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## Microalbuminuria and hyperfiltration in subjects with nephro-urological disorders

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### Abstract

**Background.** Microalbuminuria (MA) has been shown to be an early biomarker of renal damage. It is postulated that MA is the early result of hyperfiltration, which could evolve into glomerular sclerosis and renal failure if hyperfiltration is left untreated. We hypothesized that MA is a good indicator of hyperfiltration in children with kidney disorders, obviating the need to calculate the filtration fraction (FF).

**Methods.** A total of 155 children or young adults were prospectively included [42 single kidney (SK), 61 vesico-ureteral reflux, 23 obstructive uropathies, 29 other kidney diseases]. We measured inulin, para-aminohippuric acid clearances, FF and MA. Prediction of hyperfiltration was explored by studying the association between the FF and other variables such as urinary albumin (Alb), urinary albumin–creatinine ratio (ACR) and creatinine clearance.

**Results.** A significant but weak association between urinary Alb or ACR and FF was found in subjects with an SK (Spearman correlation coefficients 0.32 and 0.19, respectively). Multivariate analysis also showed that urinary Alb and ACR significantly predict FF only in subjects with an SK ( $r^2 = 0.17$ ,  $P = 0.01$  and  $r^2 = 0.13$ ,  $P = 0.02$ , respectively). This holds true only in subjects with an SK and inulin clearance  $>90$  mL/min/1.73 m<sup>2</sup> ( $r^2 = 0.41$ ,  $P < 0.001$ ). There was no association between creatinine clearance and FF.

**Conclusions.** MA is not associated with FF in our subjects with nephro-urological disorders, except in those with an SK, where the association is weak, indicating that MA is due to other mechanisms than high FF and cannot predict hyperfiltration in such groups.

**Keywords:** hyperfiltration; microalbuminuria; single kidney; urinary biomarker

### Introduction

In recent years, there has been a dramatic increase in the prevalence of chronic kidney disease (CKD) in the adult population, mainly due to an epidemic of hypertension

and diabetes mellitus (DM). It is estimated that as much as 35% of people aged 64 years and older present a low glomerular filtration rate (GFR). Although such an increase in the prevalence of CKD has not been observed in children, there are several recently recognized conditions that put them at risk of developing CKD later in life, such as low birth weight, obesity and hypertension [1].

The pathophysiology leading to CKD is complex. One of the best recognized mechanisms is hyperfiltration: a decreased nephron number [low birth weight, nephrectomy, single kidney (SK), recurrent pyelonephritis, chronic glomerulonephritis] produces a state of hyperfiltration in the remaining nephrons, which is then thought to induce focal and segmental glomerulosclerosis (FSGS), further damaging the remaining nephrons and fuelling this vicious cycle [2, 3].

The evaluation of hyperfiltration is often unavailable in most paediatric clinics. In order to do so, one needs to concomitantly measure inulin and *p*-aminohippuric acid (PAH) clearances, which is time consuming and invasive since it involves catheter-collected urine in young children. A good marker that would predict hyperfiltration and obviate the need for inulin and PAH clearances would be most desirable. Microalbuminuria (MA) has been proposed as an early marker of glomerular hyperfiltration, especially in patients with obesity, hypertension or DM [4–6].

Studies specifically looking at glomerular hyperfiltration and MA in the paediatric population are scarce, and show conflicting results. Schreuder *et al.* found that children with an SK often present MA; however, in their study, clearances and FF were not assessed [7]. In another study, Basic *et al.* looked at the presence of MA in children with vesico-ureteral reflux (VUR) [8], again with no evaluation of the FF. It is therefore impossible to know whether MA in the reported children is then secondary to a high FF or to chronic renal parenchymal damage such as interstitial fibrosis, inflammation and scars.

