

Urinary potassium to urinary potassium plus sodium ratio can accurately identify hypovolemia in nephrotic syndrome: a provisional study

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Abstract There is evidence pointing to a decrease of the glomerular filtration rate (GFR) in a subgroup of nephrotic children, likely secondary to hypovolemia. The aim of this study is to validate the use of urinary potassium to the sum of potassium plus sodium ratio (UK/UK+UNa) as an indicator of hypovolemia in nephrotic syndrome, enabling detection of those patients who will benefit from albumin infusion. We prospectively studied 44 nephrotic children and compared different parameters to a control group (36 children). Renal perfusion and glomerular permeability were assessed by measuring clearance of para-aminohippurate and inulin. Vaso-active hormones and urinary sodium and potassium were also measured. Subjects were grouped into low, normal, and high GFR groups. In the low GFR group, significantly lower renal plasma flow ($p = 0.01$), filtration fraction ($p = 0.01$), and higher UK/UK+UNa ($p = 0.03$) ratio were noted. In addition, non-significant higher plasma renin activity ($p = 0.11$) and aldosterone ($p = 0.09$) were also seen in the low GFR group.

Conclusion: A subgroup of patients in nephrotic syndrome has a decrease in glomerular filtration, apparently related to hypovolemia which likely can be detected by a urinary potassium to potassium plus sodium ratio > 0.5 – 0.6 suggesting benefit of albumin infusion in this subgroup.

What is Known:

• Volume status can be difficult to assess based on clinical parameters in nephrotic syndrome, and albumin infusion can be associated with development of pulmonary edema and fluid overload in these patients.

What is New:

• Urinary potassium to the sum of urinary potassium plus sodium ratio can accurately detect hypovolemia in nephrotic syndrome and thus identify those children who would probably respond to albumin infusion.

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Abbreviations

Cr	Creatinine
FE Na	Fractional sodium excretion
FF	Filtration fraction
GFR	Glomerular filtration rate
IARF	Idiopathic renal failure
NS	Nephrotic syndrome
PAH	Para-aminohippurate
PRA	Plasma renin activity
RPF	Renal plasma flow
UK	Urinary potassium
UNa	Urinary sodium
U pr/Cr ratio	Urinary protein/creatinine ratio

Introduction

Acute kidney injury (AKI) remains an uncommon complication of nephrotic syndrome both in children and adults. The term idiopathic acute renal failure (IARF) has been used to describe renal impairment in idiopathic nephrotic syndrome [3, 4]. A retrospective study by Chen et al. [5] showed that from 277 cases of adult idiopathic nephrotic syndrome, 34% developed acute kidney injury (AKI) based on RIFLE criteria with majority of them fully recovering. Underlying pathophysiologic mechanisms of AKI in nephrotic syndrome are not fully understood but may include acute tubular necrosis due to hypovolemia, renal venous thrombosis, and renal interstitial infiltration and edema [1, 3, 5, 8].

Previous studies on acute kidney injury in children with nephrotic syndrome showed that those who have decreased GFR exhibited reduction in filtration fraction (FF) value, possibly indicating a reduced capillary permeability (Kf). [9, 12, 14, 17].

In our current study, we intend to demonstrate evidence that there is a decrease in GFR in a subgroup of patient likely to be secondary to hypovolemia. Theoretically, we would expect that hypovolemia coincides with secondary hyperaldosteronism which would result in a higher urinary potassium to urinary potassium plus sodium ratio. In contrast, if hypervolemia is present, one would expect low plasma renin activity and aldosterone levels and increased renal plasma volume.

Methodology

Patients

Forty-four children with active nephrotic syndrome (nephrosis group) and a control group consisting of thirty-six children with a history of nephrotic syndrome but in remission were enrolled to participate into the study. The nephrosis group was further stratified to low ($n = 4$), normal ($n = 36$), and high ($n = 4$) GFR group based on calculation of mean \pm 2SD from the remission group. Included patients presented with either a relapse or a first presentation of nephrotic syndrome and were not receiving any related treatment (e.g., steroids, ACE inhibition, diuretics) at time of admission. Nephrotic syndrome state was defined as a urinary protein/creatinine ratio > 0.6 g/mmol, a plasma albumin level < 25 g/l, and presence of edema. Informed consent was obtained from parents or caretaker. The study was performed in accordance with the Declaration of Helsinki and ethical approval was obtained from the hospital ethical committee. Exclusion criteria (for safety reasons) are patients with hyponatremia, serum creatinine > 1.5 mg, anuria in last 6 h, and anasarca. The test had to

be stopped in case anuria or hyponatremia ($\text{Na} < 130$ mmol/l) developed during the test.

