyzed the distributive features of TCM syndrome types with a view to taking serum FGF23 and Klotho protein level as one indicator for TCM syndrome differentiation. This

was done to provide more accurate guidance for the clinical treatment of CKD-MBD patients with combined TCM and western medication.

Subjects and methods

Participants

Thus, 154 patients with maintenance hemodialysis in the blood purification center of Maigaoqiao, in the headquarters and southern branch of the Jiangsu Integrated Chinese and Western Medicine Hospital, were recruited from April 2016 to July 2018, including 88 men and 66 women (mean age: 58.9±13.8 years). In total, 138 patients suffered hypertension (89.61%), there were 71 cases of coronary heart disease (46.10%), 53 cases of diabetes mellitus (34.41%), 21 cases of cerebral infarction (13.63%), 60 cases of chronic glomerulonephritis (38.96%), 48 cases of diabetic nephropathy (31.17%), 17 cases of hypertensive nephropathy (11.04%), 4 cases of polycystic kidney (2.60%) and 25 others. Meanwhile, 42 healthy people in the physical examination center of the Jiangsu Provincial Integrated Chinese and Western Medicine Hospital from January 2018 to July 2018 were selected into the control group, in which 20 were male and 22 were female, with an average age of 55.8±14.2 years.

Criteria

Criteria for CKD diagnosis and staging

Routine renal replacement therapy had been performed on dialysis patients with CKD stage 5 with eGFR <15 mL/min/1.73m^2, according to the Clinical Practice Guidelines for the Evaluation and Management of Chronic Renal Disease, issued by the Global Prognosis Improvement Organization (Kidney Disease: Improving Global Outcomes, KDIGO) in 2012[6].

Criteria for CKD-MBD diagnosis

The 2012 Guidelines for the Diagnosis and Treatment of Mineral and Bone Abnormalities in Chronic Kidney Disease in China[7] covers the following manifestations:

• Abnormal metabolism in calcium, phosphorus, parathyroid hormone or vitamin D;

• Abnormal bone turnover, mineralization, bone mass, linear growth or bone strength;

• And calcification of blood vessels or other soft tissues, in which item A and C were the reference criteria for CKD-MBD diagnosis in this study.

Criteria for TCM Syndrome Diagnosis

TCM syndromes related to chronic renal failure were classified according to the 2002 edition of the Guiding Principles of Clinical Research on New Chinese Medicine[8]. The syndromological syndromes include spleen-and-kidney-qi-deficiency syndrome, spleen-and-kidney-yang-deficiency syndrome, liver-and-kidney-yin-deficiency syndrome, qi-and-yin-deficiency syndrome, and yin-and-yang-deficiency syndrome, while the symptomatic syndromes include dampness turbid, damp heat, edema, blood stasis, and stirring wind.

Inclusion criteria

Patients aged between 18 and 80 were included into the study when they met the diagnostic criteria of CKD-MBD stage 5D and had received maintenance hemodialysis 2-3 times per week for more than three months.

Exclusion criteria

Patients excluded from the study were the ones who were not in accordance with the diagnosis of CKD-MBD stage 5D or suffering from such serious systemic diseases as acute and chronic liver disease, malignant arrhythmia, hematopoietic dysfunction, malignant tumor, or suffering severe infection. Furthermore, those taking traditional Chinese medicine for tonifying kidney and supplementing essence, undergoing other clinical trials, suffering from a mental disorder or severe hearing impairment (unable to be well involved in survey), as well as aged <18 or >80 years, were also excluded.

Data collection

General data

A clinical questionnaire was designed to collect data from patients who met the inclusion criteria. Each patient was surveyed by two or more attending Chinese medical doctors, data including sex, age, dialysis vintage, complications and main causes of uremia, and symptoms, signs, tongue coating and pulse condition, were recorded for TCM syndrome differentiation.

TCM symptoms

TCM symptoms related to CKD stage 5D included fatigue, short breath, disinclination for speech, poor appetite and digestion, sore waist and knee, cold limbs, dry throat, dysphoria in chest-palm-sole, dizziness, headache, nausea, vomiting, heaviness in

limbs, dry mouth, bitter mouth, edema, pleural effusion, ascites, dark complexion, low back pain, hand and foot cramp, convulsive spasmolysis, abdominal distention, formless stool, dry stool, hydroadipsia, sticky mouth, cold pain in waist, more nocturia, yellow urine, scaly dry skin, and numbness.

