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ORIGINAL RESEARCH

Association Between Lower Serum Mitsugumin 53 Levels and the Risk of Vascular Calcification in Hemodialysis Patients

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Background: Mitsugumin 53 (MG53) plays a protective role against kidney diseases and cardiovascular diseases, but its mechanism of action is unclear. We speculate that the prevention of cardiovascular disease by MG53 may be associated with the inhibition of vascular calcification. This study was performed with the aim of investigating the potential association between the MG53 level and abdominal aortic calcification (AAC) in patients undergoing hemodialysis (HD).

Methods: A total of 263 patients undergoing HD and 65 age- and sex-matched healthy individuals were included. The patient serum MG53 level was measured by enzyme-linked immunosorbent assay (ELISA), and the abdominal aortic calcification score (ACCs) was calculated using lateral abdominal radiography parameters. The laboratory and demographic data were collected at baseline.

Results: The serum MG53 levels in HD patients were significantly lower than those in healthy individuals [24.9 (IQR: 16.1–40.1) vs 43.5 (IQR: 23.7–74.4) pg/mL, $P < 0.001$]. In addition, HD patients with AAC presented markedly lower serum MG53 levels than those without AAC [22.0 (IQR: 15.3–32.6) vs 26.9 (IQR: 16.8–44.2) pg/mL, p=0.024]. Furthermore, multiple logistic regression analysis indicated that lower serum MG53 levels, an older age, a longer dialysis vintage, a higher serum total carbon dioxide (TCO_2), and a higher serum phosphorus were independent risk factors for AAC in HD patients.

Conclusion: Our results demonstrate for the first time a correlation between lower serum MG53 levels and an increased risk of AAC in patients undergoing HD. In addition, an older age, a longer dialysis vintage, the presence of metabolic acidosis and higher serum phosphorus levels are independent risk factors for AAC in HD patients.

Keywords: Mitsugumin 5, hemodialysis, abdominal aortic calcification, chronic kidney disease

Introduction

Vascular calcification (VC) is a major risk factor for cardiovascular events, cardiovascular death, and all-cause mortality in patients with chronic kidney disease (CKD).[1–3] However, the pathogenesis of VC is very complex and unclear, and effective treatment strategies are lacking. There is a high prevalence of vascular calcification, osteoporosis, and skeletal muscle atrophy in CKD patients, suggesting that myokines act as signaling molecules in bone and muscle cross-talk, as has been identified in the general population.[4] MG53 is an E3 ubiquitin ligase, also known as a myokine, that rapidly accumulates at the site of membrane damage and plays a critical role in repairing the membranes of skeletal and cardiac muscle cells. Treatment with recombinant human MG53 (rhMG53) protects cardiac function from ischemia–reperfusion-induced oxidative stress by safeguarding mitochondrial function in cardiomyocytes.[5] In recent years, an increasing number of studies have demonstrated that MG53 plays a renoprotective role in kidney disease pathogenesis.[6] MG53 plays an important role in metabolic syndrome

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and tissue protection.[7–13] It has been reported that MG53 can lower the incidence of ischemic heart injury, and that MG53 level is correlated with adverse cardiovascular events.[1,12,14] Results from animal studies confirmed that the serum MG53 levels in rats in the CKD group were lower than those in rats in the normal control group. Moreover, Ayodele Adesanya TM et al reported that MG53 is expressed in pig and human aortic valves and that the MG53 protein protects aortic valve interstitial cells from membrane injury and fibrocalcific remodeling.[15] Both aortic valve and abdominal aorta calcification are highly prevalent in hemodialysis patients,[16] so we speculate that MG53 may play a role in the pathogenesis of vascular calcification in hemodialysis patients. Conversely, mitsugumin 53 (MG53) plays a protective role against cardiovascular diseases, and we presume that the prevention of cardiovascular disease by MG53 may be associated with the inhibition of vascular calcification. To confirm our hypothesis, in the current study, we investigated the relationship between the serum MG53 level and abdominal aortic calcification (AAC) in hemodialysis patients and then verified the factors influencing MG53 expression. Our study provides important clinical evidence of crosstalk among skeletal muscle, blood vessels, and bone.

