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Research Article

Investigation of the Risk factors of Vascular Calcification in Maintenance Hemodialysis

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Abstract

Objective: To explore the risk factors of vascular calcification by analyzing the aorta status of the Maintenance Hemodialysis (MHD) patients by lateral plain X-ray.

Methods: In total, 114 MHD patients received lateral plain X-ray of the abdomen. The scores of Abdominal Aorta Calcification (AAC) were calculated. According to the AAC score, all MHD patients were divided into the no or mild calcification group (A group), and moderate or severe calcification group (B group). The levels of total cholesterol, serum creatinine, serum iron, intact parathyroid hormone, blood glucose, blood calcium and blood phosphorous were quantitatively measured in two groups. We also calculated the adjusted calcium and recorded information such as dialysis vintage, age and gender. The risk factors of vascular calcification in MHD patients were analyzed by logistic regression analysis. The factors with $P<0.10$ analyzed by uni-variable logistic regression was included into multi-variables logistic regression analysis.

Results: Among 114 MHD patients, 80 patients were assigned into A group and 34 into B group. Compared with A group, the age of MHD patients was significantly older in B group ($P<0.05$). Uni-variable logistic regression analysis revealed that the age, adjusted calcium, blood glucose level and calcium-containing drugs intake were probably correlated with the incidence of vascular calcification (all $P<0.10$). Three parameters with statistical significance by uni-variable logistic regression, along with gender, calcium and phosphorus product and dialysis vintage were included into the multi-variables logistic regression analysis. Positive correlations were found between the severity of vascular calcification and the age ($P<0.001$), adjusted calcium ($P=0.028$) and calcium and phosphorus product ($P=0.002$).

Conclusions: The age, adjusted calcium and calcium and phosphorus product are the risk factors of vascular calcification. Lowering the serum calcium level may facilitate regression of vascular calcification in MHD patients.

Keywords: Abdominal Aorta; Maintenance Hemodialysis; Vascular Calcification

Abbreviations

BUN	:	Blood Urea Nitrogen	GLU	:	Glucose
HGB	:	Hemoglobin	CHO	:	Cholesterol
TSAT	:	Transferrin Saturation	CRP	:	C-reactive Protein
PTH	:	Parathyroid Hormone	URR	:	Urea Reduction Ratio
			ALB	:	Albumin
			TIBC	:	Total Iron Binding Capacity
			CO_2CP	:	Carbon Dioxide Combining Power

SUA	:	Serum Uric Acid
SCR	:	Creatine
LDL	:	Low-Density Lipoprotein

Introduction

Vascular calcification is defined as abnormal mineralization in the vascular soft tissue of the cardiovascular system. Vascular calcification is a marker of cardiovascular disease and mortality [1]. The incidence and prevalence of vascular calcification is higher in patients with CKD, increasing with progressive renal decline with a reported prevalence up to 80-90% in those requiring dialysis [1]. The abdominal aorta, coronary and carotid arteries are principal vascular beds used to assess vascular calcification. Importantly, AAC has been associated with an increased risk for adverse cardiovascular outcomes, including acute coronary syndromes, stroke and peripheral vascular disease, as well as an increased risk for mortality [2-4]. Kidney Disease Improving Global Outcomes (KDIGO) recommended lateral abdominal X-ray instead of CT to detect vascular calcification levels in Chronic Kidney Disease (CKD) stage 3-5 patients in 2009 [5]. There are few studies on vascular calcification in MHD patients in China. The study aimed to detect the status of the abdominal aorta in patients with MHD and explored the risk factors for vascular calcification.

Methods and Type of Study

Cohort

We performed a retrospective observation study of dialysis patients from June to August 2016 in our dialysis center (68 males, mean age 54.4±14.4 years; 46 females, mean age 54.9±12.8 years). Inclusion criteria: dialysis vintage more than 3 months, 2 or 3 times per week, 4 hours each time, blood flow 200~250 ml/min. The dialysate flow rate is 500 ml/min, and the dialysate calcium concentration is 1.25~1.5 mmol/L. Exclusion criteria: patients with history of parathyroidectomy, arrhythmia, multiple myeloma, amyloidosis, malignancy or severe infection. Demographic information, relevant clinical data and use of medications were recorded. All patients had signed informed consent.

