ORIGINAL ARTICLE

Renal volume and function in school-age children born preterm or small for gestational age

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Abstract Impaired renal development during foetal life is a proposed mechanism for adult hypertension in people born small. Whether preterm birth contributes to such adverse development is still unclear. We investigated the selective contributions from foetal growth restriction or preterm birth to renal function and volume in children with low birth weight. Three groups of 9 to 12-year-old children were studied: those born at <32 gestational weeks (preterm, $n=39$), those born at term but small for gestational age (SGA, $n=29$) and those born at the term appropriate for gestational age (controls, $n=37$). We estimated renal function by calculating glomerular filtration rate (GFR) and by measuring urinary proteins. Volumetric ultrasound of the kidneys was performed in 86 children (preterm, $n=33$; SGA, $n=25$; controls, $n=29$). Estimated glomerular filtration rate (eGFR) and urinary protein patterns were similar between the groups. Kidney volume (preterm 162 ml (31); SGA 163 ml (26) and controls 182 ml (47)) was smaller in the preterm group than in the controls, but the difference was not significant when adjusted for body surface area, gender and age ($P=0.25$). Total renal volume correlated to birth weight ($r=0.23$, $P=0.03$). No significant differences were found in renal function or volume between the three groups at school age.

Keywords Intrauterine growth restriction · Prematurity · Renal function · Renal volume · Small for gestational age

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Introduction

Low birth weight is a risk factor for the development of hypertension and cardiovascular disease later in life [1]. The causal pathways for this association are still unclear. Brenner et al. [2] and Brenner and Chertow [3] introduced the theory that poor foetal growth would result in fewer nephrons and increased renal disease later in life. Fewer nephrons, with subsequent hyperfiltration and glomerulosclerosis in the remaining nephrons, could lead to accelerated ageing and early loss of renal function. This hypothesis is supported by human post-mortem and animal studies, where low birth weight is found to correlate to fewer nephrons and, thereby, reduced kidney weight/volume [4–8]. Other studies imply that renal disease in adults can be correlated to low birth weight [9, 10].

Few studies differentiate between low birth weight due to intrauterine growth restriction (IUGR) and that due to prematurity. Very preterm infants have a precarious postnatal period, with inadequate nutrition, poor growth, medical complications and a stressful environment, which could compromise kidney development [11]. We have previously shown that preterm birth is associated with decreased renal function during the first year of life [11], higher catecholamines and heart rates in childhood [12] and higher blood pressure in adolescent and adult women and men [13–15].

We undertook this study to investigate whether premature birth and low birth weight due to IUGR are risk factors for smaller kidneys and renal impairment in childhood.

Subjects and method

Subjects

Three groups of healthy school children with different perinatal exposures were investigated: 39 children born before 32 gestational weeks (preterm), 29 born at term and small for gestational age (SGA), and 37 born at term with appropriate birth weight for gestational age (control). Gestational age was determined by ultrasound in early pregnancy [16]. Term was defined as a gestational age between 37 and 42 weeks. SGA was defined as a birth weight < mean −2 standard deviations (SDs) (i.e. below the gender-specific 2.5th centile for gestational age) according to Swedish reference data for normal foetal growth [17]. Of the 29 children in the SGA group, ten had a ponderal index (PI) <2.3, suggesting asymmetrical intrauterine growth. PI was calculated as birth weight (in kilogrammes)×100/birth length (in centimetres, cubed) [18]. In the six children in the preterm group who were also SGA, the PI was similar to that of the other preterm children [mean (SD) 2.15 (0.31) and 2.18 (0.42)].

To compare birth weights in the three groups we used the z-score, calculated by subtracting the individual birth weight from the expected birth weight, according to the Swedish reference curve [17], and dividing that difference by the standard deviation of birth weights in the three groups, respectively. The z-scores in the preterm, SGA and control groups were −0.72 (1.03), −3.14 (0.59) and −0.05 (0.87).