Materials and Methods

Subjects

Data was collected from HD patients from Beijing Ditan Hospital, Capital Medical University, Luhe Hospital Capital Medical University, and Yanqing Hospital Peking University between January 2023 and March 2023. The inclusion criteria for patients were as follows: (1) over 18 years of age; (2) diagnosed with end-stage renal disease (defined as an estimated glomerular filtration rate <15 mL/min) within the past 6 months, and received HD for at least 3 months; and (3) agreed to participate in this study. The exclusion criteria were as follows: (1) acute kidney injury patients; (2) patients who had received HD time for fewer than 3 months; (3) patients who were in the acute phase of infection or had acute gastrointestinal bleeding, heart failure, or other complications; (4) patients whose estimated survival time was less than half a year; and (5) patients whose data were incomplete. A flowchart is shown in Figure 1.

In addition, healthy participants from the same hospitals were included. Healthy individuals aged from 18 to 80 years were age- and sex- matched with the included patients undergoing HD. The exclusion criteria were as follows: (1) individuals who had diabetes, hypertension, heart failure, coronary heart disease, cancer, or other chronic diseases; and (2) individuals who were pregnant.

This study was approved by the Ethics Committee of Beijing Ditan Hospital Affiliated with Capital Medical University (KY2023-042). All the subjects voluntarily participated in this study and provided written informed consent. Our study complied with the Declaration of Helsinki.

Data Collection

Demographic and clinical data, including sex, age, height, weight; smoking status; alcohol use; the use of phosphorus binders, lipid-lowering drugs, antiplatelet drugs and vitamin D; dialysis vintage, renal pathology, and medical history, were collected. Moreover, the serum hemoglobin (Hb), C-reactive protein (CRP), albumin (Alb), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total CO_2, serum creatinine (Scr), serum urea, glucose, calcium, phosphorus, and intact parathyroid hormone (iPTH) levels were measured. Fractional urea clearance (Kt/V urea) was calculated via the Daugirdas formula.

Within two weeks of enrollment, the HD patients underwent lateral dual-energy X-ray, and their AAC score was calculated by an experienced radiologist.

Blood samples were collected before HD using vacuum tubes without anticoagulant. After centrifugation, the serum was separated and stored at −80 °C until analysis. Serum MG53 was measured using ELISA kits (LifeSpan, USA). The inter-assay and intra-assay coefficients of variation were less than 10% and 8%, respectively. The data were presented anonymously to protect patient privacy.