Biochemical Parameters

Blood samples were collected before and after dialysis. Blood routine and C Reaction Protein (CRP), partial Pressure of Carbon Dioxide ($PaCO_2$), Intact Parathyroid Hormone (iPTH), Serum blood urea nitrogen, uric acid, serum creatinine, total cholesterol, Low Density Lipoprotein (LDL), blood glucose, total iron binding, iron protein, serum iron, calcium, potassium, phosphorus, albumin, calculated Transferrin Saturation (TSAT), Urea Nitrogen Reduction Rate (URR), adjusted calcium, calcium and phosphorus product, the condition of calcium-containing drugs and active Vitamin D intake were also recorded. The formula for adjusted calcium = Serum calcium × 0.02 × (40-albumin).

Vascular Calcification

Lateral spinal radiographs that included the abdominal aorta were obtained on the next day after dialysis. The Kauppila score quantifies the severity of lumbar aortic calcifications observed on a lateral abdominal radiograph that includes from the T-10 vertebra to the first two sacral vertebra [6]. A score of 1 to 3 is assigned based on extent of calcification (i.e., one-third, two-thirds, or more than two thirds of the vertebra length involved). In brief, the anterior and posterior aspects of the aorta are divided into four segments bound by the first four lumbar vertebrae giving a total of 8 segments. For each segment, the anterior and posterior walls of the aorta are assessed separately, and the degree of vascular calcification is graded 0, 1, 2 or 3 corresponding to vascular calcification being absent, present in less than one third of the aortic wall, greater than one third but less than two thirds, or greater than two thirds of the aortic wall. Each of the 8 segments is scored from 0 to 3 so that the total score can range from 0 to 24. All X-ray films are reviewed and scored by the same radiologist. According to the method mentioned in the CORD study [7], patients with AAC ≤ 4 were included in the no or mild calcification group (A group), moderate calcification with AAC score 5 to 16 points, and severe calcification AAC score＞16 were included in moderate or severe calcification group (B group). The data were analyzed by SPSS 22.0 software. Categorical data was expressed as percentages and continuous data as mean ± Standard Deviation (SD), or for non-normal data as median and 25^{th} to 75^{th} interquartile range (IQR 25-75). The rank sum test was used for comparison between groups; the count data was expressed as a percentage, and the $\chi 2$ test was used for comparison between groups. The logistic regression analysis to analyze the risk factors, and the factors of single factor analysis ($P< 0.10$) were included in multivariate analysis. $P< 0.05$ was considered statistically significant.

Result

Baseline Characteristics

Among 114 patients (68 males, mean age 54.4±14.4 years; 46 females, mean age 54.9±12.8 years), 34 cases of abdominal aortic calcification occurred, and the rate of vascular calcification was 29.8%. 80 cases (70.2%) had no or mild calcification, 18 cases (15.8%) had moderate calcification, and 16 cases had severe calcification (14.0%). Eighty patients were included in no or mild calcification group (A group), and 34 patients in moderate or severe calcification group (B group). Compared with the MHD patients with no or mild calcification, the MHD patients with moderate or severe calcification group were older ($P<0001$). Significant difference was found regarding calcium-containing

drugs intake between two groups（P=0.037. There was no significant difference between the other parameters (P>0.05). Demographic and biochemical characteristics of the patients are shown in (Table 1).