Serum Klotho, FGF23 protein

A total of 5 ml fasting peripheral blood was collected from all subjects from 6:00 a.m. to 8:00 a.m., whose serum, after centrifugation at 4000 rpm, was isolated and then stored at -80oC. Serum FGF23 and Klotho protein were determined by ELISA (Batch number 201806, Shanghai Bangyi Biotech Co. Ltd.).

Analysis

The SPSS statistics package (SPSS V21.0, SPSS Inc., USA) was used for analysis. Counting data were expressed in frequency; measurement data were expressed in mean ± standard deviation, or in median. The counting data were compared between groups using an χ^2 test, while the metrological data were subjected to a T-test if in accordance with normal distribution (using variance homogeneity test in inter-group, and using Satterth-waite correction T-test in variance heterogeneity), and subjected to the Wilcoxon Rank Sum Test and GLM covariance if not with normal distribution. Lastly, $P<0.05$ indicated a statistically significant difference.

Results

Frequency of symptoms and distribution characteristics of TCM syndromes

Among the 154 patients, symptoms with an occurrence percentage of higher than 45% included dark complexion (87.01%), soft waist and knee (85.71%), yellow urine (80.52%), dizziness (77.92%), low back pain (63.64%), dry throat (62.34%), dry mouth (57.79%), dry stool (52.60%), fatigue (51.95%), abdominal distention (51.94%), scaly dry skin (51.30%), bitter mouth (49.35%) and limb numbness (48.05%) (see Table 1). TCM syndrome types include the syndromological syndrome and the symptomatic one. Syndromologically, liver-and-kidney-yin-deficiency showed the highest percentage (40.91%), followed by spleen-and-kidney-qi-deficiency syndrome (26.62%) and spleen-and-kidney-yang-deficiency syndrome (26.62%), yin-and-yang-deficiency syndrome (3.9%), and qi-and-yin-deficiency syndrome (1.95%). Symptomatically, blood stasis accounts for 42.21%, while damp heat, edema, and stirring wind takes up 29.22%, 15.58%, 10.38%, 2.6%, respectively (see Table 2). All of the 154 patients manifested both syndromological syndromes and symptomatic syndromes, with liver-and-kidney-yin-deficiency and blood stasis (19.48%) being the most common (see Table 3).

Symptom	Percentage	Symptom	Percentage	Symptom	Percentage
Fatigue	51.95	Dry mouth	57.79	Dry stool	52.60
Short breath and disinclination for speech	44.81	Bitter mouth	49.35	Hydroadipsia	43.51
Poor appetite and digestion	38.96	Edema	15.58	Sticky mouth	42.86
Cold limbs	20.78	Pleural effusion	7.79	Cold pain in waist	15.58
Dry throat	62.34	Ascites	6.49	Sore waist and knee	85.71
Dysphoria in chest-palm-sole	42.86	Dark complexion	87.01	More nocturia	6.49
Dizziness	77.92	Low back pain	63.64	Yellow urine	80.52
Headache	10.39	Hand and foot cramp	5.19	Scaly dry skin	51.30
Nausea	3.2	Convulsive spasmolysis	1.29	Limb numbness	48.05
Vomiting	0	Abdominal distention	51.94		
Heaviness in limbs	40.26	Formless stool	40.35		

Table 1: Frequency of TCM symptoms in patients with CKD-MBD stage 5D.

Syndromological syndrome	Number	Percentage	Symptomatic syndrome	Number	Percentage
Liver-and-kidney-yin-deficiency	63	40.91	Blood stasis	65	42.21
Spleen-and-kidney-qi-deficiency	41	26.62	Dampness turbid	45	29.22
Spleen-and-kidney-yang-deficiency	41	26.62	Damp heat	24	15.58
Qi-and-yin-deficiency	3	1.95	Edema	16	10.39
Yin-and-yang-deficiency	6	3.90	Stirring wind	4	2.60

Table 2: Characteristics of TCM syndrome types in patients with CKD-MBD stage 5D.

Group	Number (percentage)	Damp heat	Dampness turbid	Edema	Blood stasis	Stirring wind
Liver-and-kidney-yin-deficiency	63 (40.91)	14 (9.09)	15 (9.74)	0 (0.00)	30 (19.48)	4 (2.60)
Spleen-and-kidney-qi-deficiency	41 (26.62)	7 (4.55)	1d (8.44)	3 (1.95)	18 (11.69)	0 (0.00)
Spleen-and-kidney-yang-deficiency	41 (26.62)	2 (1.30)	12 (7.79)	13 (8.44)	14 (9.09)	0 (0.00)
Qi-and-yin-deficiency	3 (1.95)	0 (0.00)	2 (1.30)	0 (0.00)	1 (0.65)	0 (0.00)
Yin-and-yang-deficiency	6 (3.90)	1 (0.65)	3 (1.95)	0 (0.00)	2 (1.30)	0 (0.00)

Table 3: Characteristics of concurrent syndromes in patients with CKD-MBD stage 5D.