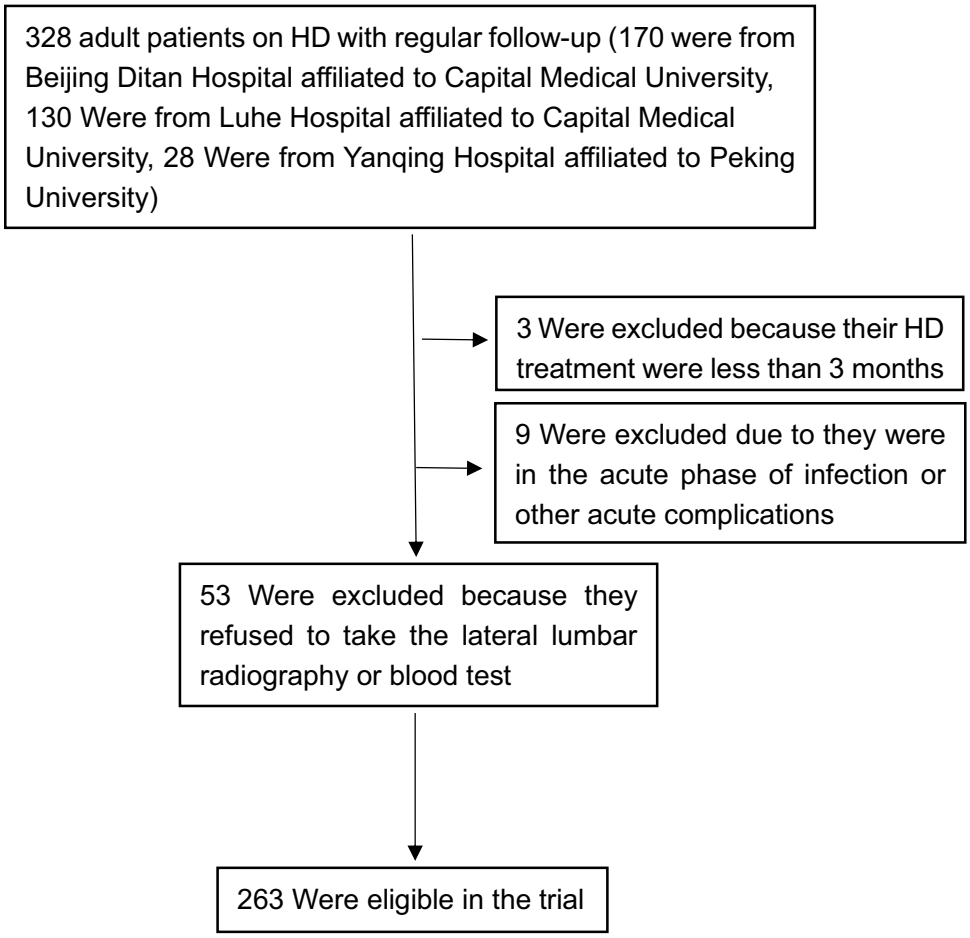

Figure 1 Flowchart of the study.

Assessment of AAC in Patients Undergoing HD

Within two months of enrollment, the patients were examined by lateral dual-energy X-ray, and the corresponding AAC scores were obtained. We used a semiquantitative scoring system to calculate ACCs, which can vary from 0 to 24, and we defined vascular calcification as an abdominal aortic calcification score ≥4.[16]

Statistical Analysis

SPSS 26.0 software (IBM Corp., Armonk, NY) was used for data analysis. The means ± standard deviations were used for continuous variables that conformed to normal distributions by Shapiro–Wilk test, and the independent sample *t* test was used for comparisons between groups. The medians (ranges) were used for nonnormally distributed variables, and comparisons between groups were performed by the Mann–Whitney nonparametric rank sum test. Categorical variables are expressed as proportions and were analyzed via the chi-square test or Fisher's exact probability method. We selected the variables for comparisons between HD patients with and without AAC and performed univariate logistic regression to determine the factors related to AAC. Then, we selected variables with P values <0.1 in the univariate logistic regression analysis and those that are suspected of being correlated with vascular calcification in clinical practice (despite having P values >0.1 in the univariate logistic regression analysis), such as corrected calcium, iPTH, and CRP levels, for inclusion in our multivariate logistic regression analysis to identify independent risk factors for AAC in HD patients. A two-tailed P value of <0.05 was considered to indicate a significant difference.

Results

Baseline Characteristics of Hemodialysis Patients and Healthy Individuals

In total, 263 HD patients and 65 healthy individuals were selected on the basis of the inclusion and exclusion criteria. The demographic and clinical characteristics are shown in Table 1. The median age of the HD patients was 60 (50, 67) years. The median HD dialysis vintage was 52 (19, 95) months. The primary renal diseases were diabetes (confirmed by kidney biopsy or diagnosed on the basis of a history of diabetes diagnosis, the results of laboratory tests, or the presence of diabetic retinopathy) (97 patients), glomerulonephritis (confirmed by kidney biopsy or on the basis of clinical characteristics such as a history of proteinuria and hematuria history and the level of urinary protein quantity) (84 patients), hypertensive glomerulosclerosis (confirmed by kidney biopsy or on the basis of clinical characteristics such as history of hypertension, the results of laboratory tests, and the presence of hypertensive retinopathy) (50 patients), polycystic kidney disease (confirmed by kidney imaging such as MRI, ultrasound, or CT scan) (15 patients), others (confirmed by medication history and the presence of chronic interstitial nephritis induced by drugs) or unknown causes (confirmed on the basis of the exclusion of diabetic kidney diseases, hypertensive glomerulosclerosis, glomerulonephritis, and polycystic kidney disease) (17 patients). We found that the HD patients had lower MG53 levels than healthy individuals did [24.9 (IQR: 16.1–40) vs 43.5 (IQR: 23.7–74.4)], as shown in Table 1. Patients undergoing HD had higher CRP, TG, LDL-C, Scr, serum urea, UA, serum glucose, and serum phosphorus levels and had lower serum Hb, Alb, HDL-C, TCO2, and corrected calcium levels than did healthy individuals.