All children were singletons, born in northern Stockholm at Karolinska Hospital, without chromosomal anomalies, congenital infections, life-threatening congenital anomalies or urogenital malformations. The preterm and SGA groups consisted of children born consecutively and cared for at the neonatal intensive care unit (NICU) and the maternity ward, respectively. Subsequently, children born at term with normal birth weights (controls) and matched for date of birth and gender were selected from the delivery room records. All control infants were healthy at birth and had not been admitted to the NICU. A total of 390 children were eligible for the study, but 133 could not be reached due to changed addresses. Of the remaining 257 invited families, 105 accepted the invitation to participate in the study. The perinatal characteristics of the children not participating were similar to those of the three study groups—the gestational age (weeks) and birth weight (grammes) were 27.5 (2.0) and 987 (243) in the preterm group, 39.5 (1.2) and

2,460 (269) in the SGA group, and 40.1 (1.0) and 3,635 (449) in the controls, respectively.

Information on maternal and neonatal characteristics was collected from the Swedish birth records. Maternal age, maternal smoking and maternal history of hypertension/pre-eclampsia [19], prenatal steroid administration, date of birth, gestational age, birth weight, Apgar scores, and highest serum creatinine value after the first postnatal week of life and highest serum C-reactive protein (CRP) level during stay in the NICU were noted. The medical charts were reviewed for pertinent data, including ventilatory support and neonatal morbidity for the preterm subjects. Maternal, perinatal and current characteristics for the 105 children investigated are presented in Tables 1, 2 and 3.

The study was approved by the Ethics Committee at Karolinska University Hospital. Written consent was obtained from the parents and children.

First study period: determination of renal function and blood pressure

Renal function tests were performed when the children were, on average, 9 years old [12]. Of the 105 children, 21 refused blood sampling. Accordingly, estimated glomerular filtration rate (eGFR), in millilitres per minute per 1.73 m^2 body surface area, was calculated in 84 children (28 preterm, 23 SGA and 33 controls) (Table 2). We used serum creatinine level, analysed by the Jaffe method (Beckman Coulters instrument LX, Fullerton, California, USA), to calculate eGFR by the Schwartz formula [20]. Serum cystatin-C was measured with the Dade Behring Cystatin C assay with the automated Dade Behring Nephelometer II (BNII).

In 55 children the preparation of the first morning urine sample was unsuccessful. Urine albumin, urine immuno-

Table 1 Maternal and perinatal characteristics of healthy children born preterm (*Preterm*), small for gestational age at term (*SGA*) or with normal birth weight at term (*Controls*). Values are numbers or means (SD)

Characteristics	Preterm (*n*=39)	SGA (*n*=29)	Controls (*n*=37)
Maternal data			
Smoking during pregnancy	8	6	7
Pre-eclampsia	10*	4*	0
Prenatal steroids	3*	0	0
Perinatal data			
Girls (%)	22 (56)	16 (55)	24 (65)
Gestational age, weeks	26.6 (2.0)	39.3 (1.4)	39.6 (1.0)
Birth weight, g	954 (203)	2436 (331)	3485 (502)
Birth length, cm	35.5 (2.9)	46.9 (2.4)	50.0 (2.2)
Ponderal index, g/cm cubed	2.16 (0.29)	2.38 (0.33)	2.79 (0.31)

*Significant difference (*P*<0.05) versus controls

Table 2 Characteristics at first visit and renal function parameters in healthy children born preterm (*Preterm*), small for gestational age at term (*SGA*) or with normal birth weight at term (*Controls*). Values are given as means (SD). Blood pressure data have previously been presented by our group [16]. *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *S-cystatin C* serum cystatin-C, *eGFR* estimated glomerular filtration rate, *Urine IgG* urine immunoglobulin G, *Urine A1M* urine-alpha-1-microglobulin, *Urine NAG* urine-*N*-acetylglucosamine

