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Correlation between Acid-base Environment and Coronary Artery Calcification in Maintenance Hemodialysis Patients

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Abstract: *Vascular calcification increases the mortality of maintenance hemodialysis patients, and the acid-base environment in maintenance hemodialysis (MHD) patients may affect the occurrence of vascular calcification. This study selected 123 MHD patients in the Department of Nephrology, the First Affiliated Hospital of Chongqing Medical University from June 2021 to June 2022. The general clinical data and laboratory indicators of the patients were collected. The coronary artery calcification score (CACS) of the patients was accurately calculated by collecting multi-slice CT. According to CACS, they were divided into a calcification group (CACS > 0) and a non-calcification group (CACS = 0). By analyzing and comparing whether there were differences in pre-HD PH, pre-HD bicarbonate, and other laboratory indicators between the two groups, the correlation between pre-HD PH, pre-hemodialysis bicarbonate, and CACS was analyzed. Among 123 MHD patients in our hospital, 56.9% of patients had coronary artery calcification (CACS > 0), including 48.6% males, with an average age of (64.87±12.35) years old. The average pre-HD AB was 23.5(20.88,26.35). There were significant differences in age, dialysis age, pre-HD AB, pre-HD SB, pre-HD CO2, serum calcium, and serum creatinine between the calcification group and the non-calcification group (P < 0.05), while there were no significant differences in serum phosphorus, calcium and phosphorus product, and iPTH. CACS were significantly positively correlated with age(r=0.283P<0.001), pre-HD AB(r=0.187 P=0.039), pre-HD CO2 (r=0.181 P=0.045) and serum calcium (r=0.203P=0.003). Multivariate analysis indicated that diabetes, age, dialysis age, and serum calcium were independently associated with CACS. Metabolic acidosis and coronary artery calcification are very common in maintenance hemodialysis patients. CACS decreases with the decrease of pre-hemodialysis bicarbonate. Diabetes, age, dialysis age, and calcium are independent risk factors for coronary artery calcification in MHD patients. Therefore, we should pay attention to early medication, and control serum glucose and serum calcium, to prevent and treat vascular calcification in clinical practice.*

Keywords: *Maintenance hemodialysis, metabolic acidosis, coronary artery calcification*

1. Introduction

Chronic kidney disease (CKD) is an increasingly serious problem worldwide, the prevalence of adult CKD in China is 10.8% [1]. The number of dialysis patients in China is increasing year by year, and by the end of 2022, there will be about 1 million dialysis patients in China. Cardiovascular events are the main cause of death in End-stage renal disease (ESRD) patients, accounting for more than 50% [2]. The mortality rate of cardiovascular disease in ESRD patients is 20 to 40 times that of the general population [3], and cardiovascular calcification is an important factor in the occurrence and development of cardiovascular disease in patients with ESRD and can independently predict future cardiovascular events and mortality [4]. Risk factors for vascular calcification include traditional factors such as dialysis duration, hypertension, diabetes, and age, while non-traditional factors such as abnormal calcium and phosphorus metabolism and oxidative stress accelerate the progress of vascular calcification [5].

Patients with end-stage renal disease are prone to acid-base metabolic imbalance, especially metabolic acidosis, which is the most common, mainly due to the intake of acidic substances, metabolic acid production in the body, and the excretion of acidic substances, resulting in a gradual decline in blood bicarbonate concentration. The acid-base fluctuation of most Maintenance hemodialysis (MHD) patients is characterized by mild metabolic acidosis before dialysis, and transient acid-base

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neutralization after dialysis leads to increased blood bicarbonate concentration [6]. For MHD patients on dialysis three times a week, the acid-base status of MHD patients fluctuates three times a week. According to KDOQI guidelines, the treatment goal of MHD patients is to maintain pre-hemodialysis bicarbonate ≥22mmol/L [7]. Some advocate maintaining pre-dialysis bicarbonate levels above 22mmol/L but below an as-yet undefined upper limit, as studies have shown that both metabolic acidosis and metabolic alkalosis are associated with increased mortality in hemodialysis patients [8, 9].