Differences in Clinical Biochemical Characteristics Between HD Patients with Higher Serum MG53 Levels and Those with Lower Serum MG53 Levels

We divided all HD patients into a higher serum MG53 level group (higher than the median) and a lower serum MG53 level group (lower than the median) according to the median MG53 level (24.9 pg/mL). Compared with those in the higher MG53 level group, patients in the lower MG53 level group had higher serum creatinine and phosphorus levels, AAC scores and likelihood of

Table 1 Comparison of the Demographic and Clinical Characteristics Between Patients Undergoing Hemodialysis and Healthy Individuals

Variables	Hemodialysis Patients (n=263)	Healthy Individuals (n=65)	P value
Age (years)	58±12	58±12	0.61
Sex (male/female)	159/104	37/28	0.672
HD vintage (months)	52(19,95)		
Hemoglobin (g/l)	116.5±13.5	142.5+14.0	<0.001
CRP (mg/l)	2.1(1.0,4.7)	0.5(0.3,1.5)	0.007
Alb (g/l)	39.4±3.9	47.8±2.5	<0.001
TG (mmol/l)	2.0±1.2	11.3±0.5	<0.001
HDL-C (mmol/l)	1.0±0.3	1.4±0.3	<0.001
LDL-C (mmol/l)	2.0±0.8	2.9±0.7	<0.001
TCO_2 (mmol/l)	21.1±3.4	25.2±1.3	<0.001
Serum creatinine (μmol/l)	846.8±233.0	67.7±13.0	<0.001
Serum BUN (mmol/l)	22.8±6.3	4.6±1.2	<0.001
Serum UA (mmol/l)	413±94.0	305.4±55.9	<0.001
Serum glucose (mmol/l)	8.9±4.2	5.6±0.9	<0.001
Serum corrected calcium (mmol/l)	2.1±0.2	2.4±0.1	<0.001
Serum phosphorus (mmol/l)	1.7±0.2	1.3±0.1	<0.001
Serum MG53 (pg/mL) (IQR)	24.9(16.1,40.1)	43.5(23.7,74.4)	<0.001

Abbreviations: HD, hemodialysis; CRP, C-reactive protein; Alb, albumin; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TCO2, total carbon dioxide; BUN, blood urea nitrogen; UA, uric acid; MG53, mitsugumin 53.

diabetes. There were no differences in age, sex, BMI, dialysis vintage, mean arterial pressure, smoking status, alcohol use, the use of phosphorus binders, lipid-lowering drugs, antiplatelet drugs, or vitamin D, the presence of hypertension or chronic kidney disease as the primary disease, Hb, CRP, Alb, TG, HDL-C, LDL-C, TCO_2, serum urea, serum glucose, serum corrected calcium, or iPTH levels, or urea KT/V, as shown in Table 2.

Table 2 Comparison of Serum MG53 Levels and Other Parameters Between Hemodialysis Patients With Lower MG53 Levels and Those With Higher MG53 Levels