The association between FF and MA in subjects with DM has been studied by several authors, and conclusions

are controversial. Ficociello *et al.* found that in adult patients with long-lasting DM, renal hyperfiltration did not have an impact on the development of MA during 5, 10 or 15 years of follow-up [9]. Yip *et al.* also found no association between hyperfiltration and MA in a 10-year prospective case-control study of adults with Type 1 DM [10]. On the other hand, several authors found a significant association between hyperfiltration and MA in children with DM [11, 12]. This has been confirmed in a recent meta-analysis [13].

Our study aimed to examine the relationship between MA and FF in subjects with common nephro-urological disorders. We hypothesized that the presence of MA in these patients would indicate a state of hyperfiltration. If correct, the hypothesis would be particularly useful in subjects with a reduced nephron mass such as children with an SK [renal agenesis (RA), multicystic dysplastic kidney (MDK)] or after nephrectomy (Nx) (renal cancer, kidney transplantation). These patients are especially at risk to present a state of glomerular hyperfiltration which can be complicated by MA, overt proteinuria, decreased renal function and, very rarely, renal failure, most often secondary to FSGS [3]. The possibility of treatment of hyperfiltration with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers also adds an invaluable additional support of potential benefits of our hypothesis.

To avoid bias produced by the choice of an arbitrary cut-off value for clearances or FF or MA, which are multiple and change with sex and age [14, 15], we explored the association between FF and MA using continuous values for all statistical purposes.

## Materials and methods

### Study sample

We prospectively studied all patients with common nephro-urological abnormalities presenting to our unit for a complete evaluation of their renal function. All patients with an SK (Group 1) or with bilateral VUR or unilateral VUR  $\geq$  Grade II (surgically corrected or not) (Group 2) or with severe uretero-pelvic or uretero-vesical junction obstruction (UPJO/UVJO) ( $T_{1/2} > 20$  min and/or differential distribution difference  $>60/40\%$ ) (surgically corrected or not) (Group 3) or other disorders such as recurrent urinary tract infections or pyelonephritis (without reflux or obstruction), autosomal dominant polycystic kidney disease or unspecified renal cystic disease, renal trauma, horseshoe kidneys, kidneys with a history of stones, bladder exstrophy) (Group 4) were included in the study. Patients with an SK were further separated into three sub-groups: patients with MDK, RA or Nx. Indications for clearance studies were left at the discretion of the physician.

Blood pressure (BP) categories were defined as follows: normal: BP values  $<90$ th percentile; pre-hypertension: BP values between 90th and 95th percentile or BP values between 120 and 139/80 and 89 mmHg; hypertension: BP values  $>95$ th percentile or BP  $>140/90$  mmHg or presence of any anti-hypertensive treatment [16]. Body mass index (BMI) categories were defined as follows: normal: BMI  $<85$ th percentile; overweight: BMI between 85th and 95th percentile; obesity: BMI  $>95$ th percentile; underweight: BMI  $<5$ th percentile (<http://www.bcm.edu/cnrc/bodycomp/bmiz2.html>). BP, weight and height were recorded to the unit, gram and centimetre, respectively.

All groups and subgroups were defined before conducting statistical analysis. Research was conducted according to the World Medical Association Declaration of Helsinki.

