International Journal of Cardiology Hypertension 4 (2020) 100025

Contents lists available at ScienceDirect

International Journal of Cardiology Hypertension

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-hypertension/

Research Paper

Matrix metalloproteinase −2, −9 and arterial stiffness in children and adolescents: The role of chronic kidney disease, diabetes, and hypertension

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ARTICLE INFO

Keywords:
Matrix metalloproteinase
Pulse wave velocity
Chronic kidney disease
Diabetes
Hypertension
Children

ABSTRACT

Background and aims: Matrix metalloproteinases (MMPs) may contribute to the pathogenesis of arterial stiffness inducing extracellular matrix remodeling. We aimed to compare MMP-2 and -9 levels in children with chronic kidney disease (CKD), type 1 diabetes (without chronic kidney disease) and healthy control and to investigate associations of MMPs levels with cardiovascular risk factors and markers of arterial stiffness.
Methods: The study population included 33 CKD, 18 type 1 diabetes patients, and 24 healthy controls. MMP-2, MMP-9, office blood pressure, pulse wave analysis, and carotid-femoral pulse wave velocity (cfPWV) measurements were performed.
Results: MMP-2 levels were higher in the CKD compared to the diabetes and control groups ($p < 0.05$). MMP-9 levels did not differ among groups. In hypertensive individuals logMMP-2 independently associated with PWV z score ($\beta = 0.744$, 95%CI 0.105 to 2.921, $p < 0.05$) after adjustment for age, sex, GRF, and phosphate levels. Creatinine levels correlated positively with MMP-2 in the CKD ($r = 0.39$, $p < 0.05$) and negatively in the diabetes group ($r = -0.72$, $p < 0.05$). Cholesterol levels correlated with MMP-2 in the diabetes group ($r = 0.70$, $p < 0.05$). Phosphate levels correlated with MMP-2 level in the control group ($r = 0.67$, $p < 0.05$). In multivariate regression model adjusted for age and sex, including phosphate and GRF as covariates, only phosphate predicted logMMP-2 levels ($\beta = 0.333$, 95%CI 0.060 to 0.671, $p < 0.05$).
Conclusions: MMP-2 associated with arterial stiffness in the presence of hypertension, while the role of MMP-9 is less clear in children with CKD or type 1 diabetes. Whether up-regulation of MMPs could predict poor outcomes in young high-risk patient groups need to be confirmed by future studies.

1. Introduction

Increased cardiovascular mortality in early adulthood arises significant concerns for the management of pediatric patients with CKD and type 1 diabetes [1,2]. Arterial alterations induced by disease-related factors during childhood and adolescence may lead to the early subclinical atherosclerotic cardiovascular disease that is evident at initial stages as accelerated for age arterial stiffness. Arterial stiffness has been reported increased in CKD and type 1 diabetes pediatric patients, and could be a critical pathway to early cardiovascular morbidity in these patient groups [3,4]. Non-invasive markers of arterial stiffness are promising tools for the assessment of cardiovascular risk in pediatric CKD and type 1 diabetes patients [5]. Carotid femoral pulse wave velocity (cfPWV) is considered the gold standard method of arterial stiffness and has been associated with glycemic control and the presence of comorbidities in type 1 diabetes [6], and Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) in CKD pediatric patients [7]. Other indices of arterial stiffness including, augmentation index (AIx) and pulse pressure (PP), have also been used in high-risk pediatric populations [8].

The pathogenetic mechanisms for cardiovascular atherosclerotic disease are complex and not fully elucidated. Matrix metalloproteinases (MMPs) may contribute to the pathogenesis of arterial stiffness inducing extracellular matrix remodeling thought alterations in vascular collagen and elastin content, proliferation, and migration of vascular smooth

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https://doi.org/10.1016/j.ijchy.2020.100025
Received 6 November 2019; Received in revised form 30 January 2020; Accepted 2 February 2020
Available online 6 February 2020

muscle cells [9]. Previous studies assessed the role of different MMPs on arterial structure in CKD and diabetes adult patients and provided inconsistent results [10–14]. However, data on the levels MMPs in pediatric patients and their associations with cardiovascular health are scarce [15,16]. Two previous studies in children with CKD found positive associations of MMP-2 and MMP-9 with biomarkers of stress response (Hsp90-alpha, anti-Hsp60), endothelial dysfunction (sE-selectin), and inflammation (high-sensitivity C-reactive protein) supporting their atherogenic role in childhood CKD [17,18].