Renal function test

Evaluation of renal function and factors involved in volume regulation was performed using the following protocol: after recumbency for 30 min, blood and urine samples were obtained and analyzed for creatinine, albumin, and total protein. Plasma colloid osmotic pressure (COP), renin, and aldosterone were also measured. Renal function was subsequently assessed through continuous inulin and para-aminohippurate (PAH) perfusion.

Thereafter a water load was given of 25 ml/kg for about 30 min followed by a continuous infusion of inulin (10%) to measure GFR and para-aminohippurate (PAH) and renal plasma flow (RPF). Water loading was commenced at the rate of 0.25 ml/min per m^2 , after a priming dose of 5 ml/kg body weight. After a period of 45 min equilibration time, three 20-min urine collections were made. In this phase, maximal urine dilution was maintained by infusion of hypotonic saline (0.225% sodium chloride in 2.5% glucose at the rate of 20 ml/min per 1.73 m^2). Blood samples were taken halfway through each urine collection period for clearance measurements. Blood and urine samples were analyzed for inulin, PAH, osmolality, sodium, and potassium. In the very small children, urine collection periods were adjusted to their spontaneous need to void. During fluid administration and thereafter, all children were monitored intensively for development of untoward side effects. The water diuresis protocol used was adopted from previously performed studies in which the water load was followed by a 0.45% sodium chloride infusion [15, 16]. We used a lower sodium chloride concentration (0.225%) to avoid volume expansion. The oral water load will cause body fluid dilution of about 4%.

Analytical technique

Sodium and potassium were measured by standard flame photometry (direct photometry) by means of a Perkin Elmer 3030 atomic absorption spectrophotometer. Osmolality was measured with an advanced osmometer. Radioimmunoassays were used to measure plasma concentrations of aldosterone and plasma renin activity. Colloid osmotic pressure (COP) was measured with a colloid osmometer built for 10- μ l samples.

Statistical analyses

Data are presented as mean in Tables 1 and 2. Standard formulas were used to calculate for clearances and fractional excretions. GFR and RPF were normalized for 1.73 m^2 .

Table 1 Renal function parameters

Variables	Low GFR (mean ± SD)	Normal GFR (mean ± SD)	High GFR (mean ± SD)	<i>p</i> value
Albumin (g/l)	18 ± 3	30 ± 14	25 ± 18	0.212
COP (mmHg)	9.5 ± 0.2	16.4 ± 7.8	12.8 ± 8.9	0.168
GFR creat (ml/min/1.73 m ²)	58 ± 22 ^a	130 ± 39	212 ± 40	< 0.01
GFR inulin (ml/min/1.73 m ²)	35 ± 10 ^b	120 ± 27	220 ± 65	< 0.01
RPF (ml/min/1.73 m ²)	347 ± 107 ^c	691 ± 257	1287 ± 496 ^f	< 0.01
FF (%)	10 ± 3 ^d	19 ± 5	18 ± 3	0.01
Log renin (mU/min)	2.2 ± 0.2	1.7 ± 0.5	1.5 ± 0.7	0.11
Log aldosterone (pg/ml)	2.4 ± 0.5	1.8 ± 0.6	1.4 ± 0.9	0.09
FENa (%)	1.5 ± 2.0	1.0 ± 0.8	1.1 ± 0.2	0.58
UK/UK+UNa (%)	73 ± 31 ^e	44 ± 22	33 ± 25	0.03

COP colloid oncotic pressure, GFR glomerular filtration rate, RPF renal plasma flow, FF filtration fraction, FENa fractional secretion of sodium, UK/UK+UNa urinary potassium over sum of urinary potassium plus sodium, SD standard deviation

^a Significant vs normal GFR and high GFR group

^b Significant vs normal GFR and high GFR group

^c Significant vs normal GFR and high GFR group

^d Significant vs normal GFR and high GFR group

^e Significant vs normal GFR and high GFR group

^f Significant vs normal GFR group

Differences between all groups were tested with the Kruskal-Wallis test for multiple group. If the *p* value was < 0.05, differences between groups were tested with the Mann-Whitney U test (with Bonferroni's protection for multiple comparisons).

