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Urinary procollagen III aminoterminal propeptide and β-catenin – New diagnostic biomarkers in solitary functioning kidney?

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ABSTRACT

Purpose: We aimed at evaluating urinary levels of procollagen III aminoterminal propeptide (PIIINP) and β-catenin and the relationship between these markers and clinical and laboratory variables in children with a solitary functioning kidney (SFK).

Patients and methods: The study group consisted of 98 (M/F: 62/36) children with an SFK with a median age of 8 years. An age-matched control group contained 54 healthy peers. Urinary levels of procollagen III aminoterminal propeptide and β-catenin were measured using a commercially available immunoassay kit.

Results: The urinary values of PIIINP (UPIIINP) were significantly increased in patients with SFK versus controls ($p < 0.01$). Our analysis revealed no significant differences in urinary β-catenin levels between the SFK patients and control subjects ($p > 0.05$). Only urinary PIIINP levels were correlated to renal function tests, such as serum creatinine, urea, uric acid, and estimated glomerular filtration rate ($p < 0.05$).

Conclusions: An increased urinary level of PIIINP may indicate early kidney impairment in children with SFK. Urinary β-catenin does not seem to play any important role as a marker of renal function in children with SFK. Further long-term studies are required in order to evaluate the clinical usefulness of these markers and their predictive value of chronic kidney disease (CKD) progression.

1. Introduction

A solitary functioning kidney (SFK) represents a particular entity in nephrology, requiring certain attention from the specialists. Studies on long-term outcomes of children with an SFK are rather controversial. SFK represents a challenge when renal impairment occurs.

In 1997, Brenner and Mackenzie [1] proposed that reduced nephron endowment might be a fundamental cause of essential hypertension and might also predispose to renal damage. The theory of glomerular hyperfiltration proposed by Brenner and Mackenzie [1] holds that functional adaptations to a reduction in renal mass include intrarenal vasodilation leading to elevated glomerular capillary pressure and hyperperfusion injury of glomeruli. This compensatory response to nephron loss leads to glomerular cell proliferation, macrophage infiltration, and the progressive accumulation of extracellular matrix components such as fibronectin, decorin, and several types of collagen including collagen type I and type III. This non-immunologic process can lead to ongoing injury to podocytes and glomerular microvasculature which leads to proteinuria, diffuse fibrosis, and progressive deterioration of renal function. Some other experimental studies provided indirect evidence of the glomerular hyperfiltration hypothesis in the pathogenesis and progression of renal disease, indicating that factors other than glomerular hyperfiltration likely contribute to the development of chronic kidney disease (CKD) [2,3].

Tubulointerstitial fibrosis is due to increased deposition of various extracellular matrix components. In a normal kidney, small amounts of collagen type III are expressed in the interstitial area, but this type of collagen remains undetectable in the glomeruli [4]. The expression of collagen type III in scarred kidneys, in contrast, is increased in the interstitium during the earliest stages of fibrosis, and procollagen III aminoterminal propeptide (PIIINP) accumulates in sclerotic glomeruli. During the processing of the procollagen before its deposition in the extracellular matrix, some of the procollagen with aminoterminal propeptides is cleaved and released in the extracellular matrix and fluids,

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including blood and urine. Circulating PIIINP levels have been shown to reflect the fibrotic process occurring during various pathologic conditions, such as liver diseases [5], systemic sclerosis [6], and vascular remodeling [7]. Certain studies have suggested that serum and urinary PIIINP (UPIIINP) levels may be useful in the assessment of renal fibrosis in the native as well as transplanted kidney [4,8].

Over the last few years, great emphasis has been placed on identifying Wnt/β-catenin unique target genes that are relevant to kidney injury and fibrosis. Chronic and progressive up-regulation of β-catenin appears to be a common pathologic feature in a wide variety of fibrotic CKD's such as obstructive nephropathy, diabetic nephropathy, remnant kidneys after a 5/6 nephrectomy, polycystic kidney disease, and chronic allograft nephropathy [9–11]. By manipulating the levels of β-catenin in animal models, studies have provided significant insight into the normal and pathogenic roles of β-catenin in kidney formation [12].

