Association of Matrix Metalloproteinase-2 and Matrix Metalloproteinase-9 With Endothelial Dysfunction, Cardiovascular Disease Risk Factors and Thrombotic Events in Children With End-stage Renal Disease

Alaleh Gheissari,[1,2] Rokhsareh Meamar,[3] Amin Abedini,[1]
Peyman Roomizadeh,[4] Mohammad Shafiei,[1]
Zahra Samaninobandegani,[5] Zhale Tabrizi,[6] Farhad Mahmoudi,[6]
Alireza Merrikhi,[1,2] Esfandiar Najafi Tavana[7]

[1]Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Pediatric Nephrology, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[4]School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[5]Bushehr University of Medical Sciences, Bushehr, Iran
[6]Medical Students' Research Center, Isfahan University of Medical sciences, Isfahan, Iran
[7]Department of Pediatrics, Isfahan University of Medical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

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Introduction. Cardiovascular disease (CVD) is the main cause of death in children with end-stage renal disease (ESRD). Matrix metalloproteinases (MMP-2 and MMP-9) are members of endopeptidases which contribute to CVD. The aim of this study was to evaluate the association of MMP-2 and MMP-9 with markers of endothelial dysfunction, soluble E-selectin and brachial flow-mediated dilatation; several biochemical risk factors of CVD; and thrombotic incidents in children with ESRD.

Materials and Methods. Thirty-one children with ESRD and 18 healthy age- and sex-adjusted controls underwent measurement of serum levels of MMP-2, MMP-9, soluble E-selectin, phosphorus, calcium, parathyroid hormone, lipid profile, thrombotic factors, and albumin. Flow-mediated dilatation was measured in both groups by Doppler ultrasonography. Thrombotic events were assessed in patients with ESRD.

Results. Matrix metalloproteinase-2 positively correlated with systolic and diastolic blood pressure, soluble E-selectin, creatinine, cholesterol, triglyceride, low-density lipoprotein cholesterol, phosphorus, and parathyroid hormone and negatively correlated with body mass index, hemoglobin, high-density lipoprotein cholesterol, and flow-mediated dilatation, while MMP-9 correlated with soluble E-selectin, phosphorus, parathyroid hormone, and albumin and negatively correlated with body mass index and hemoglobin. Six patients (19.3%) had thrombotic incidents. There was no significant difference between the levels of MMP-2 and MMP-9 in the children with and without thrombotic events.

Conclusions. This study determined the associations of MMP-2 and MMP-9 with markers of endothelial dysfunction and several traditional and uremia related CVD risk factors in children with ESRD. No associations were found between these two MMPs and thrombotic events.

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INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of death in children with end-stage renal disease (ESRD).[1] The development of CVD in children with ESRD arises from the interaction of several risk factors that can be categorized into 3

groups: (1) traditional risk factors (diabetes mellitus, smoking, obesity, hypertension, and impaired lipid profile), (2) factors related to loss of kidney function (secondary hyperparathyroidism, anemia, hypoalbuminemia, and thrombotic factors), and (3) emerging risk factors (hyperhomocysteinemia, inflammation, oxidative stress, and endothelial dysfunction).[1-5] Patients with ESRD are also at increased risk for thrombotic events including arteriovenous (AV) fistula thrombosis, central venous catheter thrombosis, deep vein thrombosis, and pulmonary thromboembolism.[6,7] The most common causes of thrombotic events in these patients are suggested to be increased levels of coagulation factors, decreased anticoagulants and fibrinolytic activity, and increased platelet activation.[7]

Matrix metalloproteinases (MMPs) are zinc-dependent proteases, which were first discovered in 1962. Matrix metalloproteinase-2 and MMP-9 are specific subtypes of this family which have significant activities in the cardiac tissue and play pivotal roles in the pathogenesis of various CVD, including acute myocardial infarction, atherosclerosis, heart failure, and aortic aneurysm[8]. These MMPs are also involved in the development of several renal disorders such as glomerulonephritis, acute kidney injury, diabetic nephropathy, and chronic kidney disease (CKD).[9,10]