The aims of the present study were: a) to assess the levels of MMP-2 and -9 in pediatric patients with CKD and type 1 diabetes (without CKD) in comparison to healthy controls b) to identify the role of CKD and diabetes per se in the arterial stiffening procedure, c) to investigate factors associated with MMP-2 and -9 levels and d) to examine for possible associations of MMP-2 and -9 with markers of arterial stiffness.

2. Patients and methods

2.1. Study population

The study population included pediatric patients with CKD stages 1–5 (24% stage 1, 22% stage 2, 22% stages 3–4, and 31% stage 5), and type 1 diabetes without microalbuminuria or other evidence of CKD followed up in the pediatric renal unit and pediatric diabetes outpatient clinic of the 1st Department of Pediatrics, located in a tertiary hospital. Patients were excluded if presenting with acute kidney injury, diabetic ketoacidosis or acute infection one month before the initiation of the study. The control group included healthy children and adolescents with similar age and sex, recruited from outpatient pediatric clinics during well-child visits who volunteered to participate in the study. The human research protocol was conducted according to the Helsinki declaration for clinical studies and approved by the constitutional review board (reference number 119494/2014). Informed consent to participate in the study was obtained from the parents and from the older (>12 years) children themselves.

2.2. Laboratory investigations

Blood samples were obtained after overnight fast. Biochemical parameters were measured in all participants. Estimated glomerular filtration rate (GFR) was calculated according to Schwartz formula: GFR (ml/min/1.73 m^2) = K x Ht ÷ Pcr where K = constant for different ages, 0.55 for children 2–12 years and females13-21 years and 0.70 for males 13–21 years, Ht = height in cm, and Pcr = plasma creatinine [19]. Plasma creatine measurements were performed in the hospital's central biochemical laboratory using the Jaffe method.

Blood samples collected to serum separator tubes, allowed to clot at room temperature and within 1 h of collection, centrifuged at 1500 g for 10 min at 4 °C. Supernatant serum removed aliquot and stored at −70 °C. Commercially available enzyme-linked immunosorbent assay (ELISA) was used for MMP-2 and MMP-9 serum levels measurement, according to the manufacturer's instructions (R&D Systems Inc., Minneapolis, USA). Total MMP-2and 92 kDa pro-and 82 kDa acVve forms were measured, but not the 65 kDa form for MMP-9. All samples were measured in duplicates. Allintra assay precision coefficients of variation were <10%. R2 values for all calibration curves were over 0.98. The lower limit of detection was 0.033 ng/mL and 0.156 ng/mL for MMP-2 and MMP-9, respectively.

2.3. Office BP measurement

Office BP was measured 3 times after 5 min of rest with the participants sited by a mercury sphygmomanometer. The appropriate size cuff was used according to the published guidelines [20]. The mean of the 3 office BP reading was used for the analysis. Hypertension was defined as BP greater than or equal to the 95th percentile by age, sex, and height, or ≥140/90 mmHg for adolescents older than 16 years [20].

2.4. Pulse wave velocity and pulse wave analysis

Carotid femoral pulse wave velocity and AIx75 were measured with the SphygmoCor XCEL device (software version 1.2, AtCor Medical, Australia), according to previous published guidelines [21]. The device has been previously validated for non-invasive measurement of cfPWV and central systolic pressure (cSP) in children [22]. cfPWV was calculated according to the equation PWV = (0.8 x D(m)/t (s)), where t denotes the transit time of the arterial pulse along the distance, and D the distance assimilated to the surface between the recording sites. Measurements were performed in supine position at the right carotid and femoral arteries. Two sequential recordings were obtained for each participant. Speaking and sleeping were avoided during measurements. Height adjusted cfPWV z score values were calculated [23]. Central systolic pressure and AIx75 were derived from PWA analysis using oscillometry, with the participants in seated position, their back and arm supported during the measurement. Appropriate cuff size according to participant's arm circumference was selected among three different cuff sizes available by the manufacturer (small adult 17–25 cm, adult 23–33 cm, large adult 31–40 cm).

2.5. Statistical analysis

The IBM SPSS 24.0 (SPSS Inc, Chicago, Illinois, USA) statistical package was used to analyze the data. We hypothesized a 200 ± 180 ng/dl difference in MMPs between CKD and controls or diabetes patients based on previous studies [11,17]. A sample size of 18 individuals in each group has been calculated to have 0.90 power with a = 0.05.