Variables	Lower MG53 (n=132)	Higher MG53 (n=131)	P value
Age (years)	57.4±11.9	58.7±11.8	0.31
Sex (male/female)	79/53	80/51	0.47
BMI (kg/m2)	23.7±3.9	23.7±4.3	0.779
Dialysis vintage (months)	34±29.4	58.3±33.9	0.189
Mean arterial pressure (mmHg)	112.2±12.4	109.0±12.2	0.8
Smoking status (n, %)	40(41.5)	57(42.9)	0.137
Alcohol use (n, %)	11(8.3)	6(4.8)	0.332
Phosphorus binder use (n)	101	103	
Non-calcium-containing phosphorus binder use (n, %)	75	81	0.426
Calcium-containing phosphorus binder use (n, %)	25	22	
Lipid-lowering drug use (n, %)	27(19.0)	35(26.7)	0.214
Antiplatelet drug use (n, %)	27(23.8)	28(21.7)	0.473
Vitamin D use (n, %)	73(55.6)	68(51.7)	0.401
Diabetes mellitus (yes/no)	87/50	77/49	0.019
Hypertension (yes/no)	116/16	122/9	0.107
Primary disease of chronic kidney disease			
Chronic glomerulonephritis (n)	38	46	
Diabetic nephropathy (n)	48	47	
Hypertensive nephropathy (n)	23	27	0.082
Polycystic kidney disease (n)	11	4	
Others (n)	12	7	
Hemoglobin (g/l)	115.4±12.3	117.7±14.6	0.131
CRP (mg/l) (IQR)	3.5 (3.5,8.9)	1.5 (1.3,2.8)	0.929
Alb (g/l)	39.2±3.7	39.6±4.1	0.103
TG (mmol/l) (IQR)	2.3 (2.3,3.1)	2.3 (1.3,4.1)	0.874
HDL-C (mmol/l)	0.9±0.3	1.0±0.3	0.796
LDL-C (mmol/l)	2.1±0.8	2.0±0.7	0.593
TCO_2 (mmol/l)	21.1±3.5	21.1±3.3	0.851
Serum creatinine (μmol//l)	924.7±251.1	829.1±201.4	0.039
Serum BUN (mmol/l)	22.6±6.4	23.1±6.3	0.926
Serum glucose (mmol/l)	8.3±4.1	10.8±4.3	0.128
Serum corrected calcium (mmol/l)	2.2±0.2	2.1±0.2	0.502
Serum phosphorus (mmol/l)	2.1±0.3	1.5±0.3	<0.001
iPTH (pg/mL)			
<150 (n)	43	42	
150–600 (n)	74	87	0.55
>600 (n)	9	8	
KT/V urea (single time)	1.4±0.2	1.6±0.2	0.434
ACC score	12 (8,18)	1 (0,2)	0.011

Abbreviations: MG53, Mitsugumin 53; BMI, body mass index; CRP, C-reactive protein; Alb, albumin; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TCO_2, total carbon dioxide; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone; ACC, abdominal aortic calcification.

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Comparison of Serum MG53 and Other Parameters Between HD Patients without AAC and HD Patients with AAC

The prevalence of AAC was 47.9% (126/263) in this study. Compared with the the HD patients without AAC, the HD patients with AAC presented significantly lower serum MG53 levels [22.0 (IQR: 15.3–32.6) vs 26.9 (IQR: 16.8–44.2) pg/mL, P=0.024]. The HD patients with AAC were older, had longer dialysis vintage, had higher mean arterial pressure, had a higher likelihood of diabetes, and had higher phosphorus levels than HD patients without AAC. However, these HD patients with AAC had lower Hb, Alb, LDL-C, TCO_2, and serum urea levels, AAC scores and urea KT/V. In addition, there were no differences in sex, BMI, smoking status, alcohol use, the use of phosphorus binders, lipid-lowering drugs, antiplatelet drugs, or vitamin D, hypertension, chronic kidney disease as the primary disease, or CRP, TG, HDL-C, serum creatinine, serum glucose, serum corrected calcium, or iPTH levels, as shown in Table 3.