In the recent years, growing bodies of evidence have indicated the influence of endothelial dysfunction in the development of atherosclerosis and arteriosclerosis in children with ESRD.[1] Brachial artery flow-mediated dilatation (FMD) is a noninvasive test for assessment of endothelial function. An impaired FMD is a reliable indicator of endothelial dysfunction.[11]Another marker of endothelial dysfunction is soluble E-selectin, which have a major role in leukocytes adherence to endothelial cells. Soluble E-selectin is the most well-known adhesion molecule, which is associated with endothelial damage in humans.[12,13]

At the present time, the studies on the role of MMP-2 and MMP-9 in the development of CVD in ESRD patients are mostly limited to the adult age groups.[14-21] Limited data is available on this topic in children with ESRD.[22-25] Also, limited data exist on the relationship between thrombotic events and contributing risk factors of ESRD in children.[26,27]

The aim of this study was to investigate the associations between MMP-2, MMP-9, and markers of endothelial dysfunction (FMD and soluble E-selectin), traditional CVD risk factors, and kidney failure-related CVD risk factors in children with ESRD. Also, we evaluated the association between the studied variables and thrombotic events in this population.

MATERIALS AND METHODS

Study Population and Data Source

This analytical cross-sectional study was conducted from November 2014 to November 2015 on children with ESRD who had been referred to Al Zahra and Imam-Hossein Hospitals, Isfahan, Iran. These hospitals are the main tertiary care center for pediatric ESRD in Isfahan province. The inclusion criteria were a confirmed diagnosis of ESRD, age less than than 20 years, and being at least 6 months under hemodialysis or peritoneal dialysis treatment. The exclusion criteria were presence of any rheumatologic disease including systemic lupus erythematous, Wegener granulomatosis, and other vasculitis which might affect the levels of endothelial markers, presence of systemic infection, having diabetes mellitus, and having history of surgery within 1 month before sampling. After enrolling the eligible children, the objectives and the protocol of the study were completely explained and a written informed consent was obtained from parents or caregivers. The study protocol was approved by the ethics committee of Isfahan University of Medical Sciences.

Clinical and Biochemical Evaluations

Overall, 31 patients met the inclusion criteria and were enrolled in the study. Eighteen age- and sex-matched healthy subjects with no known disease were enrolled as the control group. The study participants and their parents were invited to the clinic after 12 hours of overnight fasting. Demographic features and clinical data of the eligible participants were collected which included age, sex, weight, height, and body mass index (BMI; kg/m^2). Weight and height were measured twice by a trained nurse. After 15 minutes of sitting, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a suitable cuff and a standard sphygmomanometer from right hand. We determined Z scores of measured blood pressures for every children and a Z score of 1.645 and greater for age, height, and sex was defined as hypertension. Brachial artery FMD measurement

was done by an expert cardiologist.

A fasting venous blood sample was obtained from the patients and controls. The blood samples were analyzed for MMP-2, MMP-9, hemoglobin, blood urea nitrogen (BUN), serum creatinine, soluble E-selectin, triglyceride, cholesterol, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), phosphorus, calcium, and parathyroid hormone (PTH). In order to evaluate the thrombotic markers in the patients, the blood samples were also analyzed for homocysteine, fibrinogen, protein C, and protein S.

Serum levels of MMP-2, MMP-9, and soluble E-selectin were measured by commercially enzyme-linked immunosorbent assay kits (Abingdon, R&D System, UK). Protein C and protein S were measured by a coagulation-based method (Hyphen Biomed, France). Serum PTH level was measure by enzyme-linked immunosorbent assay method (Biomerica, USA). Other biochemical parameters were measured using routine and standard laboratory methods.