### Clinical evaluation of renal function and MA

Renal function was determined in the morning, in well-hydrated subjects given p.o. tap water or i.v. normal saline as follows: an intravenous priming dose of 0.2 mL/kg body weight of 25% inulin and 0.02 mL/kg body weight of 20% PAH were given, followed by a maintenance dose of inulin and PAH in 1 mL/min of saline to provide steady-state plasma serum levels of 300 and 20 mg/L for inulin and PAH, respectively. After 90 min of equilibration, three 30-min clearance periods provided the data for the inulin and PAH clearances, representing GFR and renal plasma flow, respectively. Serum creatinine was measured by means of a kinetic Jaffe method (Hitachi 917, Japan; reagents from Roche Diagnostics) and albumin was determined by immunoturbidimetry (Roche Diagnostic). Normal inulin clearance was defined as  $\geq 90$  mL/min  $\times 1.73$  m<sup>2</sup> for both girls and boys (range for girls  $>2$  years of age: 105–130 mL/min  $\times 1.73$  m<sup>2</sup>, range for boys  $>2$  years of age: 110–150 mL/min  $\times 1.73$  m<sup>2</sup>), normal PAH clearance  $\geq 500$  mL/min  $\times 1.73$  m<sup>2</sup> (range for girls  $>2$  years of age: 490–700 mL/min  $\times 1.73$  m<sup>2</sup>, range for boys  $>2$  years of age: 560–830 mL/min  $\times 1.73$  m<sup>2</sup>) and normal FF  $\leq 26\%$  (range for girls  $>2$  years of age: 0.17–0.23, extremes 0.14–0.26; range for boys  $>2$  years of age: 0.17–0.21, extremes 0.14–0.26) (reference values in our laboratory, corresponding the mean  $\pm 2$  SD in children  $>2$  years old with a creatinine clearance between 100 and 140 mL/min/1.73 m<sup>2</sup>).

Results for MA are reported as urinary albumin-creatinine ratio (ACR) (mg/mmol) and urinary albumin concentration (Alb) (mg/L), measured on a second voided morning urine specimen, during the inulin clearance.

Renal length was determined by a renal ultrasound performed at the same time as the clearance. Compensatory hypertrophy was defined as a kidney length  $>95$ th percentile for side and body length.

### Statistical analysis

Statistical analyses were performed using STATA Microsoft tools (STATA 10) and S-PLUS® 8.0 (Insightful Corp, Seattle, WA, USA). Urinary Alb, urinary ACR, FF, inulin, PAH and creatinine clearances data were included in the statistical analysis as continuous values. Basal demographic data between groups were analysed using unpaired Student's *t*-test. Results are expressed as means  $\pm$  SD, medians and ranges or percentages. Assessment of normality of data was performed using the Kolmogorov-Smirnov test, and data were log transformed when applicable.

Correlation between FF and MA was assessed using the Spearman's rank-order correlation test. The influence of age, creatinine clearance, urinary Alb or ACR on the FF was studied using a multivariate model. Median FF, urinary Alb or ACR were compared between normotensive and hypertensive patients, and also between underweight, normal- and overweight patients. Significance was defined as  $P \leq 0.05$ .

## Results

### Demographics

A total of 155 subjects were prospectively enrolled to our study. Their demographic data are shown in Table 1. Group 1 comprised of all patients with an SK ( $n = 42$ ), Group 2 patients with VUR ( $n = 61$ ), Group 3 patients with uretero-pelvic junction obstruction/uretero-vesical junction obstruction (UPJO/UVJO) ( $n = 23$ ) and Group 4 patients with other urological diseases ( $n = 29$ ). Patients with an SK were further classified according to the primary diagnosis, i.e. RA ( $n = 15$ ), MDK ( $n = 19$ ) or Nx ( $n = 8$ ). Co-morbidities in patients with an SK are listed in Table 2. Mean age  $\pm$  SD at the time of the study was  $11.3 \pm 5.0$  years, and did not differ between groups ( $P = 0.83$ ). There was a male preponderance in every group, except in Group 4. BP and BW characteristics are reported in Table 1. Patients under angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers were excluded.