Results

Table 1 outlines the results of kidney function parameters while base line characteristics are described in Table 2. The data are presented as means ± SD (standard deviation) in Table 1. For renin and aldosterone, it was calculated as a logarithm. The significant difference between GFR measured by creatinine and inulin clearance (*p* < 0.01) demonstrated that

GFR estimations based on creatinine clearance tend to overestimate the true GFR due to tubular creatinine secretion. Patients in the low GFR group had significantly lower RPF (*p* < 0.01), FF (*p* < 0.01), and higher UK/UK+UNa (*p* = 0.03).

In Fig. 1a, log renin values are plotted for patients and subgrouped according to their GFR levels: high, normal, and low, while the reference frame for GFR was calculated in the control group. All patients with low GFR show non-significant increased levels of plasma renin (*p* = 0.11) activity and plasma aldosterone (*p* = 0.09).

Figure 1b demonstrates that the subpopulation with low GFR coincides with having a low renal plasma flow. The patients with high GFR have also high renal plasma flow. Some of the values are however far beyond normal range.

Table 2 Baseline characteristics of included patients with nephrotic syndrome (*n* = 44)

Parameters at T0	Low GFR	Normal GFR	High GFR	<i>p</i> value
Age (years)	9.2 (7.7–11.7)	6.4 (0.3–13.1)	10.7 (4–16.3)	0.65
Male sex (%)	3/4 (75)	22/36 (61.1)	3/4 (75)	
Height (cm)	129 (114–134)	113 (52–161)	130 (101–154)	0.253
Weight (kg)	27.5 (21–32)	22.3 (2.7–42)	35.3 (17–54)	0.1
Minimal change NS (%)	2/4 (50)	20/36 (55)	3/4 (75)	
Albumin (g/l)	18 (13–23)	30 (7–25)	25 (9.6–22.4)	0.212
Serum Cr (mg/dl)	0.38 (0.6–1.1)	0.6 (0.23–1.6)	0.38 (0.27–0.51)	0.06
U Pr/Cr ratio (g/g)	3.2 (0.6–8.9)	2.5 (0.46–8.9)	1.0 (0.7–1.3)	0.27

Baseline characteristics are depicted as mean T0 before the water loading test was administered