Flow-mediated Dilatation Measurement

The flow-mediated dilatation measurement was done in accordance to the guidelines of the International Brachial Artery Reactivity Task Force.[28] Participants were examined in the supine position with their forearms in a semi-open splint position. The high-frequency (7 MHz) vascular transducer (EKO 7, Samsung Medison Co, Korea) was settled with a stereotactic probe-holding gadget. For achieving the goal of making a flow stimulus by reactive hyperemia, a pediatric blood pressure cuff was fixed on the participant's wrists and then radial artery was scanned in the longitudinal section 5 cm distal from antecubital fossa. After obtaining a baseline image, the blood flow velocity was assessed as average of the Doppler signal from a mid-artery sample volume. After 5 minutes interim of ischemia, cuff deflation was followed by a short high-flow state. After cuff deflation, the images of the radial artery and Doppler signal were recorded frequently for 5 minutes and 20 seconds intervals. At the end of procedure, the saved images were analyzed. Radial artery distance measurements were done at maximum systolic extension.

Retrospective Data Collection

In addition to biochemical evaluations, we retrospectively investigated the medical records of all patients for any history of thrombotic incidents. Thrombotic incidents which we investigated included AV fistula thrombosis, central venous catheter thrombosis, deep vein thrombosis, pulmonary thromboembolism, and thrombotic cerebrovascular accident.

Statistical Analyses

Continuous variables were shown as the mean ± standard deviation and categorical variables were presented as percentage. For comparisons between different groups, the independent sample *t* test and the Mann-Whitney U test were used, where appropriate. Correlation analyses for determination of associations between variables were done using the Spearman or Pearson correlation coefficients. Linear regression analysis was performed for defining the independent predictors of MMP-2 and MMP-9. Statistical analysis was performed using the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA). *P* values less than .05 were considered significant.

RESULTS

Participants

The mean age of the patients and controls were 13.93 ± 4.81 years (range, 7.0 to 19.5 years) and 13.08 ± 4.36 years (range, 6.5 to 19.5 years), respectively. The details of demographic data of the study participants are shown in Table 1. Among the patients, 26 (84%) were on hemodialysis and 5 (16 %) were on peritoneal dialysis. The causes of ESRD in the patients were as follows: kidney cystic diseases (42%), focal segmental glomerulosclerosis (29%), tubulointerstitial disease (13%), chronic glomerulonephritis (9.5%), and congenital anomaly of kidney and urinary tract (6.5%).

Matrix Metalloproteinases, Endothelial Dysfunction Markers, and Biochemical Parameters

Compared with the controls, the patients had significantly higher levels of MMP-2 (166.25 ± 26.88 ng/mL versus 126.66 ± 31.43 ng/ml; $P < .001$) and MMP-9 (347.41 ± 104.01 versus 277.77 ± 168.68 ng/mL; $P = .01$). The mean of soluble E-selectin was significantly higher in the patients (60.58 ± 18.04 ng/mL versus 48.72 ± 20.01 ng/mL; $P = .01$). The mean of FMD (4.62 ± 4.16% versus 6.59 ± 2.29%; $P = .005$) was significantly lower in the patients than

Table 1. Demographic Data of Children With End-stage Renal Disease (ESRD) and Controls*

Characteristic	Children With ESRD (n = 31)	Controls (n = 18)	*P*
Sex			
Female	19	10	
Male	12	8	.92
Age, y	13.93 ± 4.81	13.08 ± 4.36	.54
Weight, kg	31.37 ± 11.16	46.40 ± 16.52	< .001
Height, cm	131.38 ± 20.82	146.27 ± 15.04	.01
Body mass index, kg/m^2	17.81 ± 3.62	21.07 ± 5.01	.01
Body mass index, Z score	-0.88 ± 1.61	0.44 ± 1.24	.004
Systolic blood pressure, mm Hg	120.70 ± 20.67	101.11 ± 19.52	.02
Systolic blood pressure, Z score	1.06 ± 1.24	-0.29 ± 1.31	.001
Diastolic blood pressure, mmHg	72.48 ± 20.61	58.05 ± 10.02	.008
Diastolic blood pressure, Z score	0.70 ± 1.36	-0.34 ± 0.92	.006