Despite these observations, the pathological role played by β-catenin in kidney diseases is poorly understood [13]. Little is known about its function in the kidneys of children. Whether it plays any role in regulating tissue damage or protection in the SFK is completely unknown. As β-catenin binds to E-cadherin and mediates epithelial adherent interaction, this prompted us to investigate its excretion in urine.

Recently, extensive research efforts have been directed at the discovery of novel biomarkers to detect injury prior to impairments of kidney function. Serum creatinine (sCr) is a poor marker of early renal damage because the serum concentration is greatly dependent on non-renal factors independent of kidney function (age, sex, diet, muscle mass, muscle metabolism, race, infection, tubular secretion, strenuous exercise, and hydration status) [14]. Lack of specificity and slow response to alterations in disease severity or treatment are primary reasons why sCr is an unsatisfactory biomarker for renal disease. Furthermore, rises in sCr occur long after renal injury has occurred. These numerous problems with creatinine limit its usefulness in both clinical practice and the development of new therapeutics.

We undertook a prospective study to assess the UPIIINP and β-catenin levels in patients with an SFK and evaluate whether there is any association between these markers and known parameters of renal function.

2. Patients and methods

The databases of the Department of Pediatrics and Nephrology, Medical University of Bialystok and Jagiellonian University Medical College, Cracow (Poland) were retrospectively queried for pediatric patients aged between 1 month and 18 years with an initial diagnosis of SFK, who were referred to the above mentioned departments between January 2014 and May 2016.

2.1. Identification of patients

Inclusion criteria were: age between 1 month and 18 years, and a congenital SFK identified by ultrasound and renal scintigraphy. Patients were excluded if they met any of the following criteria: unwillingness to complete family and personal health histories or allow storage of biological samples; clinical and laboratory signs of infection; use of medication that might influence renal function; a history of kidney abnormalities (e.g. scarring, hydronephrosis, known vesicouretheral reflux, presence of another urinary tract anomaly or glomerular disease in the solitary kidney), co-existing hepatobiliary or splenic disease, and any systemic disease.

2.2. Identification of controls

Inclusion criteria for controls were: males and females, aged 1 month – 18 years, who were attending the general pediatric nephrology outpatient clinic at the Department of Pediatrics and Nephrology, Medical University of Bialystok and/or the Jagiellonian University Medical College, Cracow (Poland).

Serum creatinine measurements, urine tests, and renal ultrasounds were performed in all children. All estimated results were within normal ranges for age and eGFR was within norms ($>$ 90 mL/min per 1.73 m^2).

We recruited 202 subjects who initially met the inclusion criteria, of whom 48 had one or more of the prespecified exclusion criteria. The final population consisted of 154 studied and control participants. The index test for estimated markers was missing in two subjects. Ultimately 152 participants, in whom both PIIINP and β-catenin were available, were analyzed.

Demographic and clinical data were assessed. A careful clinical history, including underlying comorbidities, and a physical examination were performed in all the children. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Blood pressure was measured using either a manual auscultatory or an automatic oscillometric device. High blood pressure was defined as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) values above the 95th percentile (z-score $>$ 1.65) adjusted for age, gender, and height [15]. GFR was assessed by the updated Schwartz formula – eGFR (mL/min/1.73 m^2) = 0.413 × [height in cm/sCr] [16]. The urinary albumin/creatinine ratio (ACR) was also calculated. Children and adolescents with urinary albumin/creatinine ratios between 30–300 μg/mg were considered to have microalbuminuria. Kidney overgrowth was calculated for every child, according to a standard formula and checked against reference charts [17]: ([individual renal length - 50th centile of renal length for age, gender, and side of the body]/ individual renal length) × 100%.

2.3. Urine sample collection and processing

On the first morning urine samples were collected during regular clinic visits. All samples were subsequently frozen at −80 °C.

UPIIINP ELISA was performed using a commercially available immunoassay kit (Wuhan EIAab Science Co., China) and expressed as picograms per milliliter (pg/mL). The intra-assay coefficient of variation was ≤4.5% and inter-assay coefficient of variation was ≤7.1%.