In conclusion, vascular calcification affects mortality in MHD patients, and metabolic acidosis or alkalosis also affects mortality in MHD patients. Meanwhile, studies have shown that [10] pre-hemodialysis bicarbonate level is negatively correlated with CACS in MHD patients, and pre-hemodialysis bicarbonate level is an independent risk factor for Coronary artery calcification (CAC). Other studies have shown that pH changes during dialysis are associated with cardiovascular mortality in dialysis patients, and patients with a larger difference in pH before and after dialysis have a lower risk of all-cause death and cardiovascular disease death [11]. Therefore, we speculated that the pH and HCO3- levels of MHD patients before dialysis may affect the occurrence of vascular calcification. To assess coronary artery calcification, we used Multislice CT (MSCT) to perform Agatstonscore in MHD patients [12], and CACS was obtained after adding all coronary vessel scores. This study aims to investigate the correlation between acid-base environment and coronary artery calcification in MHD patients, analyze the risk factors of coronary artery calcification, and provide a basis for the prevention and treatment of cardiovascular calcification in clinical dialysis patients, reduce the occurrence of cardiovascular events, and improve the prognosis of patients.

2. Materials and methods

2.1 Study samples

A total of 123 MHD patients were selected from the Department of Nephrology, The First Affiliated Hospital of Chongqing Medical University from June 2021 to June 2022. The following inclusion criteria were used: (1) Patients of all genders, ≥18 years of age; (2) Regular hemodialysis two or three times a week, total hemodialysis age ≥3 months; (3) The primary disease was chronic glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, etc. The following exclusion criteria were used: (1) Patients with acute renal failure; (2) Patients with severe infection, severe liver disease, or malignant tumor; (3) Patients with severe cardiovascular and cerebrovascular events within 3 months; (4) Patients with incomplete clinical data and unable to obtain multislice spiral CT images.

2.2 Methods

2.2.1 Basic clinical data

General clinical data of all patients were collected, including age, sex, primary disease composition, dialysis age, body mass index (BMI), hypertension, diabetes, coronary heart disease history, smoking and drinking history.

2.2.2 Laboratory biochemical indicators

Arterial blood analysis of all patients before dialysis was collected: pH, actual bicarbonate (AB), standard bicarbonate (SB), and total carbon dioxide (CO2). Fasting venous serum hemoglobin (Hb), albumin (ALB), alkaline phosphatase (ALP), iparathyroid hormone (iPTH), calcium (Ca), phosphorus (P), calcium-phosphorus product(Ca*P), magnesium (Mg), creatinine (CRE), uric acid (UA), cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low density lipoprotein (LDL).

2.2.3 Coronary artery calcification score

Multi-slice spiral CT (Siemens SOMATOM Definition, Germany) images of all patients were collected, and CACS was calculated according to the Agatston score, calcification score = calcification area *peak calcification focus. The Agatston scores of the left main coronary artery, anterior descending branch, circumflex branch, and right coronary artery were calculated by Caretream.GCRIS software, and then combined to obtain CACS. According to CACS, the group with CACS > 0 was divided into the calcification group, and the group with CACS=0 was divided into the non-calcification group.

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2.3 Statistical method

Data were analyzed by using SPSS software version 26. The data are presented as the mean± SD for the normally distributed variables; otherwise, the data are presented as the median and 25th-75th percentiles. Differences between the two groups were compared by using either independent *t-tests* or Wilcoxon rank tests for the continuous variables. Frequencies between the two groups were analyzed by using the chi-square test. Spearman correlation analysis and binary logistics regression were used to analyze the influencing factors of coronary artery calcification. In our study, a two-tailed p value ≤0.05 was set to indicate a statistically significant difference.