*Values are mean ± standard deviation or frequency.

the controls. The level of MMP-2 (165.05 ± 24.99 ng/mL versus 144.62 ± 36.67 ng/mL; *P* = .04) was higher in those with hypertension than those with normal blood pressure; but the level of MMP-9 was not significantly different between the participants with and without hypertension. Table 2 presents the details of biochemical and endothelial markers in the patients and controls.

Correlation Analysis

In correlation analyses, MMP-2 was positively correlated with SBP, DBP, MMP-9, soluble E-selectin, BUN, creatinine, triglyceride, cholesterol, LDLC, serum phosphorus, calcium-phosphorus product, and PTH. Also, MMP-2 was inversely correlated with BMI, FMD, hemoglobin, and HDLC. Correlation analyses also revealed that MMP-9 was positively correlated with MMP-2, soluble E-selectin, BUN, phosphorus, calcium-phosphorus product, PTH, and albumin and negatively correlated with BMI and HDLC. Also, soluble E-selectin had a positive correlation with SBP (r = 0.3; *P* = .03) and DBP (r = 0.45; *P* = .001). The FMD was negatively correlated with SBP (r = - 0.32; *P* = .02). The details of correlation analyses of the studied variables are presented in Table 3.

Linear Regression Analyses

In linear regression analysis, the following variables were set as independent predictors

Table 2. Biochemical and Endothelial Function Parameters of Children With End-stage Renal Disease (ESRD) and Controls*

Parameter	Children With ESRD (n = 31)	Controls (n = 18)	*P*
Matrix metalloproteinase-2, ng/mL	166.25 ± 26.88	126.66 ± 31.43	< .001
Matrix metalloproteinase-9, ng/mL	347.41 ± 104.01	277.77 ± 168.68	.01
Soluble E-selectin, ng/mL	60.58 ± 18.04	48.72 ± 20.01	.01
Flow-mediated dilatation, %	4.62 ± 4.16	6.59 ± 2.29	.005
Hemoglobin, g/dL	9.8 ± 0.91	12.68 ± 0.78	< .001
Blood urea nitrogen, mg/dL	54.90 ± 12.78	12.22 ± 2.18	< .001
Creatinine, mg/dL	6.66 ± 0.93	0.63 ± 0.18	< .001
Triglyceride, mg/dL	162.45 ± 128.12	62.55 ± 17.06	< .001
Cholesterol, mg/dL	170.32 ± 38.14	162.05 ± 20.13	.16
Low-density lipoprotein cholesterol, mg/dL	95.80 ± 26.59	84.05 ± 2.07	< .001
High-density lipoprotein cholesterol, mg/dL	42.38 ± 8.89	49.66 ± 3.02	< .001
Phosphorus, mg/dL	5.67 ± 1.58	2.70 ± 0.25	< .001
Calcium, mg/dL	8.26 ± 1.27	8.88 ± 0.33	.01
Calcium-phosphorus product, mg^2/dL^2	46.80 ± 15.36	24.03 ± 2.42	< .001
Parathyroid hormone, pg/mL	391.13 ± 242.65	45.77 ± 10.55	< .001
Albumin, g/dL	3.93 ± 0.76	4.43 ± 0.65	.02

*Values are mean ± standard deviation.