Urinary β-catenin ELISA was performed using a commercially available kit (Cloud-Clone Corp., China). Urinary β-catenin concentration was expressed as picograms per milliliter (pg/mL). The intra-assay coefficient of variation was ≤10% and inter-assay coefficient of variation was ≤12%.

Creatinine levels were measured in the same urine samples and urinary concentrations were normalized to urinary creatinine concentrations (UPIIINP/Cr, β-catenin/Cr).

2.4. Ethical issues

The study was approved by the Ethics Committees of the Medical University of Bialystok and Jagiellonian University Medical College, Cracow (Poland) (approval numbers: R-I-002/337/2015; R-I-002/346/2015).

2.5. Statistical analyses

All data were analyzed using SPSS Statistics 12.0 (StatSoft, Tulsa*,OK,* USA). The examination of the distribution normality of variables was done using the Shapiro-Wilk W test. The Student's *t*-test and Mann-Whitney *U* test were used for comparison of the two groups. A chi-*square test* was used to examine the association between categorical variables. Correlations were analyzed by Pearson's or Spearman's correlation tests, as appropriate. A $p < 0.05$ was considered as statistically significant. A Receiver Operating Characteristic (ROC) curve was used to determine the cut-off values of estimated markers that gave the best sensitivity and specificity. ROC curve analyses were established for assessing how well a marker is capable of discriminating between

Table 1
Clinical characteristics at presentation.

Variable	Patients n = 98	Controls n = 54	*p* value
Age, years	8.0 (5.3–13.0)	8.6 (4.0–13.0)	NS
Age at the time of diagnosis, years	5.0 (1.0–9.0)	–	–
Gender M/F	62/36	29/25	–
BMI z score	1.08 (0.5–1.53)	0.06 (−0.59 to 1.29)	0.0017
SBP, mmHg	106 (100–117)	102 (94–116)	NS
DBP, mmHg	66 (60–70)	65 (60–72)	NS
Kidney size, mm	104 (92–122)	–	–
Kidney overgrowth, %	21.5 (3.1–42.22)	–	–
Urea, mg/dL	26 (21–30)	27 (21–30)	NS
Uric acid, mg/dL	4.59 (3.67–5.15)	4.69 (3.9–5.12)	NS
eGFR, mL/min per 1.73 m^2	105.5 (97.81–116.52)	118.13 (103.44–142.18)	0.002
Microalbuminuria, mcg/mL	124.6 (32–217.3)	35.35 (19.6–79.5)	NS
ACR, mcg/mg	122.33 (19.29–225.37)	36.42 (22.23–76.74)	NS
PIIINP, pg/mL	205 (131–319)	137 (0–199.5)	0.002
PIIINP/Cr, pg/mg Cr	219.84 (94.71–550.51)	79.28 (0–184.86)	0.0008
β-catenin, pg/mL	0 (0–8.15)	0 (0–8.15)	NS
β-catenin/Cr, pg/mg Cr	0 (0–5.63)	0 (0–6.13)	NS

Median values (lower – upper quartile) of analyzed parameters.
BMI - body mass index; SBP - systolic blood pressure; DBP - diastolic blood pressure; eGFR - estimated glomerular filtration rate estimated using updated Schwartz formula; ACR - urinary albumin/creatinine ratio; PIIINP - procollagen III aminoterminal propeptide.

individuals who experience SFK and healthy individuals, as well as in identifying children with renal impairment (eGFR < 90 mL/min/1.73m^2) among patients with SFK.

3. Results

Clinical characteristics of the studied and control subjects are presented in Table 1. In the group with SFK, there were more boys as well as more SFK on the left side (66%). Age, blood pressure, serum creatinine, urea, and uric acid levels did not significantly differ among the groups ($p > 0.05$).

None of our patients had proteinuria in the morning urine samples. Microalbuminuria was diagnosed in 6 patients with SFK. At the time of diagnosis, eGFR < 90 mL/min per 1.73 m^2 was present in a total of 13% of the SFK patients.

Levels of UPIIINP were significantly increased when compared to the control group ($p = 0.02$; Table 1). Our analyses revealed no statistically significant differences in urinary β-catenin levels between the studied and control subjects (p > 0.05).