Standard descriptive statistics, one-way anova or non-parametric methods were used as appropriate for the comparison between the groups. The correlation analysis was performed using Spearman's test for non-normal distribution. Log-transformation was performed for variables with a skewed distribution (MMP-2 and MMP-9). Linear regression analysis was applied to examine associations between levels of logMMP-2, and logMMP- 9 on the one hand, and cardiovascular risk factors or arterial stiffness markers on the other. Analysis of covariance (ANCOVA) was used to examine the effect of MMP-2 and CKD group on PWV z score levels. Estimated marginal means after Bonferroni adjustment for multiple comparisons were further used to assess for differences on PWV z score levels between CKD groups. A p value less than 0.05 was regarded as statistically significant.

3. Results

3.1. Patients' characteristics

Demographic, clinical, and laboratory data are described in Table 1. The 3 groups did not differ in age and sex. MMP-2 levels were higher in the CKD group compared to controls ($p < 0.05$) (Fig. 1a). The diabetes group presented similar MMP-2 levels to the control group, and lower than those of the CKD group ($p = 0.05$) (Fig. 1b). MMP-9 levels did not differ among groups.

Arterial stiffness indices, PWV z score and AIx75 were higher in the CKD group compared to controls (Table 1). PWV z scores were also higher in the diabetes group, while AIx75 did not reach statistical significance. Arterial stiffness indices did not differ between the CKD and the diabetes group.

We further divided CKD patients in 2 groups early stage group (stage 1–2) and advance stage (stage 3–5). MMP-2 levels were higher in the advanced CKD group, but MMP-9, and PWV levels did not differ between the groups. In ANCOVA analysis with dependent variable PWV z score and independent variables age, sex, phosphate, CKD stage group (early

Table 1
Demographic, clinical and laboratory characteristics of the population.

	CKD (n = 33)	Diabetes (n = 18)	Controls (n = 24)
Age (years)	13 (9–15)	16 (11–16.37)	12 (7–16)
Sex (male/%)	18 (42.9)	13 (31)	11 (26.2)
Height (cm)	147.2 ± 22.0	160.5 ± 22.5	148.9 ± 23.9
Height z score	0.04 (−1.03 to 0.36)	0.04 (−0.48 to 1.65)	1.05 (0.2–1.70)[a]
BMI (kg/m^2)	18.75 ± 3.00	20.18 ± 4.38	19.98 ± 3.89
BMI z score	0.33 (−0.65 to 1.11)	0.29 (−0.20 to 1.66)	1.11 (0.52–1.90)
Office SBP (mmHg)	119.3 ± 12.9	117.8 ± 11.4	116.4 ± 11.4
Office DBP (mmHg)	73.7 ± 13.7	71.5 ± 7.5	73.2 ± 8.5
Office HR (beats/min)	88.1 ± 14.3	90.1 ± 12.7	88.5 ± 17.4
Office SBP z score	1.25 ± 1.39	0.73 ± 0.92	0.95 ± 1.06
Office DBP z score	0.95 ± 1.43	0.45 ± 1.02	0.67 ± 1.33
cSP (mmHg)	105.5 ± 13.5	102.6 ± 8.5	101.5 ± 8.4
cSP z score	0.44 (−1.22 to 2.51)	−0.42 (−0.7 to 0.85)	0.20 (−0.67 to 1.79)
cPP (mmHg)	29.9 ± 13.5	29.3 ± 7.4	26.6 ± 6.1
AIx75 (%)	17.6 ± 17.5	13.1 ± 14.6	2.4 ± 15.7[b]
PWV (m/sec)	6.93 ± 1.11	6.99 ± 1.07	5.96 ± 1.24[a]
PWV z score	2.62 ± 1.92	2.27 ± 0.88	1.33 ± 0.92[c]
HbA1c (%)	5.2 ± 0.57	8.22 ± 2.16[d]	NA
Total Cholesterol (mg/dl)	173.0 ± 49.4	150.4 ± 29.7	131.7 ± 14.2
Phosphate (mg/dl)	4.85 ± 1.23	4.63 ± 0.52	4.10 ± 0.78
Uric acid (mg/dl)	6.51 ± 1.87	2.40 ± 1.40	4.14 ± 1.60
Serum albumin (mg/dl)	4.25 ± 0.87	4.15 ± 0.91	4.73 ± 0.05
Creatinine (mg/dl)	2.07 ± 1.44	0.65 ± 0.06[c]	0.79 ± 0.22[c]
eGFR (ml/min/1.73 m^2)	49.9 ± 33.5	139.6 ± 35.6[c]	114.6 ± 20.9[c]
Duration of disease (years)	8.36 ± 3.45	6.77 ± 3.55	NA