Table 3 Comparison of Serum MG53 Levels and Other Parameters Between Hemodialysis Patients Without ACC and Those With ACC

Variables	Without ACC (n=137)	With ACC (n=126)	P value
Age (years)	55.9±12.5	60.2±10.7	0.002
Sex (male/female)	82/55	78/48	0.801
BMI (kg/m2)	23.5±3.8	23.4±4.1	0.224
Smoking status (n, %)	48(35.2)	44(35.2)	0.345
Alcohol use (n,%)	6(2.9)	10(4.2)	0.331
Phosphorus binder use (n)	95	89	
Non-calcium-containing phosphorus binder use (n, %)	80(58.1)	90(71.2)	0.092
Calcium-containing phosphorus binder use(n, %)	29(21.0)	22(17.3)	
Lipid-lowering drug use (n, %)	27(21.1)	24(17.3)	0.386
Antiplatelet drug use (n, %)	11(8.3)	20(15.4)	0.152
Vitamin D use (n, %)	82(59.6)	62(49.2)	0.171
Dialysis vintage (months) (IQR)	35(12,79)	59(24,102)	0.014
Mean arterial pressure (mmHg)	98.7±14.2	104.3±13.4	<0.001
Diabetes mellitus (yes/no)	87/50	77/49	0.019
Hypertension (yes/no)	127/10	117/9	0.107
Primary disease of chronic kidney disease			
Chronic glomerulonephritis (n)	42	42	
Diabetic nephropathy (n)	51	44	
Hypertensive nephropathy (n)	26	24	0.987
Polycystic kidney disease (n)	8	7	
Others (n)	10	8	
Hemoglobin (g/l)	118±12	112±14.5	0.025
CRP (mg/l) (IQR)	2.1(0.9,4.2)	2.1(1.1,5.1)	0.408
Alb (g/l)	39.9±3.2	38.8±4.5	0.048
TG (mmol/l) (IQR)	1.6(1.1,2.5)	1.6(1.2,2.4)	0.87
HDL-C (mmol/l)	1.0±0.3	0.9±0.3	0.227
LDL-C (mmol/l)	2.2±0.8	1.9±0.7	0.031
TCO_2 (mmol/l)	22.5±3.1	19.4±2.9	<0.001
Serum creatinine (μmol/l)	862.7±218.3	842±351.9	0.292
Serum BUN (mmol/l)	23.6±6.4	21.9±6.2	0.029
Serum glucose (mmol/l)	8.4±3.8	9.4±4.5	0.128
Serum corrected calcium (mmol/l)	2.1±0.2	2.1±0.2	0.377

(*Continued*)

Table 3 (Continued).

Variables	Without ACC (n=137)	With ACC (n=126)	P value
Serum phosphorus (mmol/l)	1.49±0.44	1.79±0.46	0.008
iPTH (pg/mL)			
<150 (n)	43	42	
150–600 (n)	74	87	0.661
>600 (n)	9	8	
KT/V urea (single time)	1.4±0.3	1.2±0.4	0.034
Serum MG53 (pg/mL) (IQR)	26.9(16.8, 44.2)	22.0(15.3, 32.6)	0.024
ACC score	1(0,2)	12(8,18)	<0.001

Abbreviations: MG53, Mitsugumin 53; BMI, body mass index; CRP, C-reactive protein; Alb, albumin; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TCO_2, total carbon dioxide; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone; ACC, abdominal aortic calcification.

Independent Factors for AAC in Hemodialysis Patients According to Multivariate Logistic Regression

To eliminate the impact of confounding variables on VC, a multivariate logistic regression model was used to identify the independent risk factors for VC in HD patients. The variables that were significantly related to ACC in the univariate logistic regression analysis included the MG53 level, age, dialysis vintage, mean arterial blood pressure, the presence of diabetes mellitus, Alb, LDL-C, TCO2, serum urea, and serum phosphorus levels, and urea KT/V. We selected variables with P values <0.1 in the univariate logistic regression analysis, as well as those that may be correlated with vascular calcification in clinical practice (despite p values >0.1 in the univariate logistic regression analysis), such as corrected calcium, iPTH, and CRP levels, for inclusion in our multivariate logistic regression analysis. In the multivariate analysis, serum MG53 level (OR=0.982, P=0.012, 95% CI 0.968–0.996), dialysis vintage (OR=1.006, P=0.007, 95% CI 1.002–1.011), age (OR=1.032, P=0.007, 95% CI 1.009–1.057), serum TCO_2 level (OR=0.668, P=0,003, 95% CI 0.584–0.763), and serum phosphorus level (OR=1.045, P=0.034, 95% CI 1.045–1.176) were independently associated with AAC in HD patients, as shown in Table 4.