As shown in Table 2, urinary β-catenin/Cr significantly correlated only with age in a univariate analysis. Further tests were carried out to identify correlations of estimated markers with parameters of renal function. (Table 2; Fig. 1A–D) UPIIINP/Cr displayed positive correlation with serum creatinine (r = 0.2; p = 0.02) as well as negative correlation with eGFR (r = −0.24; p = 0.01). As with serum creatinine, the correlation of UPIIINP with other parameters of renal function (urea and uric acid) showed statistically significant relations ($p = 0.01$ and p = 0.02, respectively). A correlation was also found between SBP, DBP, and UPIIINP/Cr levels. Conversely, there was no association of any marker with height, weight, body mass index, z-score, or microalbuminuria. Furthermore, neither UPIIINP nor β-catenin levels correlated with compensatory overgrowth of the kidney.

Table 2
Significant correlations.

Item	r	p
Urinary PIIINP/Cr (pg/mg Cr) with:		
Serum creatinine, mg/dL	0.20	0.02
Serum urea, mg/dL	0.26	0.01
Serum uric acid, mg/dL	0.24	0.02
eGFR, mL/min/1.73 m^2	−0.24	0.01
SBP, mmHg	0.27	0.02
DBP, mmHg	0.24	0.04
Urinary β-catenin/Cr (pg/mg Cr) with:		
Age, years	0.16	0.04

PIIINP - procollagen III aminoterminal propeptide; eGFR - estimated glomerular filtration rate estimated using updated Schwartz formula; SBP - systolic blood pressure; DBP - diastolic blood pressure.

The factors that were found to have a significant correlation with UPIIINP/Cr (pg/mg Cr) in the single regression analyses were used as explanatory variables to create the multiple regression models. In multivariable analysis, only serum creatinine levels accounted for more than 32.74% of the variations in UPIIINP/Cr levels ($R = 0.3$; $p = 0.03$).

ROC analyses were performed in order to define the diagnostic efficiency of urinary PIIINP/Cr and β-catenin/Cr in identifying children with SFK among all examined children as well as in identifying children with renal impairment (eGFR < 90 mL/min/1.73m^2) among patients with SFK (Table 3). In the first analysis in children with SFK, the area under the curve (AUC) for UPIIINP/Cr was 0.672 and for β-catenin/Cr 0.496. In a subsequent analysis, we assessed the AUC for UPIIINP/Cr and β-catenin/Cr as biomarkers of renal impairment (eGFR < 90 mL/min/1.73m^2) which resulted in the AUC for urinary PIIINP/Cr and β-catenin/Cr being 0.641 and 0.583, respectively. The ROC's for UPIIINP/Cr and β-catenin/Cr and serum creatinine were compared in patients with eGFR < 90 mL/min/1.73m^2. No statistically significant differences between all three AUCs were found (Fig. 2).

ROC analyses for UPIIINP and β-catenin not corrected for urinary creatinine showed similar values.

4. Discussion

Children with an SFK form an important subgroup of congenital anomalies. However, the consequences for patients born with a „single kidney" are not clear. Precautions in the early phases of this condition and appropriate treatment play a critical role in the prevention of progression to CKD. It is of high clinical value to look for potential markers which may help identify patients with a high risk for disease progression [18].

Although ultrasound and scintigraphy are available for establishing the presence of SFK, correlation between histological findings and deterioration of renal function has been unsatisfactory. Moreover, it has been demonstrated that severe lesions may be present even in patients with a normal serum creatinine and eGFR. Therefore, more sensitive laboratory tests are required to screen for renal impairment in SFK.

We evaluated urinary PIIINP and β-catenin levels concomitantly in children with SFK with normal serum creatinine, comparing the results with clinical and laboratory parameters in order to assess the viability of these markers in clinical practice. No such study evaluating urinary PIIINP and β-catenin levels in pediatric SFK patients was found in the available literature.

The most interesting finding of this cross-sectional study is that urinary levels of PIIINP were higher in children with SFK. Moreover, there were significant correlations between urinary levels of PIIINP and serum creatinine, urea, uric acid, and eGFR. Another important finding is that urinary β-catenin levels in SFK children did not differ from values observed in healthy participants.