Values are present as mean ± SD or median (IQR). [a] $p < 0.05$ versus CKD and DM group, [b] $p < 0.05$ versus CKD group, [c] $p < 0.005$ versus CKD and DM group, [d] $p < 0.005$ versus CKD group.
Abbreviations: SBP, systolic blood pressure, DBP, diastolic blood pressure, HR, heart rate, cSP, central systolic pressure, AIx75, augmentation index, PWV, pulse wave velocity, eGFR, estimated glomerular filtration rate by Schwartz equation.

vs. advanced) and logMMP2 we did not find any significant effect of CKD stage group on PWV z score. Furthermore, performing Bonferroni analysis for multiple comparisons, PWV z score estimated marginal means did not differ between early and advanced CKD stage group after adjustment for age, sex, phosphate, and logMMP2 (2.19, 95%CI 0.22–4.16 versus 3.29, 95%CI 1.25–4.86, p = 0.37).

3.2. Associations of MMPs with biochemical parameters and arterial stiffness indices

The associations of MMPs with clinical and biochemical parameters are presented in Table 2. MMP-2 and MMP-9 levels did not correlate with BMI z score, peripheral office BP parameters, as well as central systolic pressure in the CKD and diabetes groups (data not shown). Creatinine levels correlated positively with MMP-2 in the CKD group (r = 0.39, $p < 0.05$), and negatively in the diabetes group (r = −0.72, $p < 0.05$). Cholesterol levels also correlated with MMP-2 in the diabetes group (r = 0.70, $p < 0.05$). Phosphate levels correlated with MMP-2 level in the control group (r = 0.67, $p < 0.05$). Duration of disease was also not associated with MMPs levels in the diabetes or the CKD group.

In simple linear regression models logMMP-2 increased linearly with creatinine, phosphate, and cholesterol levels, and negatively with GFR (Table 3) in all study population subjects. In a multivariate regression model adjusted for age and sex, including phosphate and GRF as covariates, only phosphate significantly predicted logMMP-2 levels (β = 0.333, 95%CI 0.060 to 0.671, $p < 0.05$).

MMP-2 and MMP-9 levels did not correlate with PWV z score and AIx in the patient groups. However, in those with hypertension (n = 11) logMMP-2 independently associated with PWV z score (β = 0.744, 95%CI 0.105 to 2.921, $p < 0.05$) after adjustment for age, sex, GRF and phosphate levels.

4. Discussion

In the present study we found higher MMP-2 levels in pediatric patients with CKD, while MMP-2 levels in type 1 diabetes without CKD were similar to those of the control group. MMP-2 linearly increased with phosphate levels in our population suggesting a possible role of phosphate homeostasis in the arterial stiffness pathogenesis. Furthermore, in patients with co-existing hypertension MMP-2 associated with increased cfPWV independently of possible confounders providing evidence of a role of MMP-2 in the pathogenesis of arterial stiffening in hypertensive subjects.

Previous studies have assessed the levels of different MMPs in CKD and diabetes adult patients. In a pooled analysis of 3 cohort studies, MMP-1, -2, and -3 associated positively with markers of arterial stiffening, MMP-3 with cfPWV, MMP-2 with brachial 24 h PP, and MMP-1 and MMP-2 with office PP [12]. MMP-2 upregulation has been suggested as a key process to explain the abnormalities in arterial structure and function seen in CKD. MMP-2 was inversely associated with GFR in our study including pediatric patients with different CKD stages. Chung et al., found increased levels of MMP-2 in CKD patients and reported a