3. Results

3.1 Comparison of general clinical data and laboratory biochemical indexes between the calcified and non-calcified MHD patients

In this study, a total of 123 MHD patients in the Department of Renal Medicine of our hospital were selected,70 patients (56.9%) developed coronary artery calcification (CACS > 0), including 34 males (48.6%), with an average age of 64.87±12.35 years old. There were 58 patients (82.9%) with hypertension, 20 patients (28.6%) with diabetes and 12 patients (17.1%) with coronary heart disease. There were significant differences in age, dialysis age, pre-HD AB, pre-HD SB, pre-HD CO2, Ca, and CRE between the calcification group and the non-calcification group *(P < 0.05)*.BMI, pre-HD pH, Hb, ALB, ALP, iPTH, P, Ca*P, Mg, UA, TC, TG, HDL, and LDL were not statistically significant between the two groups Differences (Table 1).

Table 1: Comparison of clinical data and biochemical indexes between the two groups

variate	non-calcification group(n=53)	calcification group(n=70)	*P*
Sex(Male,%)	22,41.5%	34,48.6%	
Hypertension(n,%)	37,69.8%	58,82.9%	
Diabetes(n,%)	7,13.2%	20,28.6%	
Coronary heart disease(n,%)	3,5.7%	12,17.1%	
Age(years)	58.32±12.19	64.87±12.35	0.004
BMI(kg/m^2)	22.22(19.22,24.17)	22.81(20.75,25.58)	0.225
Dialysis age(months)	36(18,72)	70.5(24,98.5)	0.01
pre-HD pH	7.396±0.048	7.402±0.046	0.427
pre-HD AB(mmol/L)	22.4(20.25,24.8)	23.5(20.88,26.35)	0.04
pre-HD SB(mmol/L)	23.2(21.6,24.8)	23.95(22.05,26.4)	0.053
pre-HD CO_2(mmol/L)	23.3(20.85,26.1)	24.4(21.98,27.4)	0.045
Hb(g/L)	102(86.5,128.5)	108.5(97.75,123)	0.459
ALB(g/L)	41(33,45)	41(38,45.25)	0.097
ALP(U/L)	110(95,149.5)	97.5(81.75,144.5)	0.203
Ca(mmol/L)	2.15±0.24	2.29±0.25	0.001
P(mmol/L)	1.88±0.54	1.88±0.65	1
Ca*P	46.17(39.15,62.48)	48.83(40.70,65.62)	0.332
Mg(mmol/L)	0.99±0.16	0.97±0.15	0.471
iPTH(pg/mL)	249.2(134.5,575.8)	294.85(107.7,599.3)	0.925
CRE (umo1/1)	837.45±266.43	799.74±255.75	0.428
UA(umol/1)	378(311,476)	364(311.25,420.5)	0.418
TC (mmol/L)	3.65(2.80,4.30)	3.73(3.05,4.38)	0.925
TG (mmol/L)	1.24(0.86,1.98)	1.455(0.94,1.99)	0.407
HDL(mmo1/L)	1.05(0.81,1.38)	1.09(0.86,1.34)	0.685
LDL(mmol/L)	1.83(1.31,2.45)	2.16(1.63,2.54)	0.702

Body mass index: BMI; pre-hemodialysis pH: pre-HD pH; pre-hemodialysis actual bicarbonate: pre-HD AB; pre-hemodialysis standard bicarbonate: pre-HD SB; pre-hemodialysis carbon dioxide: pre-HD CO2; hemoglobin: Hb; albumin: ALB; alkaline phosphatase: ALP; iparathyroid hormone: iPTH; calcium: Ca; phosphorus: P; calci-phosphorus produc: Ca*P; magnesium: Mg; creatinine: CRE; uric acid: UA; cholesterol: TC; triglyceride: TG; high-density lipoprotein: HDL; low density lipoprotein: LDL.