**Table 1.** Demographics and main findings

	SK	VUR	UPJO/UVJO	Others <sup>a</sup>	Total
Sample size, <i>n</i>	42	61	23	29	155
Age (years), median [min–max]	13 [4;21]	10 [4;24]	11 [5;22]	12 [3;21]	11 [3;24]
Sex ratio (M/F)	1.63	1.35	1.88	0.71	1.31
Albumin (mg/L), median [min–max]	6.5 [2.0;1497.0]	8.0 [1.7;412]	9.0 [3.0;75.0]	14.0 [3.0;208]	9.0 [1.7;1497]
ACR (mg/mol creatinine), median [min–max]	0.8 [0.3;120.0]	1.1 [0.4;26.6]	0.9 [0.3;10.4]	1.9 [0.5;26.4]	1.1 [0.3;120.0]
FF%, median [min–max]	24 [16;45]	23 [10;37]	23 [15;31]	22 [17;36]	24 [10;45]
PAH, median [min–max]	360 [126;682]	427 [258;1135]	425 [229;719]	429 [230;617]	406 [126;1135]
Inulin clearance, median [min–max]	93 [21;191]	96 [53;136]	103 [71;145]	99 [49;138]	97 [21;191]
Hypertension (percentile >90), <i>n</i> (%)	7/42 (16.7%)	6/59 (10.2%)	5/23 (21.7%)	5/29 (17.2%)	23/153 (15.0%)
Obesity, <i>n</i> (%)					
Underweight	5/42 (11.9%)	5/61 (8.2%)	2/23 (8.7%)	1/29 (3.4%)	13/155 (8.4%)
Normal	31/42 (73.8%)	41/61 (67.2%)	19/23 (82.6%)	19/29 (65.5%)	110/155 (71.0%)
Overweight/obesity	6/42 (14.3%)	15/61 (24.6%)	2/23 (8.7%)	9/29 (31.0%)	32/155 (20.6%)

<sup>a</sup>Others include: recurrent urinary tract infections or pyelonephritis (without reflux or obstruction), autosomal dominant polycystic kidney disease or unspecified renal cystic disease, renal trauma, horseshoe kidneys, urolithiasis, bladder extrophy.

ACR, albumin–creatinine ratio; F, female; FF, filtration fraction; M, male; PAH, para-aminohippurate; SK, single kidney; UPJO/UVJO, uretero-pelvic junction obstruction/uretero-vesical junction obstruction; VUR, vesico-ureteral reflux.

**Table 2.** Associated urological anomalies or medical complications in children with a single kidney

	RA, <i>n</i> = 15	MDK, <i>n</i> = 19	Nx, <i>n</i> = 8
VUR	3	–	2
UPJO/UVJO	–	1	2
History of PN	–	1	–
Increased echogenicity/ dysplasia	3	2	–
Chemotherapy	–	–	1
Total	6 (40%)	4 (21%)	5 (63%)

MDK, multicystic dysplastic kidney; Nx, nephrectomy; PN, pyelonephritis; RA, renal agenesis; UPJO/UVJO, uretero-pelvic junction obstruction/uretero-vesical junction obstruction; VUR, vesico-ureteral reflux.

#### Determinants of MA and association between MA and FF

The values (median and range) for urinary Alb excretion, inulin and PAH clearances and FF are reported in Table 1. The median of inulin and PAH clearances, FF and albumin excretion were not different between the groups except for a significantly diminished median PAH clearance in the SK group ( $P < 0.001$ ).

The association between MA and FF was studied using the Spearman's correlation coefficients. There was a weak but significant correlation between urinary Alb and FF ( $r = 0.32$ ) or ACR and FF ( $r = 0.19$ ) but this is only in the SK group (Table 3).

There were no significant differences in medians of urinary Alb, ACR and FF between subjects with normal and abnormal BP or between subjects with normal or abnormal BW (data not shown).

In a multivariate model (Table 4), the urinary Alb ( $r^2 = 0.17$ ,  $P = 0.01$ ) or ACR ( $r^2 = 0.13$ ,  $P = 0.02$ ) was significantly associated with FF in the SK group only. Significant association between MA and FF was lost in patients with an SK and a GFR  $< 90$  mL/min/1.73 m<sup>2</sup>, but maintained in the SK group with GFR  $> 90$  mL/min/1.73 m<sup>2</sup> (Table 5). Using the same prediction model, urinary Alb

**Table 3.** Correlation with FF (Spearman correlation coefficients)

	SK	VUR	UPJO/UVJO	Others
Albumin, logarithm	0.32	0.05	0.04	0.19
ACR, logarithm	0.19	–0.11	–0.23	0.08
Creatinine	0.12	0.13	0.02	0.00

Alb, urinary albumin concentration; ACR, urinary albumin/creatinine ratio; FF, filtration fraction.

and ACR were still significantly associated with FF in the subgroup of congenital SK (Table 6). Age was not associated with FF in the SK group (Table 4), whereas it was in the VUR group ( $0.42$ ,  $P = 0.001$ ) and in the UPJO/UVJO group ( $0.46$ ,  $P = 0.04$ ). Figure 1 shows the correlation between MA and FF in the four groups. Given the poor association between MA and FF in the SK group, we chose not to calculate cut-off values using ROC curve analysis.