Parameter	Preterm	SGA	Controls
Characteristics at first visit			
	$n=39$	$n=29$	$n=37$
Age, years	9.6 (0.3)*	9.8 (0.3)	9.8 (0.2)
Weight, kg	32 (7.2)*	32 (7.3)*	38 (9.0)
Height, cm	134 (6.6)*	137 (7.1)*	142 (7.6)
Body mass index, kg/m^2	17.7 (3.0)	16.8 (2.5)*	18.5 (3.2)
Body surface area, m^2	1.09 (0.14)*	1.09 (0.15)*	1.21 (0.17)
SBP at rest	105 (9)	103 (8)	107 (10)
SBP standing up	107 (10)	103 (9)	106 (8)
SBP after mental stress	109 (9)	107 (7)	110 (8)
DBP at rest	58 (8)	59 (8)	58 (7)
DBP standing up	62 (8)	61 (9)	61 (6)
DBP after mental stress	64 (8)	62 (8)	64 (7)
Renal function			
	$n=28$	$n=23$	$n=33$
S-creatinine, mmol/l	77.1 (1.8)	77.9 (1.9)	81.6 (1.6)
S-cystatin C, mg/l	0.91 (0.03)	0.88 (0.03)	0.83 (0.03)
eGFR ml/min per 1.73 m^2 body surface area	89.6 (13.5)	88.8 (12.3)	88.3 (10.7)
Urinary protein excretion/urinary creatinine			
	$n=12$	$n=22$	$n=16$
Urine albumin, mg/mmol	0.6 (0.4)	0.8 (0.7)	0.7 (1.0)
Urine IgG, mg/mmol	0.2 (0.1)	0.3 (0.2)	0.4 (0.4)
Urine A1M, mg/mmol	0.7 (0.7)	0.6 (0.6)	0.6 (0.7)
Urine NAG, nkat/mmol	4.7 (3.4)	3.2 (1.5)	3.7 (3.5)

*Significant difference (*P*<0.05) compared to controls

Table 3 Unadjusted renal volumes in healthy children born preterm (*Preterm*), small for gestational age at term (*SGA*) and with normal birth weight at term (*Controls*). Values are given as means (SD)

Parameter	Preterm ($n=33$)	SGA ($n=24$)	Controls ($n=29$)
Characteristics in kidney volume studies			
Age, years	12.9 (0.3)	12.0 (0.3)*	12.7 (0.2)
Weight, kg	47.5 (10.4)*	43.9 (10.6)*	52.2 (12.8)
Height, cm	153.9 (9.4)*	152.9 (9.5)*	159.2 (8.9)
Body mass index, kg/m^2	20.1 (3.2)	18.3 (3.0)*	20.6 (3.7)
Body surface area, m^2	1.42 (0.19)	1.35 (0.20)*	1.51 (0.22)
Kidney volume			
Total kidney volume, ml	162 (31)*	163 (26)	182 (47)
Left kidney volume, ml	79.5 (15.2)	84.8 (16.5)	90.4 (22.8)
Right kidney volume, ml	82.4 (19.3)	78.4 (15.4)	91.1 (27.4)

*Significant differences between Preterm or SGA compared to Controls

globulin G (U-IgG) and urine alpha-1 microglobulin (U-A1M) were analysed by the immunonephelometry method, and urinary *N*-acetylglucosamine (U-NAG) was analysed by the colorimetric method (Cobas Mira, Hoffmann–La Roche AG, Basel, Switzerland) in 12 preterm, 22 SGA and 16 control children. Urinary protein excretions were calculated as ratios to urinary creatinine, in milligrammes or nanokatals per millimole creatinine. The urinary proteins were used as markers not only of glomerular damage due to hyperfiltration but also for signs of tubular damage due to dysplasia or interstitial fibrosis.