Age and TCM syndrome distribution

In this study, 154 patients were divided into groups of <45 years old, 45~60 years old, and >60 years old. Syndromologically, patients <45 had the most deficiency of spleen-and kidney-qi, while patients aged 45~60 years and >60 years had the most

common liver-and-kidney-yin-deficiency syndrome. Symptomatically, blood stasis was common in all three groups (see Table 4).

Syndrome	<45 y Number (percentage)	45~60 y Number (percentage)	>60 y Number (percentage)
Liver-and-kidney-yin-deficiency	7 (4.55)	27 (17.53)	29 (18.83)
Spleen-and-kidney-qi-deficiency	10 (6.49)	9 (5.84)	22 (14.29)
Spleen-and-kidney-yang-deficiency	9 (5.84)	11 (7.15)	21 (13.63)
Qi-and-yin-deficiency	1 (0.65)	0 (0.00)	2 (1.30)
Yin-and-yang-deficiency	3 (1.95)	1 (0.65)	2 (1.30)
Stirring wind	2 (1.30)	1 (0.65)	1 (0.65)
Damp heat	5 (3.25)	9 (5.84)	10 (6.49)
Dampness turbid	8 (5.19)	14 (9.09)	23 (14.93)
Edema	5 (3.25)	4 (2.60)	7 (4.54)
Blood stasis	10 (6.49)	16 (10.39)	39 (25.33)

Table 4: Characteristics of TCM syndromes at different ages.

Distribution of dialysis vintage and TCM syndrome type

The 154 patients were divided into groups of <12 months, 12~60 months and >60 months according to their dialysis vintage. Patients with dialysis vintage for 12~60 months accounted for the highest percentage. Syndromologically, liver-and-kidney-yin-deficiency ranked first (20.13%) and spleen-and-kidney-qi-deficiency second (16.88%). Symptomatically, blood stasis ranked first (24.68%) and dampness turbid second (12.99%) (see Table 5).

Syndrome	<12 m Number (percentage)	12~60 m Number (percentage)	>60 m Number (percentage)
Liver-and-kidney-yin-deficiency	12 (7.79)	31 (20.13)	20 (12.99)
Spleen-and-kidney-qi-deficiency	6 (3.90)	26 (16.88)	9 (5.84)
Spleen-and-kidney-yang-deficiency	7 (4.55)	20 (12.99)	14 (9.09)
Qi-and-yin-deficiency	2 (1.30)	1 (0.65)	0 (0.00)
Yin-and-yang-deficiency	1 (0.65)	4 (2.60)	1 (0.65)
Stirring wind	1 (0.65)	2 (1.30)	1 (0.65)
Damp heat	5 (3.25)	15 (9.74)	4 (2.60)
Dampness turbid	11 (7.14)	20 (12.99)	14 (9.09)
Edema	2 (1.30)	8 (5.19)	6 (3.90)
Blood stasis	8 (5.19)	38 (24.68)	19 (12.34)

Table 5: Characteristics of TCM syndromes in patients with different dialysis vintage.

Comparison between FGF23, Klotho and FGF23/Klotho in different syndromes

Of all TCM syndromes, compared with the control group, the FGF23 level and the FGF23/Klotho ratio of patients with CKD-MBD stage 5D significantly increased, while the Kltho protein level decreased, with P<0.05 taken as statistical significance. Syndromologically, the FGF23 level and FGF23/Klotho ratio of the patients with spleen-and-kidney-qi-deficiency syndrome were the highest, while the Klotho protein level was the lowest, which were statistically significant compared with the liver-and-kidney-yin-deficiency, spleen-and-kidney-yang-deficiency and qi-and-yin-deficiency (P<0.05). Symptomatically, the FGF23 level and the FGF23/Klotho ratio were the highest, while the Klotho protein level was the lowest in patients with damp heat. Compared with that in patients with blood stasis and stirring wind, the difference was statistically significant (P<0.05) (see Table 6).