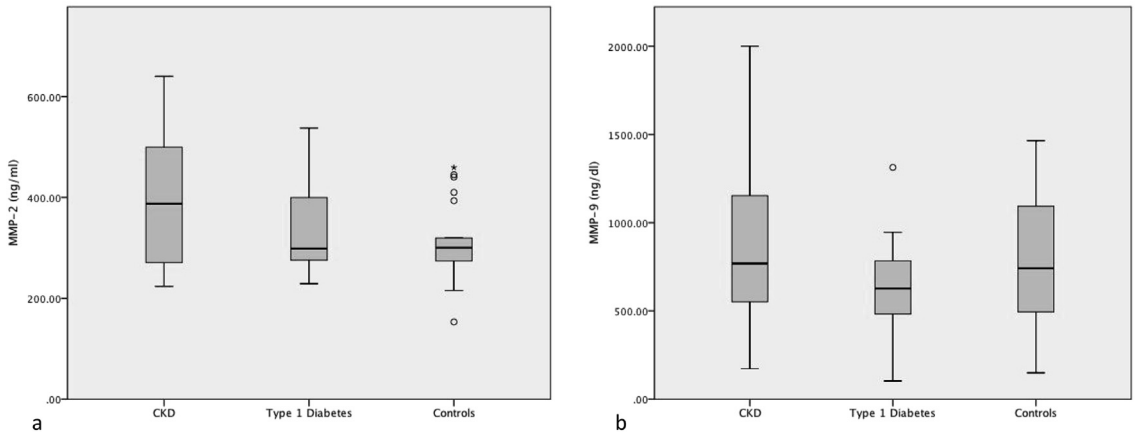

Fig. 1. MMPs levels in the groups: a) Median MMP-2 levels were 387.6 (IQR 270.2 to 507.2) in the CKD, 298.7 (IQR 269.55 to 400.0) in the diabetes, and 300.3 (IQR 269.5 to 319.7) ng/mL in the control group ($p < 0.05$ CKD vs. control group, $p < 0.05$ CKD vs. diabetes group), b) Median MMP-9 levels were 769.0 (IQR 530.5 to 1183.5) in the CKD, 628.0 (IQR 478.0 to 789.75) in the diabetes, and 741.0 (IQR 474.0 to 1114.0) ng/mL in the control group.

Table 2
Correlations between MMP-2 and demographic, clinical and biochemical parameters. No significant associations were found for MMP-9.

	SBP z score	DBP z score	BMI z score	Cr	P	Total Chol	HbA1c
MMP-2							
CKD	r = −0.01	r = −0.06	r = −0.30	**r = 0.39**	r = 0.26	r = 0.19	r = −0.70
	$p = 0.95$	$p = 0.71$	$p = 0.10$	**$p = 0.022$**	$p = 0.13$	$p = 0.33$	$p = 0.18$
Diabetes	r = 0.03	r = 0.28	r = 0.03	**r = -0.72**	r = 0.09	**r = 0.70**	r = 0.24
	$p = 0.88$	$p = 0.28$	$p = 0.90$	**$p = 0.018$**	$p = 0.81$	**$p = 0.016$**	$p = 0.37$
Controls	r = 0.24	r = 0.26	r = 0.19	r = 0.02	**r = 0.67**	r = 0.50	
	$p = 0.27$	$p = 0.23$	$p = 0.36$	$p = 0.91$	**$p = 0.012$**	$p = 0.66$	

Values in bold represent statistically significant spearman correlations.
Abbreviations: SBP, systolic blood pressure, DBP, diastolic blood pressure, Cr, creatinine, P, phosphate, Chol, cholesterol.

Table 3
Simple linear regression associations between logMMP-2 and biochemical parameters.

Variable	β	95% CI	*p*
logMMP2			
Phosphate (mg/dl)	0.378	0.125–0.644	<0.005
Cholesterol (mg/dl)	0.388	0.097–0.714	<0.05
Creatinine (mg/dl)	0.294	0.053–0.554	<0.05
eGFR (ml/min/1.73 m^2)	−0.439	00.724-(-0.209)	0.001

Abbreviations: β, standardized regression coefficient indicates increase in logMMP-2 per 1 SD increase in phosphate, cholesterol, creatinine, eGFR, CI confidence interval.

2-fold greater activity in dialysis ones. Arterial stiffness assessed by PWV and medial calcium deposition was positively related to MMP-2 activity, while reduced endothelium-dependent vasodilatation was negatively related [10]. In the same study the arteries in dialyzed patients harvested during transplantation procedure showed pronounced elastic fiber degradation, and a negative correlation between the ratio of external elastic lamina to media and MMP-2 activity. In another study by the same group combined MMP-2 and MMP-9 activity in arteries of diabetic CKD patients was greater and associated with phosphate levels [11].

In the present study phosphate associated with MMP-2 levels independently of GFR, and MMP-2 in turn predicted arterial stiffness in the hypertensive pediatric patients. The role of phosphate as a vascular toxin has been previously described. Phosphate levels present linear association, even within normal limits, with the incidence of cardiovascular disease in the community, and independently predicted cardiovascular mortality in CKD adult patients [24–26]. MMPs are secreted by smooth muscle cells and inflammatory cells in the adventitia or media leading to degradation of medial elastic fiber [9]. MMP-2 may also release transforming growth factor β from the extracellular matrix inducing increase in fibroblast production [27]. Inflammatory and hemodynamic factors in CKD and diabetes, including oxidative stress, hyperphosphatemia, and upregulation of cytokines, have been described to promote MMP-2 activation [9,14,28]. Moreover, hyperphosphatemia may accelerate calcification by inducing release of matrix vesicles and apoptosis [29]. Finally, increases MMP-2 and -9 have been reported to increase angiostatin production, an angiogenic inhibitor, resulting in impaired angiogenesis [11].