Blood pressure and anthropometric measurements were performed by the same research nurse during a morning visit to Karolinska University Hospital [12]. Briefly, after the children had fasted overnight and rested for at least 15 min, their blood pressures (BPs) were recorded while they were lying down with their arms at heart level. An automated, non-invasive oscillometric technique (Dinamap) [21] was used, and an average of three readings determined the resting BP values. The intra-individual coefficient of variation for resting BP in children has been found to vary between 6% and 9% in our laboratory [13]. Following resting measurements, the subjects were asked to stand up. An average of three consecutive BP measurements obtained 30 s after the subjects had stood up was calculated and designated the standing BP. After the subjects had sat down and resting for at least 15 min, a mathematical stress test was performed after which BP was determined.

Second study period: determination of kidney volume

Kidney volumes were measured when the children had reached an average age of 12 years. At this time, 19/105 declined to participate. The volumes were measured by ultrasound in 86 children (33 preterm, 24 SGA and 29 controls). All investigations were done by the same investigator using the same ultrasound system (Accuson 128XP with three 5.5 MHz linear transducers). The children were examined while in a prone position, and a pillow ventral to the upper abdomen was used to compensate for lumbar lordosis. The kidney was identified in the sagittal plane along the longitudinal axis. In this position, up to three longitudinal measurements of the largest length and width were performed. The probe was than rotated 90° and the measurements of depth and width at the hilar level were taken. The highest measurements were consistently used for calculations. Renal volume was established by the formula for an ellipsoid: length × thickness × width × 0.5233, and calculated in cubic centimetres (cm^3) [22]. Left and right kidney volumes were separately investigated and then the values were added together to provide the total kidney volume.

Anthropometric data were obtained for all children by the same research nurse who performed the same measurements for the first study period. Body mass index (BMI) was calculated by the formula: weight (kg)/height (m²). Body surface area (BSA), in square metres, was measured according to the formula from Haycock ($0.024265 \times$ height $(cm)^{0.3964} \times$ weight$(kg)^{0.5378}$) [23].

Statistics

Data are presented as numbers or as mean values with one standard deviation (SD).

Normal probability plots confirmed the normal distribution for the different variables, including renal volume in the three groups. In two control children, total renal volume (300 ml and 340 ml, respectively) exceeded +3 SDs from the mean (169 ml). These observations where considered as outliers and were excluded from further statistical testing. Bartlett's test did not disclose any significant differences in variances between the three groups ($P = 0.59$).

Analyses were computed with the STATA software package, version 9, using the analysis of variance (ANOVA) command presenting regression coefficients for the specified models. Reported P values from the ANOVA command were the P values for the regression coefficients for the preterm and term SGA categories. A P value of less than 0.05 was defined as significant. We used analyses of variance to analyse group differences in kidney function and volumes.

For renal volume comparisons, we adjusted for gender, age, and BSA. BSA and age were entered as continuous variables and gender as a categorical variable (boys/girls). Associations between renal volume and weight, length and BSA at 13 years of age—for all children and for the individual groups—were all significant and similar, with the exception of the SGA group where none of the variables was statistically correlated.

Due to the heterogeneous body dimensions in the three groups of children we thought that it would be reasonable to adjust for BMI as well as for BSA (Table 3). We therefore also present the results after adjusting for BMI instead of BSA (Table 4), as supported by other authors [24–26]. It is important to mention that the significant differences between the groups was stronger for BSA than for BMI ($P = 0.017$ versus $P = 0.045$), supporting BSA as the better adjustment factor.

We considered group differences in renal function and renal volume of 10% as important. For this purpose we calculated the sample size to 30 in each group, with 80% power and a significance level of 0.05.

Analyses of BP were adjusted for height and maternal pre-eclampsia. Besides being potential confounders, both factors were unequally distributed in the three study groups.