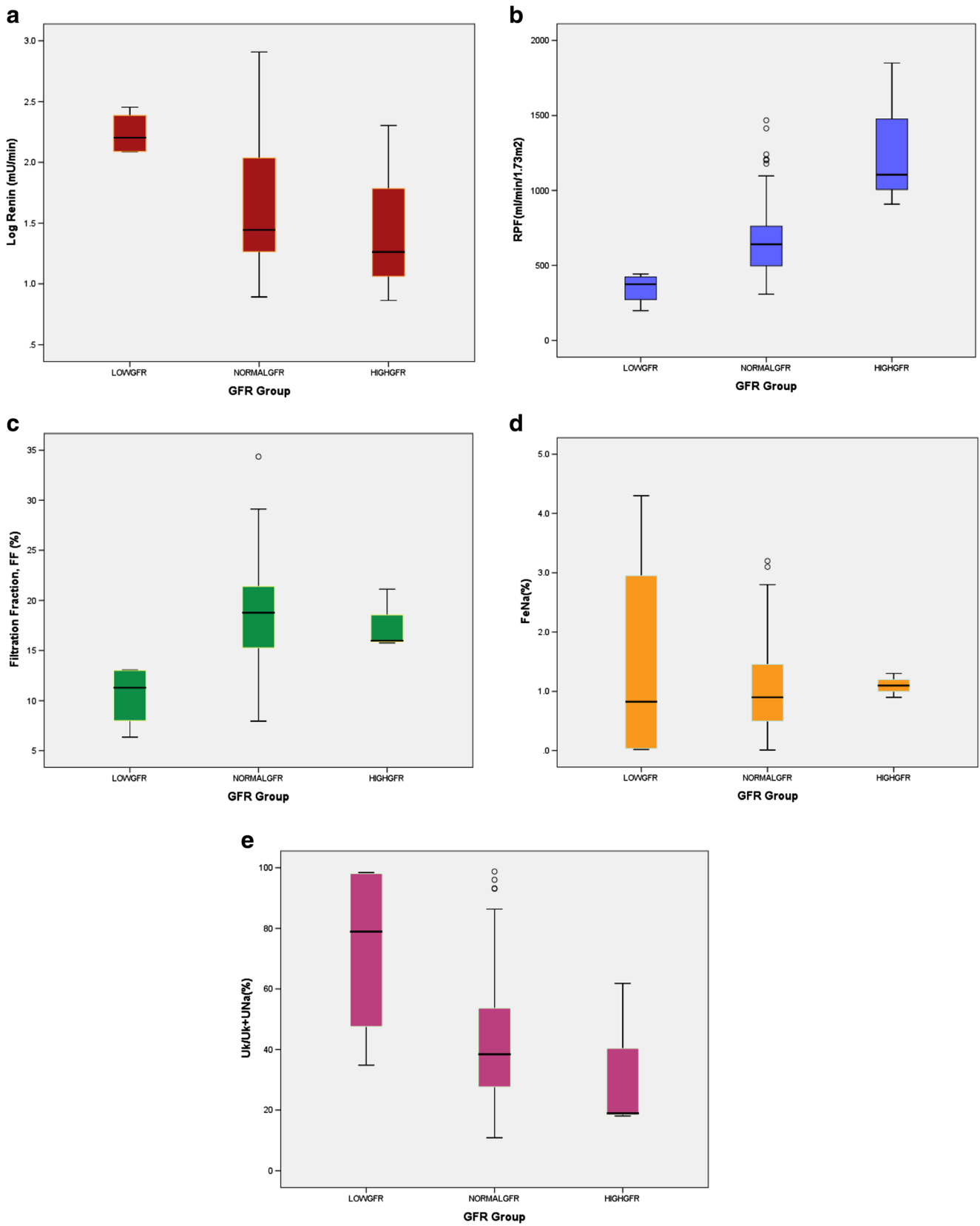


Fig. 1 **a** Plasma renin activity related to GFR. The box plot demonstrates the mean value of PRA in logarithm (mU/min) in three different GFR groups. Median value is indicated by thick vertical line. **b** Renal plasma flow related to GFR. The box plot demonstrates the mean value of renal plasma flow (RPF) (ml/min/1.73 m²) in three different GFR groups. Median value is indicated by thick vertical black line. Outliers are represented with round white dot. **c** Filtration fraction related to GFR. The box plot demonstrates the mean value of filtration fraction (FF) (%) in three different GFR groups. Median value is indicated by thick vertical line. Outlier is represented by round white dot. **d** Fractional sodium excretion related to GFR. The box plot demonstrates the mean value of fractional excretion sodium FENa (%) in three different GFR groups. Median value is indicated by thick vertical line. Outlier is represented by round white dot. **e** UK/UK+UNa ratio related to GFR. The boxplot demonstrates the mean value of UK/UK+UNa in three different GFR groups. Median value is indicated by thick vertical line. Outlier is represented by round white dot

Figure 1c shows that patients with low GFR also have a low FF. The subpopulation with low normal GFR has low normal FF but with wide variability (see SD).

Figure 1d demonstrated that most patients in the low GFR group have wide variability in FENa values.

Figure 1e showed that high UK/UK+UNa ratio (> 0.5–0.6) in the low GFR correlates well with high renin and aldosterone.