The progression of CKD is characterized histologically by progressive glomerulosclerosis and tubulointerstitial fibrosis. Such fibrosis is due to increased deposition of a wide range of extracellular matrix components within scarred kidneys [4]. Attempts to evaluate the role of circulating and urinary extracellular matrix components for the diagnosis of tissue fibrosis have been prompted by observations made in patients with hepatic fibrogenic diseases where changes in circulating

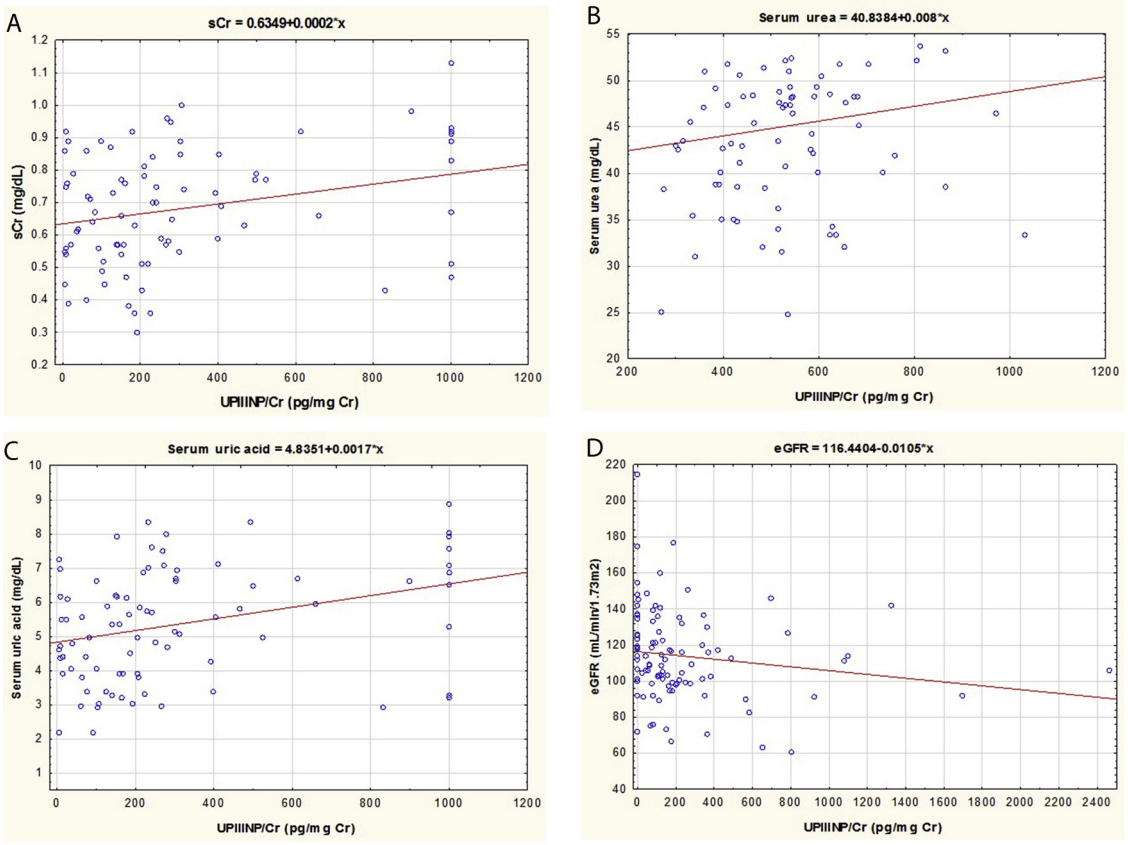

Fig. 1. Scatter plot for UPIIINP/Cr (pg/mg Cr) versus serum creatinine (A), urea (B), uric acid (C) and eGFR (D) levels in studied group.

Table 3
Receiver Operating Characteristic (ROC) analyses for urinary PIIINP/Cr and β-catenin/Cr (pg/mg Cr) levels in (A) children with SFK among all examined children, and (B) in children with impaired renal function (eGFR < 90 mL/min/1.73 m^2).