The absence of evident kidney damage in our type 1 diabetes pediatric patients, despite the higher GFR suggesting a hyperfiltration stage, may explain the low MMP-2 values and the negative association with creatinine levels. The absence of microalbuminuria may also explain the lower levels of MMP-9 in the diabetes group. MMP-9 activity has been associated with resistant albuminuria, both in a diabetic rat model and in diabetes patients [30]. Similar to our findings one previous study showed low levels of urinary MMP-9 in type 1 diabetes pediatric patients without microalbuminuria [31].

Younger age and shorter exposure to disease factors compared to adult patients could explain the absence of correlation of cfPWV and MMP-2 or -9 in pediatric patients. Peeters et al., previously reported lack of association between MMP-9 and cfPWV in large diabetic cohorts [12]. In the presence of co-existing hypertension, as addictive hit evoking acceleration of vascular aging the relation with MMP-2 becomes evident even in children. We have previously demonstrated significant associations between hypertension and arterial stiffness in children and adolescents [8]. Of note, in the study by Chung et al., showing that MMP-2 and MMP-9 exacerbate stiffness in CKD and diabetes, all patients were hypertensive [10]. The authors also acknowledged the synergistic adverse effects of hypertension on vascular function that could enhance the observed differences attributed to CKD and diabetes.

MMPs are evolving as prognostic factors for cardiovascular morbidity and are considered as potential therapeutic targets [32]. MMP-2 could predict 5 years mortality in hemodialysis patients [33]. In coronary artery disease patients MMP-2 and -9 independently associated with non-diabetic kidney disease progression [34]. Peeters et al., showed that higher MMP-2 plasma levels in type 1 diabetes were significantly associated with higher incidence of cardiovascular events [HR 1.49 (95% CI 1.11; 1.99)] in a 12 years follow up study [35]. However, the predictive value of MMPs in pediatric patients needs to be examined by prospective studies.

The results of the present study should be interpreted taking into account several limitations. First, the study included a relatively small number of patients. The small number of patients in the subgroups could have limited our ability to detect statistical associations because of power to detect true differences of moderate magnitude and negative findings may reflect a type II error. However, we demonstrated statistically significant differences in biological and clinical biomarkers, and associations with key cardiovascular risk factors. Moreover, the cross-sectional study design does not allow to determine cause and effect, but only to describe the associations of MMPs in CKD, type 1 diabetes without CKD and controls. On the other hand, to our knowledge this is the 1st study comparing pediatric patients with CKD and type 1 diabetes without CKD. The absence of evident kidney damage in the diabetes group provides insights for the role of MMPs on cardiovascular risk in the early stages of disease. Detailed information on current drug treatments of the patients in the study were not available and the effects of any treatment on the associations described above could not assessed. Finally, the study included a wide range of CKD stages. However, the results did not change if either stage 1 or end stage renal patients were excluded from the analysis.

In conclusion, we described increased MMP-2 levels in CKD pediatric patients. Type 1 diabetes pediatric patients without microalbuminuria presented lower MMP-2 and MMP-9 levels than the CKD group. Declining GFR with lower kidney function in the CKD group presented positive association with MMP-2. The relatively high GFR levels in the diabetes group may suggest hyperfiltration as an early kidney effect that could explain the negative association of creatine with MMP-2 in this group. While MMP-2 may associate with arterial stiffness in the co-presence of hypertension, the role of MMP-9 is less clear in these risk patient groups. Whether up-regulation of MMP-2 or MMP-9 could predict poor outcomes in young CKD and type 1 diabetes pediatric patients need to be confirmed by future studies. The evidence for the associations of MMPs with well-known cardiovascular risk factors, especially phosphate and hypertension, may reinforce the role of preventive strategies to reduce modifiable risk factors in the high-risk pediatric patient.

Compliance with ethical standards

Disclosure of potential conflicts of interest

Funding: Procter and Gamble Company have supported this work with a research grant for the period 2014–2015.

Conflict of Interest: The authors declare that they have no conflict of interest.

Research involving human participants

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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