Table 3. Correlations Between Matrix Metalloproteinases (MMPs) and Other Variables

Variable	MMP-2		MMP-9	
	r	*P*	r	*P*
Age, y	-0.07	.61	0.03	.83
Body mass index, kg/m^2	-0.29	.04	-0.33	.02
Body mass index, Z score	-0.28	.04	-0.17	.22
Systolic blood pressure, mm Hg	0.35	.01	0.14	.33
Systolic blood pressure, Z score	0.35	.01	0.17	.22
Diastolic blood pressure, mmHg	0.31	.02	0.15	.28
Diastolic blood pressure, Z score	0.33	.01	0.17	.22
Matrix metalloproteinase -9, ng/mL	0.36	.01	…	…
Soluble E-selectin, ng/mL	0.48	< .001	0.27	.04
Flow-mediated dilatation, %	-0.29	.04	-0.18	.19
Hemoglobin, g/dL	-0.31	.02	-0.27	.05
Blood urea nitrogen, mg/dL	0.43	.002	0.24	.09
Creatinine, mg/dL	0.51	.003	0.22	.12
Triglyceride, mg/dL	0.33	.02	0.12	.41
Cholesterol, mg/dL	0.29	.04	-0.23	.1
Low-density lipoprotein cholesterol, mg/dL	0.43	.002	-0.07	.61
High-density lipoprotein cholesterol, mg/dL	-0.30	.03	-0.33	.01
Phosphorus, mg/dL	0.46	.001	0.38	.007
Calcium, mg/dL	-0.15	.28	-0.15	.3
Calcium-phosphorus product, mg^2/dL^2	0.42	.002	0.31	.02
Parathyroid hormone, pg/mL	0.48	< .001	0.36	.01
Albumin, g/dL	0.16	.38	0.37	.03

of MMP-2: SBP, SBP (Z score), DBP (Z score), soluble E-selectin, hemoglobin, BUN, creatinine, triglyceride, cholesterol, HDLC, phosphorus, calcium-phosphorus product, and PTH. Also, predictors of MMP-9 were as follows: BMI, soluble E-selectin, phosphorus, and calcium-phosphorus product. Information about linear regression analysis are presented in Table 4.

Thrombotic Incidents

The investigation of medical records of the patients revealed that 6 (19.3 %) patients had

Table 4. Predictors of Matrix Metalloproteinases Measured by Linear Regression Analysis

Predictors	B Coefficient	Constant Term	Standard Error	Adjusted R^2	*P*
Matrix metalloproteinase-2					
Systolic blood pressure, mm Hg	0.58	84.90	31.99	0.12	.007
Systolic blood pressure, Z score	10.11	145.95	31.40	0.16	.003
Diastolic blood pressure, Z score	8.68	148.94	32.62	0.09	.01
Soluble E-selectin, ng/mL	0.74	109.69	31.34	0.16	.002
Hemoglobin, g/dL	-8.11	239.91	31.87	0.15	.006
Blood urea nitrogen, mg/dL	0.70	124.24	30.49	0.20	.001
Creatinine, mg/dL	5.79	125.92	29.71	0.24	< .001
Triglyceride, mg/dL	0.15	132.87	30.11	0.22	< .001
Cholesterol, mg/dL	0.3	100.78	33.12	0.06	.04
High-density lipoprotein cholesterol, mg/dL	-1.43	216.45	32.57	0.09	.01
Phosphorus, mg/dL	8.33	113.51	30.60	0.20	.001
Parathyroid hormone, pg/mL	0.04	140.08	32.70	0.08	.02
Calcium-phosphorus product, mg^2/dL^2	0.78	121.36	32.01	0.12	.007
Matrix metalloproteinase-9					
Body mass index, kg/m^2	-9.9	511.57	127.96	0.09	.02
Soluble E-selectin, ng/mL	1.92	213.81	130.17	0.05	.04
Phosphorus, mg/dL	21.63	222.70	128.88	0.07	.03
Calcium-phosphorus product, mg^2/dL^2	2.53	224.30	128.78	0.07	.02

Table 5. Matrix Metalloproteinases, Endothelial Dysfunction Markers, and Thrombotic and Antithrombotic Factors in Patients With and Without History of Thrombotic Events