	AUC	*SE*	*−95%*	*+95%*
PIIINP/Cr (pg/mg Cr) **(A)**	0.672	0.048	0.578	0.766
β-catenin/Cr (pg/mg Cr) **(A)**	0.496	0.049	0.400	0.592
PIIINP/Cr (pg/mg Cr) **(B)**	0.641	0.088	0.469	0.813
β-catenin/Cr (pg/mg Cr) **(B)**	0.583	0.087	0.413	0.752

PIIINP - procollagen III aminoterminal propeptide; AUC - area under curve; SE - standard error.

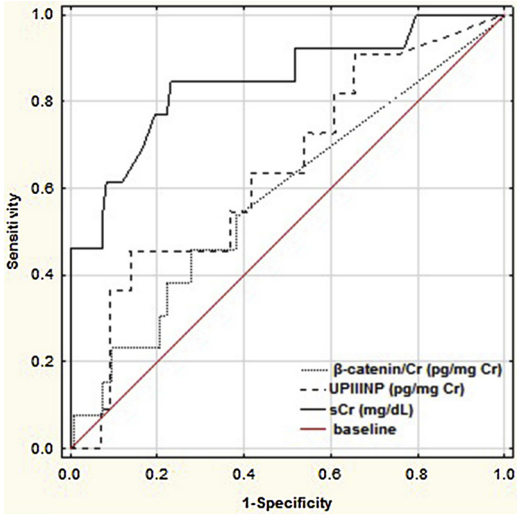

Fig. 2. Receiver Operating Characteristic curves for urinary PIIINP/Cr, β-catenin/Cr (pg/mg Cr) and serum creatinine (sCr, mg/dL) levels in SFK children with impaired renal function (eGFR < 90 mL/min/1.73 m^2); AUC (PIIINP/Cr) - 0.641, AUC (β-catenin/Cr) - 0.583, AUC (sCr) – 0.846.

levels of PIIINP reflected the severity of organ fibrosis [19].

We demonstrated that UPIIINP successfully discriminated between children with SFK and healthy controls. UPIIINP levels were shown to be significantly higher in the study group than in healthy individuals ($p < 0.001$). This study confirms previous observations concerning changes in urinary PIIINP in a variety of nephropathies [20,21].

Furthermore, and interestingly, we observed significant relationships between PIIINP concentration and serum creatinine concentration and eGFR, suggesting a valuable role for UPIIINP in predicting renal impairment. Our results did not differ from those reported by Ghoul et al. [22], who confirmed significant correlations between UPIIINP levels, serum creatinine concentrations, and GFR. However, their study was performed in patients with CKD. Similar findings were shown in a study of renal transplant recipients [8]. The rise of urinary levels of PIIINP that we detected is also consistent with observations made by Keller et al. [23] in acute/chronic glomerulonephritis and interstitial nephritis.

Detecting higher urinary levels of PIIINP in SFK patients than in healthy controls supports the notion that tubules are damaged during initial stages of kidney hypertrophy [24]. No association was demonstrated in the present study between PIIINP and microalbuminuria. However, *there was a* small number of individuals with microalbuminuria. PIIINP may be of limited use in this condition. A large multicenter prospective observational study should be undertaken to further explore the potential clinical applications of this marker.

Swine-based studies have shown some renal extraction and degradation of smaller PIIINP fragments [25]. Therefore, increased filtration of PIIINP by scarred glomeruli and/or a decreased degradation

of this peptide or smaller degradation fragments by diseased tubules cannot be excluded.

Surprisingly, we did not observe any difference in the levels of urinary β-catenin in SFK children. However, in reviewing the literature, no data was found on urinary β-catenin excretion in SFK children and adolescents. We established a weak correlation between β-catenin levels and age ($p = 0.04$). No correlation was detected between parameters of renal function and urinary β-catenin concentrations ($p > 0.05$). These findings may indicate that urinary β-catenin elimination does not depend on renal function. This lack of correlation in our study may be also explained by the fact that all of the enrolled children had normal renal function. However, our data also substantiate the assertion that unchanged β-catenin urinary excretion is not solely a reflection of renal insufficiency, as there was no correlation between these levels and renal function.