The absence of contralateral kidney hypertrophy (defined as a total kidney length  $< 95$ th percentile according to patient's height and kidney side) in patients with an SK is a very strong indicator ( $P < 0.001$ , exact Fisher test) of low GFR (inulin clearance  $< 90$  mL/min/1.73 m<sup>2</sup>). But there is no significant association between the presence or absence of contralateral kidney hypertrophy and the presence of MA.

## Discussion

We prospectively studied 155 patients with concomitant measurement of their renal function and albumin excretion. We found a male preponderance in all our groups with malformation (VUR, UPJO/UVJO, MDK), except in Group 4 (children with recurrent urinary tract infection, Table 1), which is already reported in the literature [17, 18].

Our hypothesis was that a decreased nephron mass would lead to first hyperfiltration and then progressively

**Table 4.** Multivariate model

	SK	VUR	UPJO/UVJO	Others
Age (per year)	*	0.42 (0.12), P = 0.001	0.46 (0.21), P = 0.04	***
Creatinine	0.04 (0.03), P = 0.17	0.00 (0.01), P = 0.73	-0.02 (0.04), P = 0.55	0.02 (0.04), P = 0.64
Albumin, logarithm	1.15 (0.45), P = 0.01	-0.43 (0.51), P = 0.40	-0.06 (0.94), P = 0.95	0.54 (0.69), P = 0.44
R-squared	0.17	0.18	0.20	0.03
Age (per year)	**	0.39 (0.11), P = 0.001	0.42 (0.21), P = 0.053	****
ACR, logarithm	1.17 (0.48), P = 0.02	-0.53 (0.60), P = 0.38	-0.36 (0.97), P = 0.71	0.29 (0.78), P = 0.71
R <sup>2</sup>	0.13	0.18	0.19	0.01

All SK subjects are included ( $n = 42$ ).

Alb, urinary albumin concentration; ACR, urinary albumin/creatinine ratio; FF, filtration fraction.

\*Not significant ( $P = 0.75$ ), removed from the model.

\*\*Not significant ( $P = 0.85$ ), removed from the model.

\*\*\*Not significant ( $P = 0.70$ ), removed from the model.

\*\*\*\*Not significant ( $P = 0.79$ ), removed from the model.

**Table 5.** Prediction model in subjects with an SK according to the GFR level

	SK/inulin GFR <90 mL/min/1.73 m <sup>2</sup>	SK/inulin GFR >90 mL/min/1.73 m <sup>2</sup>
Creatinine clearance	0.10 (0.04), P = 0.03	-0.01 (0.05), P = 0.79
Albumin, logarithm	-0.36 (0.60), P = 0.56	2.09 (0.54), P = 0.001
R <sup>2</sup>	0.27	0.44
ACR, logarithm	-0.12 (0.74), P = 0.87	2.18 (0.57), P < 0.001
R <sup>2</sup>	<0.01	0.41

All SK subjects are included ( $n = 42$ ).

ACR, urinary albumin/creatinine ratio; GFR, glomerular filtration rate; SK, single kidney.

**Table 6.** Prediction model in subjects with congenital SK

	Congenital SK
Albumin, logarithm	1.29 (0.46), P = 0.081
ACR, logarithm	1.50 (0.47), P = 0.034

Only subjects with congenital SK are included ( $n = 34$ ).

ACR, urinary albumin/creatinine ratio; SK, single kidney.

to MA, macroalbuminuria and proteinuria, secondary to haemodynamically mediated glomerular injury [3].