Parameter	A group（n=80)	B group（n=34）	P
Age (year）	51.51±13.76	62.12±10.62	0.000
vintage（year）	2.78±2.71	3.02±2.37	0.200
Pre-dialysis BUN（mmol/L)	30.14±9.904	30.02±7.27	0.824
Post dialysis BUN（mmol/L)	7.92±4.196	8.41±3.06	0.403
Potassium（mmol/L)	5.04±0.80	5.19±0.93	0.607
HGB（g/L）	99.22±23.55	100.91±20.28	0.973
Fe^{2+}（mmol/L)	11.44±4.71	10.98±4.44	0.400
Ferritin（ug/L）	332.71±366.33	455.03±470.863	0.323
TSAT（%）	26.21±11.38	25.77±11.68	0.528
PTH（pg/ml）	564.67±668.11	482.76±519.49	0.247
Phosphorus（mmol/L)	2.36±0.90	2.47±0.81	0.530
Calcium-phosphorus product	59.75±21.21	66.20±21.343	0.189
GLU（mmol/L)	7.81±3.21	9.97±5.79	0.054
CHO（mmol/L)	4.47±1.10	4.36±0.89	0.874
CRP（mg/L）	6.36±13.19	9.91±23.14	0.650
sex（male n (%)）	40.21±4.71	40.21±4.71	0.764
URR（%）	74.32±6.89	72.63±5.99	0.218
ALB（g/L）	41.07±3.54	40.21±4.71	0.291
TIBC (μmol/L)	44.83±7.64	43.96±6.26	0.561
Ca（mmol/L)	2.19±0.29	2.28±0.31	0.121
Adjusted Calcium （mmol/L)	2.15±0.29	2.27±0.30	0.053
CO2CP（mmol/L)	16.55±3.44	16.92±3.58	0.611
UA(μmol/L)	526.70±104.91	535.62±81.39	0.659
CREA(μmol/L)	1193.84±360.68	1200.47±438.95	0.933
LDL（mmol/L)	2.13±0.73	2.13±0.78	0.997
The rate of calcium-containing drugs intake n (%)	18（15.8%）	96（84.2）	0.037
The rate of the rate of taking the active vitamin D3 n (%)	85（74.6%）	29(25.4%)	0.448

Table 1: Demographic and biochemical characteristics of the patients.

Logistic Regression Analysis

Univariate logistic regression analysis showed that age, adjusted calcium, blood glucose, calcium and calcium-containing drugs intake were associated with the calcification of abdominal aorta in patients with MHD ($P < 0.10$), as shown in (Table 2).

Parameter	B value	P value	Exp（B） value	95% CI for EXP（B）	
				lower limit	upper limit
Age (year）	1.079	0.000	2.942	1.604	5.395
sex（male%）	-0.126	0.764	0.882	0.387	2.007
vintage（year）	0.126	0.583	1.134	0.724	1.778
Pre-dialysis BUN（mmol/L)	-0.110	0.710	0.896	0.502	1.600
Post dialysis BUN（mmol/L)	0.088	0.731	1.092	0.660	1.808
URR（%）	-0.346	0.218	0.707	0.407	1.228
ALB（g/L）	-0.257	0.292	0.773	0.479	1.248
Potassium（mmol/L)	0.122	0.619	1.130	0.699	1.826
HGB（g/L）	0.029	0.921	1.029	0.578	1.832
Fe^{2+}（mmol/L)	-0.178	0.459	0.837	0.523	1.340
Ferritin（ug/L）	0.294	0.170	1.342	0.882	2.043
TIBC（μmol/L）	-0.160	0.557	0.852	0.498	1.456
TSAT（%）	-0.102	0.641	0.903	0.589	1.385
PTH（ng／L）	-0.113	0.466	0.893	0.658	1.211
Ca（mmol/L)	0.381	0.125	1.464	0.899	2.385
Phosphorus（mmol/L)	0.103	0.718	1.108	0.634	1.935
Adjusted Calcium （mmol/L)	0.470	0.059	1.601	0.982	2.611
calcium-phosphorus product	0.429	0.221	1.536	0.772	3.057
$PaCO_2$ （mmol/L)	0.137	0.608	1.146	0.680	1.932
SUA（mmol/L)	0.107	0.656	1.113	0.695	1.784
SCr（umol/L）	0.024	0.932	1.024	0.591	1.775
GLU（mmol/L)	0.360	0.032	1.433	1.031	1.991
CHO（mmol/L)	0.027	0.934	1.028	0.540	1.956
LDL（mmol/L)	0.002	0.997	1.002	0.495	2.027
CRP（mmol/L)	0.003	0.997	1.003	0.205	4.902
The rate of calcium-containing drugs intake	-1.099	S	0.333	0.119	0.936
The rate of the active vitamin D3 intake	0.350	0.448	1.419	0.575	3.500

Table 2: Uni-variable logistic regression.