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3.2 Analysis of influencing factors of coronary artery calcification in MHD patients

To further understand the risk factors of coronary artery calcification, it can be concluded by using Spearman correlation analysis that age, pre-HD AB, pre-HD CO2, and serum calcium were significantly positively correlated with CACS (Table 2, Figure 1), and other indicators were not correlated with CACS.

Table 2: Correlation analysis of CACS

variate	CACS	
	r/rs	*P*
Age(years)	0.283	<0.001
BMI(kg/m^2)	0.115	0.205
Dialysis age(months)	0.156	0.084
pre-HD pH	0.058	0.527
pre-HD AB(mmol/L)	0.187	0.039
pre-HD SB(mmol/L)	0.166	0.060
pre-HD CO_2(mmol/L)	0.181	0.045
Hb(g/L)	0.075	0.411
ALB(g/L)	0.094	0.303
ALP(U/L)	-0.075	0.408
Mg(mmol/L)	-0.082	0.365
Ca(mmol/L)	0.263	0.003
P(mmol/L)	-0.05	0.586
Ca*P	0.028	0.755
CRE (umo1/1)	-0.084	0.357
UA(umol/1)	-0.022	0.812
iPTH(pg/mL)	0.005	0.959
TC (mmol/L)	0.055	0.544
TG (mmol/L)	0.022	0.809
HDL(mmo1/L)	0.068	0.452
LDL(mmol/L)	0.117	0.197

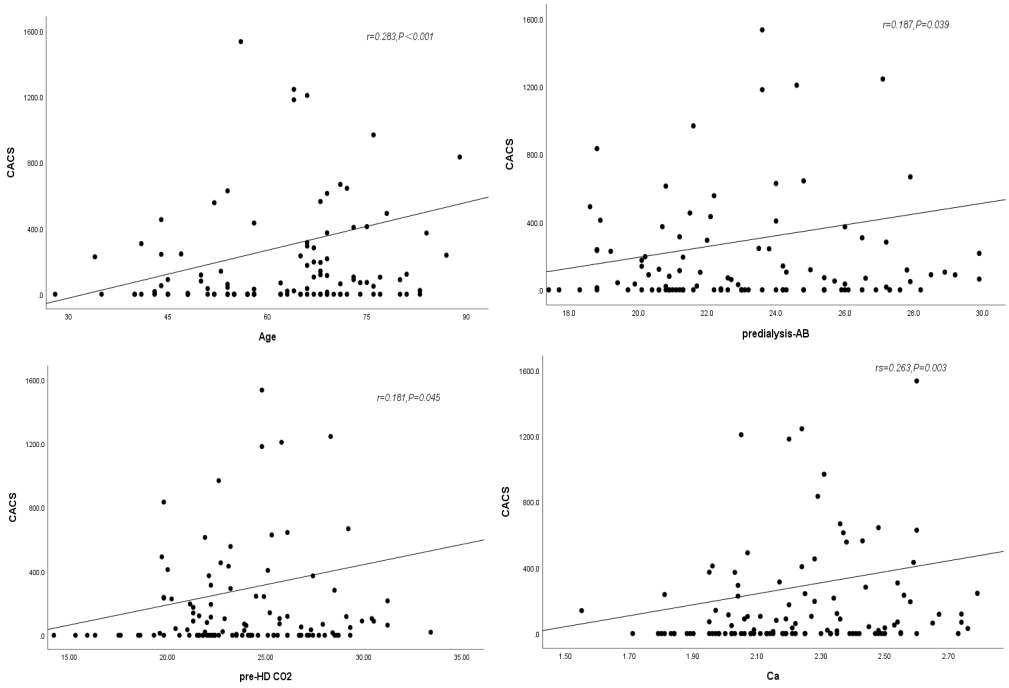

Figure 1: Correlation of CACS with age, pre-HD AB, pre-HD CO2, and Ca

With the occurrence of coronary artery calcification as the dependent variable, single factor Logistic regression analysis was performed on diabetes, age, pre-HD pH, pre-HD AB, pre-HD SB, pre-dialysis CO2, Ca, P, calcium-phosphorus product, iPTH, ALB and ALP. The results showed that diabetes, age,