Group	FGF23 protein (pg/ml)	Klotho protein (pg/ml)	FGF23/Klotho
Healthy control group	356.1±70.2	1761.0±174.1	0.204±0.047
Liver-and-kidney-yin-deficiency	956.4 ±86.1*	505.1 ±60.9*	2.286 ±1.22*
Spleen-and-kidney-qi-deficiency	1064.0±127.3*&	313.0±37.0*&	3.997±2.376*&
Spleen-and-kidney-yang-deficiency	1026.0±114.6*	471.4±48.5*	2.563±1.418*
Qi-and-yin-deficiency	893.9±79.4*	660.1±71.6*	2.636±1.032*
Yin-and-yang-deficiency	1007±86.1*	374.1±46.4*	3.132±2.409*
Stirring wind	941.2±79.11*	440.3±51.8*	2.737±1.319*
Damp heat	1024±56.77*#	331.2±44.3*#	4.069±3.072*#
Dampness turbid	932.1±71.27*	412.9±63.1*	3.031±1.624*
Edema	890.5±98.9*	678.6 ±76.9*	1.555 ±0.7193*
Blood stasis	956.9±94.67*	478.8±43.4*	2.571±1.445*

Table 6: Comparison of FGF23 and Klotho protein levels in different syndromes.

*Note: Compared with the control group, *P<0.05; spleen-and-kidney-qi-deficiency compared with other groups syndromologically, P<0.05; damp heat compared with other groups symptomatically, #P<0.05.*

Relationship between laboratory indexes and FGF23, Klotho, and FGF23/Klotho

Based on the ideal Ca concentration (2.10~2.37 mmol/L), P concentration (1.13~1.78mmol/L), and PTH concentration (150 and 300 ng/L), the lower-than-ideal-value group, ideal-value group and higher-than-idea-value group were designed, respectively. We found that based on P concentrations, the difference was statistically significant (P<0.05) when the FGF23/Klotho ratio in the lower-than-ideal-value group was higher than that in the higher-than-ideal-value group. Based on PTH concentrations, the Klotho protein concentration was higher in the idea-value group than that in the lower-than-ideal-value group (P<0.05) (see Table 7).

Item	Group	Number	FGF23 protein (pg/ml)	Klotho protein (pg/ml)	FGF23/Klotho
Ca concentration	Lower	49	972.63±75.5	389.3 ±201.1	2.548 ±1.307
	Ideal	70	987.9±92.75	448.5±182.2	2.977 ±1.603
	Higher	35	974.4±93.64	532.3±297.4	2.743 ±1.46
P concentration	Lower	17	1007.0±114.3	478.9 ±187.6	3.651 ±1. 613*
	Ideal	78	985.2±82.93	436.2±235.9	2.843 ±1.499
	Higher	59	966.3±84.46	456.5±217.6	2.487 ±1.353
PTH concentration	Lower	55	985.1±75.92	399.3 ±173.2	2.874±1.567
	Ideal	52	981.4±91.18	515.3±259.2#	2.735±1.348
	Higher	47	981.2±80.39	433.2±215.8	2.804±1.531

Table 7: Relationship between FGF23 and Klotho protein levels and laboratory indexes.
*Note: Compared with higher-than-ideal-value group, *P<0.05; compared with lower-than-ideal-value-group, #P<0.05.*

Discussion

Patients with renal disease at the end stage suffer from visceral deficiency, showing complicated syndromes by deficiency and excess. The current clinical studies on TCM syndromes of CKD-MBD are mainly centered on the 3-5 stages, but little on CKD stage 5D. Among the 154 patients with CKD-MBD stage 5D, the most common syndromes are liver-and-kidney-yin-deficiency, spleen-and-kidney-qi-deficiency and spleen-and-kidney-yang-deficiency, in which the liver-and-kidney-yin-deficiency is the most common in patients over 45 years old. For this age group, dialysis vintage lasts more than one year, featuring blood stasis symptomatically.

The disease involves the liver, kidney and spleen; the kidney is the origin of congenital constitution, dominating storage, and taking charge of bones. Patients with CKD suffer from long-term hemodialysis, causing further loss of kidney essence and life-gate fire. According to the Collected Records of Differentiation of Symptoms and Signs, if the kidney is injured, the kidney water can't nourish the liver, which, in return, may destroy the spleen. In turn, the spleen and kidney will both be injured.

Moreover, the homogeny of the liver and the kidney means that if the kidney essence declines, the essence of the liver and kidney cannot grow together and bones will not be nourished or strengthened. Thus, when a kidney deficiency occurs, the spleen will suffer, leading to the qi and blood to lack production and transformation. The qi dominates blood but cannot move blood if it is deficient, which may result in blood obstruction and stasis and eventually lead to heumatism and bone wilting, as well as fatigue, abdominal distention, dark complexion, cold pain in the waist, scaly dry skin, limb numbness and other symptoms.