This association between hyperfiltration and MA and this pattern of progression have already been described, mainly in subjects with DM (although with conflicting results) [6, 9–13] or hypertension [5].

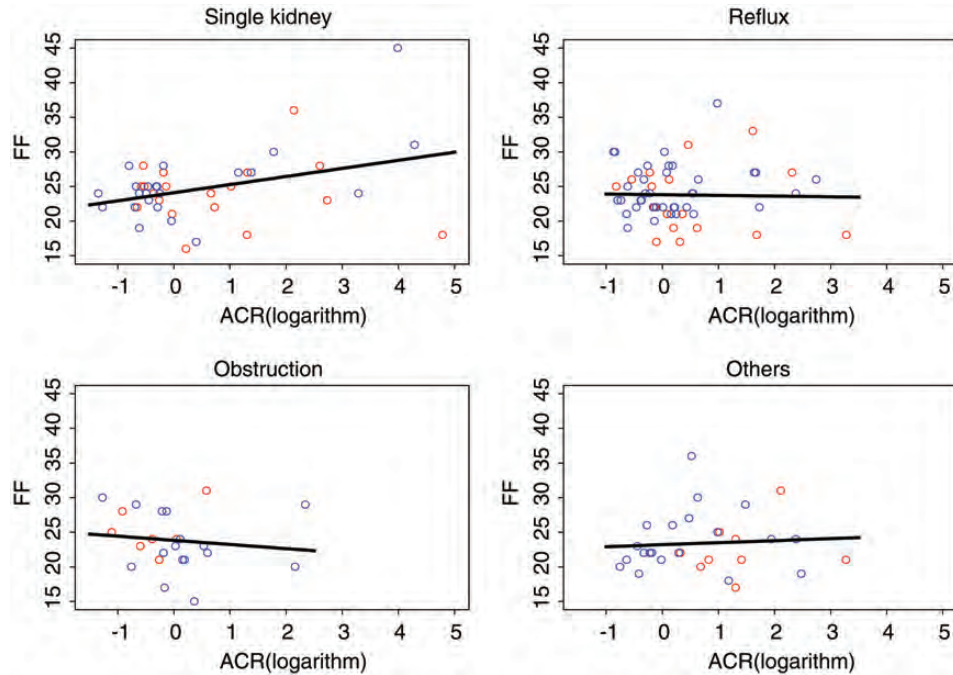
We found that MA is associated with FF only in subjects with an SK, but this association is very poor. Furthermore, in that group, this holds true only for subjects with a normal GFR, i.e.  $\geq 90$  mL/min/1.73 m<sup>2</sup>, but not in subjects with an SK and lower GFRs. MA is not associated with FF in subjects with VUR, UPJO/UVJO or other renal diseases.

The association between high FF and MA in patients with an SK has rarely been studied according to the literature, with the notable exception of long-term evaluation of donor kidney patients. We found three studies in which

the investigators performed inulin and PAH clearance in patients with an SK. Regazzoni *et al.* found no increased FF in adults after childhood nephrectomy [19]. Unfortunately, the presence of MA was not reported. Chevallier *et al.* studied children after unilateral nephrectomy for Wilms tumour [20]. Although some children (14 of 33 children) presented a high FF, the authors found no correlation between MA and hyperfiltration, after a mean follow-up of 4.6 years. Bock *et al.* [21] found only three patients (out of 27) with MA in adult kidney donors, again with no correlation to hyperfiltration. In that study, the follow-up was restricted to 1 year post nephrectomy. Other studies relied on an abnormally high inulin or creatinine clearance (often  $\geq 2$  SD) for an SK to diagnose hyperfiltration, without performing PAH clearance. Baudoin *et al.* found an inverse correlation between MA excretion and GFR [22] in adult patients. Nieto *et al.* [23] studied 38 children after nephrectomy and found no patient with an abnormal MA, even in the presence of hyperfiltration (defined by an abnormally high creatinine clearance). Morales *et al.* [24] found no relationship between MA and hyperfiltration in 85 subjects after nephrectomy. Christensen *et al.* conducted a similar study and also found MA in only one of their adult patients [25]. In these aforementioned studies, the occurrence of MA seems to be rather low, and without any relation to a hyperfiltration state. Other studies found conflicting results as to the presence [26–30] or not [31] of MA in the long-term follow-up of patients with an SK, with no reference to hyperfiltration.