Discussion

The first report describing hypovolemia in nephrotic syndrome came from Meltzer et al. [10] where authors stated that the nephrosis state is characterized by a subgroup of patients presenting with hypervolemia, low renin, and aldosterone compared to hypovolemia and renin-induced vasoconstriction in another subgroup [10]. Nephrotic syndrome is defined by proteinuria (> 3.5 g/l/day), hypoalbuminemia (< 25 g/l), generalized anasarca, and hypertriglyceridemia. As a result of this, patients are prone to develop complications such as hypovolemia, peritonitis, thromboembolic complications secondary to hypercoagulability, and renal impairment. Substantial variations in the management of nephrotic syndrome exist especially concerning the treatment of hypoalbuminemia [13].

Treatment with albumin infusion and/or diuretics aimed at restoring or maintaining intravascular volume in patients with hypoalbuminemia and edema has been a subject of controversy [7, 13]. Clinical assessment of intravascular volume status in these patients can be hampered by factors such as overt edema and tachycardia secondary to infection or patient discomfort. AKI can in theory be caused by circulatory collapse secondary to hypovolemia-related massive loss of albumin and septicemia with acute aggravation of the capillary leak [18]. Our data suggest that a particular subgroup of patients with nephrotic syndrome exhibits features consistent with hypovolemia resulting in decreased GFR. Correctly diagnosing hypovolemia in nephrotic syndrome has important clinical

implications since those patients will most likely benefit from volume restitution by albumine infusion with less risk of hypervolemia. The risk of lung edema secondary to fluid overload after albumin infusion is an important drawback of albumin administration in nephrotic syndrome [11] and emphasizes the importance of correctly assessing intravascular volume status. Untreated hypovolemia on the other hand can be associated with circulatory failure and increased risk of thrombotic complications [11]. Our data showed lower albumin in the low GFR group with higher levels of vaso-active hormones. FENa values showed a wide variability and significant overlap with the other GFR groups which makes this a less useful indicator of volume status, consistent with earlier observations [16]. In addition, significantly lower renal plasma flow (RPF) and higher UK/UK+UNa ratio in the low GFR group confirmed our theory that the low GFR group actually represent patients with hypovolemia.

UK/UK+UNa ratio can be successfully used by clinicians now to differentiate which patients might benefit from albumin infusion. We hypothesize that the higher the PRA and aldosterone levels (due to secondary hyperaldosteronism) reflecting volume depletion, the higher the urinary potassium excretion and sodium reabsorption explaining the fact that hypovolemia coincides with higher UK/UK+UNa ratio. This equation was first reported in a previous study [16] in which was shown that higher UK/UK+UNa (ratio > 0.5–0.6) coincided with volume contraction and higher aldosterone levels.

In nephrotic syndrome, albumin levels tend to influence tubular excretion of creatinine [2] which adds to the inaccuracy of creatinine-based estimation of GFR. By concomitantly measuring GFR based on creatinine and inulin (in addition to RPF) in this study, it is clear that even though an overestimation of GFR is seen in the creatinine-based estimation, this does not alter the conclusive findings since GFR remains significantly lower in a specific subset of patients.

Our study did have some limitations. The relatively small sample size ($N = 44$) of the study limits the ability to generalize these findings, and the presence of residual confounding cannot be completely excluded. The fact that parameters such serum albumin, PRA, and aldosterone levels were not significantly different in the groups could be a consequence of the limited sample size. However, we believe that our associations are accurate since these associations are consistent with previous studies [6, 10, 16]. Our data suggests that a subgroup of pediatric patients has a decrease of GFR, associated with significant decrease of renal blood flow, as measured by paraaminohippuric acid, and likely coinciding with high renin-aldosterone levels. The combination of these three parameters can only be explained by functional hypovolemia. On the other hand of the spectrum, there is a group of patients with high GFR, high renal blood flow, and low vaso-active hormones, having all the characteristics of hypervolemia. Assessing intravascular volume status in nephrotic syndrome

remains challenging but this study suggests that measuring UK/UK+UNa can provide important information enabling adequate treatment decisions to be made.

Authors' contributions Werner Keenswijk and Mohamad Ikram Ilias wrote the initial draft of this manuscript. All authors contributed to drafting, revising, and finalizing the manuscript and agreed with submission to the European journal of pediatrics.

Compliance with ethical standards The study was performed in accordance with the Declaration of Helsinki and ethical approval was obtained from the hospital ethical committee.

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

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