We enlarge the scope of multifactor analysis according to previous literatures [7]. We included age, adjusted calcium, glucose and calcium Gender, calcium-phosphorus product, iPTH, dialysis vintage and calcium-containing drugs intake in multivariate logistic regression analysis. Positive correlations were found between the severity of vascular calcification and the age, adjusted calcium and calcium and phosphorus product (all $P<0.05$), see (Table 3).

Parameter	B value	SE value	Wald value	P value	Exp(B) value	95.0% CI for EXP(B)	
						lower limit	upper limit
Sex	-0.358	0.529	0.457	0.499	0.699	0.248	1.972
Age	0.116	0.029	15.707	0.000	1.123	1.060	1.189
Vintage	0.055	0.121	0.208	0.648	1.057	0.834	1.340
PTH	0.000	0.001	0.239	0.625	1.000	0.999	1.001
Adjusted Calcium	2.253	1.027	4.809	0.028	9.512	1.270	71.227
calcium-phosphorus product	0.048	0.016	9.251	0.002	1.049	1.017	1.082
GLU	0.128	0.066	3.750	0.053	1.137	0.998	1.294
The rate of calcium-containing drugs intake	-0.522	0.633	0.678	0.410	0.594	0.172	2.054

Table 3: Multi-variables logistic regression analysis.

Discussion

Cardiovascular disease is the most common cause of death in patients with CKD, including dialysis-dependent CKD. The high cardiovascular risk may be due in part to excess vascular calcification. The reported prevalence of vascular calcification detected by Computed Tomography (CT) scan is > 80 percent among dialysis patient [8-10]. Among CKD patients, there are two types of vascular calcification including medial or intimal calcification, with different pathogeneses. It is not known whether intimal and medial calcification both contribute to increased mortality, because it has been difficult to differentiate these lesions using standard radiographic techniques. Among CKD patients, vascular calcification is associated with increased cardiovascular risk and mortality. In a prospective study [11] including 104 hemodialysis patients, mortality was higher among patients with a Coronary Artery Calcification (CAC) score above the median compared with those below the median (98 versus 34 per 1000 patient-years, respectively). Calcification of large conduit arteries like the aorta increases arterial stiffness [12]. Arterial stiffness or lack of distensibility causes hypertension and increased pulse pressure, which are risk factors for left ventricular dysfunction and heart failure among CKD patients [12-14]. In one study of hemodialysis patients, those with intimal calcification (with or without medial calcification) had the worst clinical outcome [15].

Positive correlations were found in our study between vascular calcification and the age, adjusted calcium in line with former studies [9,16]. Increasing age and time on dialysis are associated with increased prevalence of vascular calcification. In one study that included 364 skeletal radiographs in 152 CKD patients, vascular calcification was observed in 30 and 50 percent of patients aged 15 to 30 and 40 to 50 years, respectively [16]. Persistent hypercalcemia, drives the initiation and progression of vascular calcification. The serum concentrations, particularly of calcium, do not necessarily reflect local concentrations, which, particularly at sites of inflammation like the arterial wall, can be much higher. Among dialysis patients, calcium-containing phosphate binders have clearly been associated with increased progression of vascular calcification compared with the non-calcium-containing binder, sevelamer [9,17]. Not line with previous studies [1,9,10,12], the dialysis vintage, iPTH, and serum phosphorus levels were not associated with vascular calcification in this study. This may be due to the fact that most of the patients in this study were poor farmers, and the hospital was located in the underdeveloped area of Guangdong Province, China. The dialysis was insufficient due to low income level, bad traffic problems, medical insurance, etc. The patients usually perform dialysis every four days. In addition, weak-potency calcium-containing phosphate binders were widely used in patients with hyperphosphatemia. Increased oral calcium intake has been associated with higher risk of calcification [9].

In summary, in patients with MHD, the use of abdominal lateral X-ray film can better detect vascular calcification. The age, adjusted calcium, and calcium-phosphorus product are the risk factor of vascular calcification. It is of significance way to reduce the degree of vascular calcification in patients through effective treatment of hypercalcemia.

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