Recently, Abou Jaoudé *et al.* reported [32] a cohort of 97 children with (congenital or acquired) SK. Seventeen per cent had MA. Because FF was not measured, an association between a hyperfiltration state and the presence of MA was not available.

The fact that we found a high prevalence of MA in our patients with an SK might be well explained by the fact that 15 out of 42 children with an SK had moderate to severe abnormalities in their solitary kidney (VUR or mild hyperechogenicity or a history of recurrent pyelonephritis), probably lowering further their renal mass and their renal function (Table 2). This strongly emphasizes the fact that any secondary aggression to an SK



**Fig. 1.** ACR, albumin–creatinine ratio. Red dots denote inulin GFR <90 mL/min/1.73 m<sup>2</sup>, blue dots inulin GFR ≥90 mL/min/1.73 m<sup>2</sup>. There is a weak association between ACR and FF only in subjects with a SK.

(hypertension, DM, obesity, chemotherapy, pyelonephritis) will contribute to the development or acceleration of MA, independently of the initial insult.

The prevalence of MA in patients with VUR has rarely been studied. Most of the studies found an inverse correlation between MA and decreased GFR and/or between MA and the number of scars [33–36]. Interestingly, MA was not related to hyperfiltration in two studies [33, 35]. In one study [34], MA did not increase after an oral protein load, leading the authors to conclude that patients who had bilateral VUR showed an impaired renal response to protein load, with no renal functional reserve capacity. Although our patients with VUR had MA, we found no significant association between MA and FF in that group. It seems that renal scars by themselves (in the case of VUR), independently or in addition to haemodynamic factors, could induce MA in children with VUR. The occurrence of hyperfiltration in these patients will nevertheless play an additional role in the appearance of MA, and should be managed as such.

In summary, we found a weak association between FF and MA, and only in subjects with an SK and GFRs >90 mL/min/1.73 m<sup>2</sup>. In all other groups, MA is not associated with FF. MA cannot be used to predict hyperfiltration in children with common nephro-urological disorders.

This leads to two final remarks: there must be other biomarkers, yet unidentified, that could better predict hyperfiltration. MA in children with nephro-urological disorders must also be secondary to other factors than a high FF. Most of the filtered albumin is reabsorbed at the proximal tubule level [37]. Pathological MA could also be present secondary to cellular proximal tubular dysfunction [38].

We are aware of a few limitations in our study. The method most commonly used to measure MA relies on a

timed urine collection, either a 24-h or overnight specimen, which is time-consuming and often inaccurate in children. MA has been measured only once in our study, during the clearance studies, in the second morning urine specimen. Several studies have shown an excellent correlation between the MA excretion measured in 24-h urine collections and the random urine ACR [39]. The benefit of MA treatment in children with an SK remains to be proven as well with long-term outcome studies. Furthermore, our population with an SK had a very high incidence of associated and potentially deleterious conditions such as pyelonephritis, cancer, reflux, obstruction. This might have increased the prevalence of MA in such a selected population, and therefore the strength of association between MA and FF. The results we found might not apply in a more general population. Hence, additional studies should be conducted in a more representative population, and in children with isolated SK and no other anomalies/conditions.

## Conclusion

Hyperfiltration is not associated with MA in subjects with chronic kidney disorders, except in children with an SK and normal GFR. However, the association between FF and MA in that subgroup is very weak. MA cannot be used as a surrogate marker for hyperfiltration. Other unidentified factors must play a role in the development of MA in patients with nephro-urological disorders.

*Conflict of interest statement.* None declared.

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