Variable	All Patients (n = 31)	Patients With Thrombotic Events (n = 6)	Patients Without Thrombotic Events (n = 25)	*P*
Matrix metalloproteinase-2, ng/mL	166.25 ± 26.88	148.33 ± 34.88	170.56 ± 23.45	.41
Matrix metalloproteinase-9, ng/mL	347.41 ± 104.01	365.00 ± 47.22	343.20 ± 113.86	.67
Soluble E-selectin, ng/mL	60.58 ± 18.04	68.50 ± 23.20	58.68 ± 16.59	.36
Flow-mediated dilatation, %	4.62 ± 4.16	3.58 ± 2.07	4.88 ± 4.52	.30
Homocysteine, μmol/L	11.54 ± 4.52	12.16 ± 3.71	11.39 ± 4.74	.41
Fibrinogen, mg/dL	327.70 ± 108.32	313.50 ± 128.53	331.12 ± 105.65	.60
Protein C, %	73.89 ± 14.68	58.33 ± 8.35	77.62 ± 13.42	.002
Protein S, %	55.29 ± 13.45	38.33 ± 11.14	59.36 ± 10.55	.001

thrombotic incident that included central venous catheter thrombosis in 2 (6.4%), pulmonary thromboembolism in 3 (9.6%), and thrombotic cerebrovascular accident in 1 (3.2%). The mean levels of MMP-2, MMP-9, soluble E-selectin, FMD, homocysteine, and fibrinogen were not significantly different between the patients with and without thrombotic incidents. The mean of activity of protein C and protein S were significantly lower in the patients with thrombotic events. Table 5 presents the mean levels of studied variables in patients with and without thrombotic events.

DISCUSSION

In this study, we determined the associations of MMP-2, MMP-9, with markers of endothelial dysfunction, several traditional CVD risk factors, and kidney failure-related CVD risk factors in children with ESRD. We also evaluated the association of the study variables with the thrombotic events in our sample. As the traditional CVD risk factors such as smoking, obesity and diabetes mellitus are less common causes of CVD in children with ESRD,[1,2,15] our study mainly focused on the on emerging risk factors (markers of endothelial dysfunction) and the kidney failure-related risk factors. Interestingly, it should be noted that the traditional CVD risk factors like diabetes mellitus, smoking, and obesity can influence the endothelial function,[13] and hence, they can be considered as confounding factors when evaluating the role of endothelial dysfunction in the development of CVD. However, these confounding factors are very rare in children, and therefore, we were able to better evaluate the associations of endothelial dysfunction with CVD in our study.

In present study, the levels of MMP-2 and MMP-9 were significantly higher in the patients than the controls. This observation is comparable with the previous studies of the field, although some controversies exist in the literature. In 3 studies on children with CKD or ESRD, the levels of MMP-2 and MMP-9 were higher in patients,[22-24] but in one study, the level of MMP-9 was not different between the patients and the controls.[25] These discrepancies might be due to differences in epidemiological features, methodological approaches, and research settings used across the studies.[20]

Hypertension is a common problem in children with ESRD. In addition to the traditional etiologies of hypertension like volume overload and renin-angiotensin activation pathway, there are some newly discovered etiologies including endothelial dysfunction, hyperparathyroidism, and sympathetic activation.[29] Also, it is demonstrated that MMP-2 anf MMP-9 may play important roles in the development of hypertension via alterations in extracellular matrix.[30] In our study, significant correlations were found between markers of endothelial dysfunction and SBP and DBP, which indicated the role of endothelial dysfunction in the development of hypertension in these patients. In our study, the level of MMP-2 was higher in those with hypertension. Furthermore, positive correlations between MMP-2 and both SBP and DBP were found. However, we did not find similar correlations with MMP-9.