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dialysis age, pre-HD AB, pre-HD SB, pre-dialysis CO2, ALB, and Ca were associated with coronary artery calcification (Table 3). After adjusting for the above factors, multifactor Logistic regression showed that diabetes, age, dialysis age, and calcium were independent risk factors for vascular calcification(Table 4). ($P<0.05$)

Table 3: Univariate logistic regression analysis of coronary artery calcification

variate	OR(Exp)	95%CI	P
diabetes	2.629	1.017~6.792	0.046
Age(years)	1.044	1.013~1.077	0.006
Dialysis age(months)	1.012	1.003~1.022	0.009
pre-HD pH	23.051	0.011~50452.131	0.424
pre-HD AB(mmol/L)	1.154	1.040~1.282	0.007
pre-HD SB(mmol/L)	1.174	1.032~1.336	0.015
pre-HD CO_2(mmol/L)	1.103	1.009~1.205	0.031
ALB(g/L)	1.064	1.005~1.127	0.033
ALP(U/L)	1.001	0.997~1.005	0.513
Ca(mmol/L)	13.091	2.633~65.083	0.002
P(mmol/L)	1.000	0.551~1.816	1.000
Ca*P	1.012	0.991~1.033	0.255
iPTH(pg/mL)	1.000	0.999~1.001	0.495
LDL(mmol/L)	0.985	0.944~1.028	0.498

Table 4: Multivariate logistic regression analysis of coronary artery calcification

variate	OR	95%CI	P
diabetes	4.283	1.333~16.763	0.015
Age(years)	1.078	1.0351.124	<0.001
Dialysis age(months)	1.017	1.005~1.029	0.007
pre-HD AB(mmol/L)	1.44	0.816~2.544	0.209
pre-HD SB(mmol/L)	0.686	0.351~1.342	0.271
pre-HD CO_2(mmol/L)	0.992	0.841~1.170	0.925
ALB(g/L)	1.061	0.977~1.152	0.158
Ca(mmol/L)	11.572	1.609~83.219	0.015

4. Discussion

The incidence and mortality of CVD are high in ESRD patients. Vascular calcification is an independent risk factor for cardiovascular mortality in ESRD patients. The diagnosis of vascular calcification is mainly based on the detection of imaging methods. MSCT can quantitatively calculate CACS, which is the "gold standard" for detecting vascular calcification [13].In this study, 123 hemodialysis patients were selected for MSCT to calculate CACS, and it was found that the positive rate of coronary artery calcification was about 56.9%, indicating that the proportion of vascular calcification in MHD patients was relatively high. Traditional risk factors for coronary artery calcification include advanced age, diabetes, hypertension, hyperlipidemia [14], etc., and some uremia and dialysis-related factors such as residual renal function, dialysis age, volume overload, nutrition [15], anemia, calcium and phosphorus metabolism disorders [16], inflammation [17] may play a more important role in this process. We compared the general data and possible related test indicators between the coronary calcification group and the non-coronary calcification group. We found that CACS was positively correlated with age, pre-HD AB, pre-HD CO2, and calcium. In contrast, diabetes, age, dialysis age, and blood calcium were correlated with the occurrence of coronary artery calcification, which was consistent with the above conclusions.