The available literature points to β-catenin as a central player in kidney development and the pathogenesis of renal dysplasia [22]. In healthy individuals, β-catenin synthesized in very little amounts is secreted in the urine after renal damage. Although a renoprotective role of β-catenin has been firmly established, its involvement in kidney repair remains poorly understood [26,27].

Mo et al. [28] reported that the level of β-catenin in 5/6 nephrectomized rats was high, mostly in the glomerular mesangial and tubulointerstitial area. The Wnt signaling pathway is silent within normal mature kidneys [10]. However, a small amount of free β-catenin exists in the cytoplasm with most forming complexes in the cell membrane, playing a crucial role in preventing cell migration [29].

Notably, β-catenin is a 'dual-function' protein, that has been identified in acute kidney injury as initially protecting against tubular-cell injury, yet suppressing kidney repair during the recovery chase [13]. Interestingly, β-catenin activation was frequently detected in fibrotic kidney tissues [29] and inhibition of β-catenin signaling reduced fibrosis in a model of obstructive nephropathy [30].

In an animal study by Benali et al. [31], serum creatinine concentration, and urine protein-to-creatinine ratio were all increased and β-catenin expression decreased in dogs with primary glomerular disease compared with dogs with acute tubular necrosis. β-catenin expression was negatively correlated to fibrosis and inflammation.

We undertook our study to assess the correlation between urinary PIIINP and β-catenin with patient characteristics and determine the relevance of both assessed markers as potential tests for renal impairment. However, based on the ROC analyses performed to define the diagnostic efficiency of estimated markers in identifying children with SFK among all examined children, which revealed an AUC value of urinary PIIINP/Cr of 0.672 and β-catenin/Cr of 0.496, discrimination between SFK and control participants was not found. Analysis carried out to identify children with renal impairment (eGFR < 90 mL/min/1.73m^2) among SFK patients, showed similar values (AUC - 0.641 and 0.583, respectively). The relevance of PIIINP for the assessment of renal fibrosis in native kidneys has been previously evaluated in a study conducted by Soylemezoglu et al. [4] in patients mainly with primary glomerulonephritis. Their report undeniably documents the close correlation between UPIIINP and severity of renal interstitial fibrosis. In contrast to our study, their data showed no correlation between UPIIINP and serum creatinine, underlying the fact that renal fibrosis is a major determinant of renal function [4]. Ghoul et al. [22] concluded that UPIIINP/Cr probably is a useful fibro-test for the kidney and may alleviate the need for a kidney biopsy in select patients with CKD.

4.1. Limitations of study

Our study has a few limitations. This is a small cohort study. Therefore, future diagnostic value of our observations can only be speculated upon. In view of the cross-sectional nature of our study, it is difficult to determine whether the changes in urinary PIIINP and β-catenin have prognostic values and whether they can serve as major potential markers in nephrological patients in the monitoring of renal impairment. Nevertheless, this is possible considering the close correlation between urinary levels of PIIINP with renal function parameters. However, it would be important to demonstrate predictive role of this biomarker in patients with different degree of CKD, expecting that patients with higher UPIIINP excretion should be at higher risk of kidney disease progression compared to patients with lower levels of urinary procollagen III aminoterminal propeptide in patients with similar eGFR and serum creatinine at entry. Therefore, urinary PIIINP and β-catenin clinical relevance and predictive value for the progression of renal impairment deserve further evaluation in prospective studies.

5. Conclusions

In conclusion, we provide novel data documenting that elevated levels of UPIIINP were detected in children with SFK and UPIIINP levels were correlated negatively with eGFR. Future studies are required to confirm the potential application of PIIINP as a useful biomarker for renal impairment and as a (monitoring) parameter in preventing the development and progression of CKD.

To evaluate the utility of these evaluated markers, it may prove useful to take repeated measurements at the onset of the disease and sometime after (measured in years). This information may enlighten us of the predictive power of these markers.

No less important, these results provide important diagnostic potential which must be further validated in larger populations. Further investigations would provide more salutary information.

Conflict of interest

The authors declare no conflicts of interest regarding the content herein.

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