The initial factors and later aggravating ones for CKD-MBD occurrence are the disorders of calcium and phosphorus metabolism[1, 3]. The FGF23-Klotho axis regulates calcium and phosphorus through a variety of mechanisms. As CKD progresses, the upregulation of FGF23 and/or the downregulation of Klotho can cause an imbalance in the paired co-receptor, leading to the occurrence of FGF23 resistance and disorder of the mineral metabolism. Consequently, the level of FGF23, Klotho, and their ratio can reflect the disease's severity and its prognosis[9]. This study found that the FGF23 level and FGF23/Klotho ratio of patients with CKD-MBD stage 5D increased significantly, and the Klotho protein level decreased dramatically. Additionally, the difference was statistically significant compared with the control group. Syndromologically, the FGF23 protein level and FGF23/Klotho ratio in patients with spleen-and-kidney-qi-deficiency were the highest and the Klotho protein level was the lowest, both of which show statistical difference compared with those in liver-and-kidney-yin-deficiency, spleen-and-kidney-yang-deficiency and qi-and-yin-deficiency.

Symptomatically, the FGF23 protein level and FGF23/Klotho ratio in patients with damp heat were the highest and Klotho protein level was the lowest; compared with those in blood stasis and stirring wind, the difference is statistically significant. Liu et al.[10] surveyed 165 cases of hemodialysis patients with renal osteopathy and found that the TCM syndrome types were mainly comprised of five basic syndromes: liver-and-kidney-yin-deficiency, turbid-toxin-accumulation, kidney-yang-deficiency, internal-stagnation-of-fluid-dampness, and blood-stasis-blocking-collaterals, which were basically consistent with the results of this study. Chen Jinyan[11] found that the level of serum FGF23 and Klotho protein in CKD patients was closely related to different TCM syndromes.

The FGF23 level, spleen-and-kidney-qi-deficiency, dampness turbid and blood stasis were risk factors for the thickening of carotid intima-media in CKD patients, suggesting that FGF23 and Klotho protein level could be used as an objective indicator for TCM syndrome differentiation. The serum FGF23 level and FGF23/Klotho ratio of patients with spleen-and-kidney-qi-deficiency and damp

heat were higher than those of other groups, while the Klotho level was lower than that of other groups. The significant statistical difference suggests that Klotho protein and FGF23 could be used as an indicator for syndrome differentiation of spleen-and-kidney-qi-deficiency and damp heat syndrome.

Only 50.65% of the subjects reached the standard in blood phosphorus in this study, and the FGF23/Klotho ratio in patients with hypophosphatemia was high, which is statistically significant compared with the higher-than-the-idea-value group. Based on PTH, the Klotho protein concentration in the ideal-value group was significantly higher than that in the lower-than-the-ideal-value group, and the difference is of statistical significance. One clinical study of 1,126 subjects with maintenance hemodialysis in Taiwan showed all-cause mortality has a close correlation with hyperphosphatemia (>1.52 mmol/l), hypophosphatemia (0.65~0.81 mmol/l), low PTH (<144pg/ml) and very low PTH (<60pg/ml) levels[12].

Clinically, therefore, attention should be paid to patients with FGF23-Klotho axis dysfunction, hypophosphoric and hypo PTHemia. Yin C et al.[13] found that Rong Huang granule can fundamentally relieve non-dialysis patients with CKD-MBD clinical symptoms and regulate disorders of the calcium and phosphorus metabolism.

Thus, its working mechanism should be that Chinese medicinal herbs can decrease the FGF23 level and increase the Klotho protein level. Furthermore, it has been found[14] that Astragalus membranaceus can inhibit an FGF23 increase, promote the expression of the Klotho protein, regulate disorder of calcium and phosphorus metabolism, alleviate pathological damage of the kidneys in CKD rats, and delay the worsening of renal function. Consequently, we believe that in the TCM treatment of patients with CKD-MBD stage 5D, it is advisable to emphasize tonifying kidney and supplementing essence, regulating the liver and the spleen, promoting blood circulation and removing blood stasis, dispelling internal diseases, as well as eliminating dampness and heat, so as to strengthen muscles and bones, and restore qi and blood.

Conclusion

The disease of patients with CKD-MBD stage 5D is mainly related to the liver, kidney, and spleen. Liver-and-kidney-yin-deficiency, spleen-and-kidney-qi-deficiency and spleen-and-kidney-yang-deficiency are syndromologically commonly shown, and blood stasis is symptomatically commonly manifested. Thus, there is a clear relationship between the decrease of Klotho protein, the increase of FGF23 level and spleen-and-kidney-qi-deficiency and damp heat, which can be an indicator for the diagnosis of these two syndromes.

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