The acid-base environment of ESRD patients will change, among which metabolic acidosis is more common [18], while the acid-base environment of MHD patients fluctuates. Kirschbaum et al. [19] studied the effect of high bicarbonate hemodialysis on ionized calcium and the risk of metastatic calcification, they found a significant increase in pH and total CO2 concentration in the blood after dialysis, an increase in total and ionized calcium in patients who used only a central venous catheter for dialysis, and no significant change in calcium concentration in patients who used an arteriovenous fistula for dialysis. The phosphate concentration decreased in all patients, but the phosphate concentration increased 2 hours after the end of dialysis, and the risk of metastasizing calcification

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increased by 2.8 times in HD patients. This study suggests that an alkaline environment may promote vascular calcification in MHD patients. Mendoza et al. [20] showed that metabolic acidosis could inhibit vascular calcification and deposition of calcium and phosphorus in soft tissues in rats with renal failure induced by calcitriol. This study showed that there was a positive correlation between the pre-dialysis bicarbonate level and CACS in MHD patients, and CACS increased with the increase of the pre-dialysis bicarbonate level. All these suggest that an acidic environment in vivo may inhibit vascular calcification. It may be because the solubility of calcium and phosphorus is enhanced under acidic conditions, which reduces the deposition of calcium and phosphorus in blood vessels and soft tissues. However, contrary to the results of the aforementioned Oka [10] study, it may be that the sample size of the Oka study is small and the experimental conclusion is unreliable.

Disorders of calcium and phosphorus metabolism can also increase the risk of vascular calcification. Masumoto et al. [21] showed that the calcification rate of blood vessels in rats exposed only to a high phosphorus environment was significantly lower than that in the high calcium and phosphorus group, suggesting that blood calcium and phosphorus may play a synergistic effect in promoting vascular calcification. Our study confirmed that serum calcium level is positively correlated with CACS and is an independent risk factor for coronary artery calcification, indicating that patients with higher serum calcium levels are more likely to have vascular calcification. When calcium concentration is too high in the body, it can promote the formation of vascular calcification crystals and change the phenotype of vascular smooth muscle cells, and abnormal bone metabolism, leading to an increased risk of vascular calcification. High blood phosphorus can affect VSMC function and lead to vascular calcification. Elevated blood phosphorus mediates the expression of osteogenic transcription factors in VSMC, directly promotes VSMC from contractile phenotype to osteogenic phenotype, and stimulates osteogenesis [22]. However, serum phosphorus was not an influencing factor of coronary calcification in our study, which may be related to the clinical intervention treatment of hyperphosphatemia in dialysis patients and the small sample size.

Age [23], diabetes, and long dialysis duration are traditional influencing factors of vascular calcification, which is consistent with the results of our study that age, diabetes, and increased dialysis duration are independent risk factors for vascular calcification in MHD patients. With the increase of age, the vascular function of MHD patients decreases gradually, and calcium is easy to deposit in the vessel wall. At the same time, degenerative changes of vascular elastic fibers occur, resulting in decreased vascular elasticity and vascular damage, and increasing the risk of vascular calcification. The inflammatory state of diabetic patients also predisposes them to vascular calcification. Patients with longer dialysis time are more likely to have vascular calcification, which may be due to the disorder of calcium and phosphorus metabolism in maintenance dialysis patients and the use of high calcium dialysate during dialysis.

As this study is an observational and cross-sectional study with a small number of cases, there are some limitations. Although studies have shown an association between metabolic acidosis and CAC, a large randomized prospective study is needed to further clarify the role of metabolic acidosis in CAC in HD patients.

5. Conclusion

Age, pre-HD AB, pre-HD CO2, and serum calcium of MHD patients were significantly positively correlated with coronary artery calcification. For dialysis patients, maintaining a low level of pre-hemodialysis bicarbonate (no less than 22mmol/L but the upper limit could not be determined) may reduce the occurrence of coronary artery calcification. However, more prospective studies are needed to further elucidate the role of metabolic acidosis in CAC in HD patients. Diabetes, age, dialysis age, and serum calcium are independent risk factors for coronary artery calcification in MHD patients. Therefore, we should pay attention to early drug use in clinical practice to control blood sugar and blood calcium, to prevent and treat vascular calcification.

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