Table 4 Independent Determining Factors for ACC According to Univariate and Multivariate Logistic Regression Analysis in HD Patients

Variables	Univariate			Multivariate		
	P value	OR	95% CI	OR	95% CI	P value
lnMG53	0.009	0.983	0.969–0.994	0.982	0.968–0.996	0.012
Sex (male/female)	0.645	1.123	0.685–1.844			
Age (years)	0.003	1.033	1.011–1.055	1.032	1.009–1.057	0.007
BMI (kg/m2)	0.359	1.028	0.969–1.092			
Dialysis vintage	0.004	1.006	1.002–1.010	1.006	1.002–1.011	0.007
Mean arterial blood pressure (mmHg)	0.045	1.030	1.012–1.050	Not selected	Not selected	Not selected
Diabetes mellitus (yes/no)	0.047	1.003	1.001–1.009	Not selected	Not selected	Not selected
Hypertension (yes/no)	0.106	1.728	0.967–2.488			
Hemoglobin (g/l)	0.087	1.016	0.967–1.003	Not selected	Not selected	Not selected
CRP (mg/l)	0.454	1.009	0.989–1.032	Not selected	Not selected	Not selected

(*Continued*)

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Table 4 (Continued).

Variables	Univariate			Multivariate		
	P value	OR	95% CI	OR	95% CI	P value
Alb (g/l)	0.036	0.929	0.870–0.991	Not selected	Not selected	Not selected
TG (mmol/l)	0.558	0.942	0.773–1.149			
HDL-C (mmol/l)	0.205	0.583	0.253–1.343			
LDL-C (mmol/l)	0.042	0.571	0.402–0.810	Not selected	Not selected	Not selected
TCO_2 (mmol/l)	0.001	1.082	1.003–1.167	0.668	0.584–0.763	0.003
Serum creatine (μmol/l)	0.249	0.999	0.998–1.000			
Serum BUN (mmol/l)	0.038	0.957	0.919–0.995	Not selected	Not selected	Not selected
Serum glucose (mmol/l)	0.066	1.058	0.996–1.123	Not selected	Not selected	Not selected
Serum corrected calcium (mmol/l)	0.616	0.737	0.223–2.432	Not selected	Not selected	Not selected
Serum phosphorus (mmol/l)	0.018	1.204	1.178–1.279	1.045	1.045–1.176	0.034
iPTH (pg/mL)	0.601	1	0.999–1.001	Not selected	Not selected	Not selected
KT/V urea	0.032	0.366	0.167–0.801	Not selected	Not selected	Not selected

Abbreviations: CI, confidence interval; LnMG53, natural logarithm of Mitsugumin 53; BMI, body mass index; CRP, C-reactive protein; Alb, albumin; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TCO_2, total carbon dioxide; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone; ACC, abdominal aortic calcification. Not selected means variables with P<0.1 in the univariate analysis but they were not reached significantly differences (P <0.05) in the multivariate logistic regression analysis.

Discussion

The present study revealed that 47.9% of hemodialysis patients suffered from vascular calcification. Moreover, the serum MG53 levels were significantly lower in HD patients than in healthy individuals. We also found that MG53 levels were lower in HD patients with AAC than in HD patients without ACC. A lower MG53 level was an independent risk factor for AAC in HD patients, along with older age, longer dialysis vintage, metabolic acidosis and higher serum phosphorus levels.

Previous studies reported that the prevalence of aortic calcification in patients undergoing HD was 46.8%–93%,[1–3,17,18] which was consistent with our findings.