Endothelial dysfunction is an emerging risk factor for CVD in children with ESRD.[1] In our study, we showed significant correlations between MMP-2, MMP-9, and markers of endothelial dysfunction. In addition, we showed that soluble E-selectin, as a well-known marker of endothelial dysfunction, is a predictor of MMP-2. In one study which was conducted on children with ESRD, Musial and Zwolinska showed that soluble E-selectin was a

predictor of MMP-2 and MMP-9.[24] Comparably, in our study, we found similar results only for MMP-2, but not for MMP-9.

The roles of MMP-2 and MMP-9 in the pathogenesis of CVD in patients with CKD were evaluated in some studies. Peiskerova and colleagues showed that the level of MMP-2 was higher in patients with a history of CVD, but they did not find similar results for MMP-9.[19] In a study on children with CKD, Musial and Zwolinska found no correlation between MMP-2, MMP-9, and lipid profile variables.[24] However, in our study we showed significant correlations between MMP-2 and cholesterol, triglyceride, LDLC, and HDLC, and also we found correlations between MMP-9 and HDLC. In fact, in our study we showed the relationship between MMP-2, MMP-9, and several traditional CVD risk factors and this association can be helpful for evaluating the role of MMP-2 and MMP-9 in CVD progression in children with ESRD.

High serum levels of phosphate and calcium-phosphorus product and high levels of PTH are suggested as causes of arterial stiffness and medial calcification of vessels in patients with ESRD.[1,31] In the present study, we indicated positive correlations between MMP-2, MMP-9, and phosphorus, PTH and calcium-phosphorus product. In the study by Peiskerova and colleagues, the authors reported a correlation between MMP-2 and phosphorus, but they could not find a correlation between MMP-2 and PTH.[19] Chung and coworkers showed correlations of summation of MMP-2 and MMP-9 activities with phosphorus and PTH in diabetic patients with CKD.[32] Such findings can elucidate the pathophysiological aspects of arterial stiffness in children with ESRD. In several studies on adults with CKD, correlations between MMP-2, MMP-9, and the carotid intima-media thickness, as an indicator of subclinical atherosclerosis, were well-established.[14-16,18,21,33] Therefore, we suggest future studies on carotid intima-media thickness and MMPs for establishing the associations of MMP-2, MMP-9, and atherosclerosis in children.

Thrombotic events are common in adults with ESRD.[6] In this study, we showed that thrombotic events were also not uncommon in children with ESRD. At the present time, the studies on thrombosis events in children with ESRD are limited to vascular access thrombosis,[26,27,34] but we evaluated all common thrombotic events in our analyses. Among the identified risk factors of thrombotic events, we showed that protein C and S (antithrombotic molecules) are lower in patients with thrombotic incidents. In our study, FMD was lower and soluble E-selectin were higher in patients with history of thrombosis, but these variables did not reach to a significant threshold which was probably due to our small sample size. Consistent with our results, Fadel and coworkers showed that children with AV fistula thrombosis have higher level of soluble E-selectin and indicated the role of endothelial dysfunction in the pathogenesis of thrombotic events in ESRD patients.[34] In a study on patients with AV fistula thrombosis, it was shown that the expression of MMP-2 was not different between patients with and without AV fistula thrombosis.[35] More studies are needed to evaluate the role of these MMPs in the development of thrombosis in patients with ESRD.

The main limitation of our study was our relatively small sample size which might affect the results, especially those related to the thrombotic events as some analyses did not reach to a significant threshold.

CONCLUSIONS

In this study we determined the associations of MMP-2 and MMP-9 with markers of endothelial dysfunction and several traditional and uremia-related CVD risk factors in children with ESRD, but we did not find associations between these two MMPs and thrombotic events in these patients. Future studies with a cohort design and a larger sample size are suggested to shed more light in this topic.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Amin Abedini, MD
Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Hezar Jerib St, Postal Code: 81746-73695, Iran
Tel: +98 913 289 0262
Fax: +98 31 4261 3636
E-mail: amin69.med@gmail.com

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