To our knowledge, the present study is the first to show that the serum MG53 levels were significantly lower in 263 HD patients than in 65 healthy sex- and age-matched individuals. A previous animal study also supports our findings.[9] We believe that there are several reasons for the lower serum MG53 levels in hemodialysis patients. First, uremic toxins under hemodialysis circumstances may inhibit skeletal muscle synthesis or secretion of MG53. Second, protein energy wasting and skeletal muscle atrophy are common in patients undergoing HD, as MG53 secretion is decreased by low muscle mass, and it is common for CKD patients to have a lack of exercise; thus, MG53 levels are decreased in hemodialysis patients. In the next step, we will confirm these explanations.

Another important finding in our study was that lower MG53 levels were independently associated with increased AAC in HD patients, which was verified for the first time in patients undergoing HD. Vascular calcification can be divided into 5 types: intimal calcification, medial calcification, outer membrane calcification, calciphylaxis, and cardiac valve calcification. Medial artery calcification is the most common vascular calcification in patients with CKD, and the severity of vascular calcification is associated with cardiovascular events and all-cause mortality.[11,12] Other studies have shown that the MG53 level is a valuable prognostic factor for major adverse cardiovascular events (MACEs) in patients with acute myocardial infarction (AMI),[14] but the mechanism underlying the relationship between the MG53 level and vascular calcification is unclear. Therefore, we speculate that MG53 may affect cardiovascular outcomes in patients undergoing HD through the regulation of vascular calcification.

Traditional risk factors for vascular calcification in CKD patients include age, sex, race, the presence of diabetes, hypertension, or dyslipidemia; and genetics, among other factors, whereas nontraditional risk factors include longer

dialysis vintage, the presence of hyperphosphatemia, positive balance of calcium and phosphorus intake, the use of vitamin D or oral vitamin K inhibitors, decreased Klotho receptor levels, and elevated levels of FGF-23.[19] The results of our study also show that age and dialysis vintage were independent risk factors for vascular calcification in patients undergoing HD. To date, many new studies have investigated the mechanism of vascular calcification. The basement membrane protein Nidogen-2, an important part of the vascular extracellular matrix microenvironment, is involved in the differentiation of vascular smooth muscle cells (VSMCs) and vascular calcification.[20] Our research group previously reported that irisin alleviates vascular calcification by inhibiting VSMC osteoblastic transformation and mitochondrial dysfunction via the AMPK/Drp1 signaling pathway in chronic kidney disease.[21] In addition, irisin, a myokine, protects against vascular calcification by activating autophagy and inhibiting NLRP3-mediated vascular smooth muscle cell pyroptosis in chronic kidney disease pathogenesis.[22]

There are several possible mechanisms that may underlie the correlation between lower MG53 levels and increased AAC:[1] In vitro exams have shown that the expression of Ambra1 and MG53 in the skeletal muscle of CKD rats is significantly decreased,[23] and we speculate that circular MG53 expression is also decreased and that the capacity to inhibit vascular calcification is reduced.[2] Patients with lower MG53 levels had higher serum phosphorus levels than did those with higher MG53 levels [2.1±0.3 mmol/l vs 1.5±0.3 mmol/l, $P<0.001$], and lower MG53 levels were associated with increased AAC. Whether higher MG53 levels can directly inhibit vascular calcification or indirectly alleviate vascular calcification through lowering serum phosphorus levels requires further study.

Previous studies have demonstrated that MG53 can alleviate kidney fibrosis by inhibiting chronic inflammation.[17] However, our study did not find a correlation between serum MG53 and CRP levels in HD patients. We speculate that MG53 may alleviate vascular calcification by inhibiting inflammation.

Moreover, the MG53 protein has been reported to protect aortic valve interstitial cells from membrane injury and fibrocalcific remodeling.[15] Consequently, we speculate that the MG53 protein can protect vascular smooth muscle cells from aortic calcification caused by membrane injury and calcification, which is a topic worth further study.

There are certain limitations to the present study. The sample size of this study was small. Moreover, the results may be affected by many confounding factors. Therefore, the above results should be interpreted with caution.

Conclusion

Our results indicate for the first time the correlation between lower serum MG53 levels and an increased risk of AAC in patients undergoing HD. Our results suggest that exercise or the addition of MG53 might be a new direction for preventing vascular calcification in CKD patients.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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