Table 4 Total kidney volume, adjusted for age and gender, of healthy children born preterm ($n=33$) or small for gestational age (*SGA*) at term ($n=24$), compared with that of controls born with normal birth weight at term ($n=27$). Body mass index (*BMI*) or body surface area (*BSA*) were used as indices of body size. Estimates are based on ANOVA

Parameter	Regression coefficient, ml	SEM	P
Regression model 1a: kidney volume vs birth category, BMI, age and gender			
Preterm birth	−14.3	7.05	0.046
SGA at term	−1.72	7.43	0.820
BMI, kg/m²	4.62	0.87	<0.0001
Model 1b: kidney volume vs birth category, BMI, age and gender (preterm SGA excluded, $n=6$)			
Preterm birth	−19.9	7.66	0.011
Born SGA at term	−2.19	7.50	0.771
BMI, kg/m²	4.5	0.91	<0.0001
Model 2a: kidney volume vs birth category, BSA, age and gender			
Preterm birth	−7.54	6.58	0.255
Born SGA at term	2.07	6.92	0.765
BSA, m²	91.4	13.4	<0.0001
Model 2b: kidney volume vs birth category, BSA, age and gender (preterm SGA excluded, $n=6$)			
Preterm birth	−12.9	7.18	0.076
Born SGA at term	1.43	7.02	0.84
BSA, m²	89.0	14.1	<0.0001

We used regression analyses to study possible associations between kidney function and volume and perinatal factors. Simple logistic regression was used for continuous variables, and the chi-square test was used for binary variables. We used stepwise forward regression, entering independent variables with $P < 0.20$ in simple regression analyses. Independent variables included: gestational age at birth, birth weight, gender, Apgar score at 10 min, birth weight z-score, maternal hypertension during pregnancy, delivery mode, prenatal and/or postnatal steroid administration, patent ductus arteriosus (PDA) and duration of continuous positive pressure support. Independent variables tested, but not included in the regression analysis, were: age at study, respiratory distress syndrome, bronchopulmonary dysplasia, necrotising enterocolitis and intraventricular haemorrhage.

Results

Kidney function

The mean eGFR was 88.8 ml/min per 1.73m² (12.0) and it did not differ significantly between the three groups (Table 2). Concentrations of serum creatinine and serum

cystatin C did not differ between the groups ($P=0.146$ and $P=0.113$, respectively). In addition, the urinary protein patterns for albumin, NAG, IgG and A1M in relation to urinary creatinine were similar in the three groups (Table 2).

BP results have been presented in a previous publication (Table 2) [12]. There were no differences between the groups. Twelve children (five preterm, three SGA, four controls) had resting blood pressure in the hypertensive range, after adjustment for age and gender, and height-adjusted diastolic or systolic BP≥90th percentile on the study day.

Kidney volume

The total kidney volume was 162 (31) ml in children born preterm, 163 (26) ml in children born SGA and 182 (47) ml in the control group ($P=0.073$ between all groups; $P=0.035$ preterm versus control; $P=0.069$ SGA versus control). Separate values for the right and left kidney volumes are presented in Table 3. After adjustment for BSA and gender, differences in total kidney volume between preterm and control groups became non-significant (7.5 ml lower in preterm, $P=0.255$), as also after we had excluded the six subjects born SGA in the preterm group (12.9 ml lower in preterm, $P=0.076$, Table 4). In the SGA group, renal volume was not different from that of controls (Table 4).

Birth weight correlated to total renal volume ($r=0.23$, $P=0.03$). In the preterm children, total renal volume did not correlate to gestational age ($r=0.33$, $P=0.06$) but it correlated to birth length ($r=0.36$, $P=0.04$).

After adjusting for, gender and age, and BMI instead of BSA, we found that total kidney volume was 14.3 ml lower in children born preterm than in controls ($P=0.046$) (Table 4). The difference increased to a 19.9 ml lower kidney volume in preterm children compared with controls after exclusion of the six subjects born SGA in the preterm group ($P=0.011$).

None of the blood pressure measurements correlated to eGFR.

Risk factors for reduced kidney volume after preterm birth

Neonatal serum creatinine ($P=0.35$), serum C-reactive protein (S-CRP) ($P=0.72$), dopamine administration ($P=0.51$) or the presence of a patent ductus arteriosis ($P=0.33$) did not correlate to renal volume. There was neonatal renal failure, defined as serum creatinine >100 mmol/ml after 1 week postnatal age, in seven preterm children. The two with the highest serum creatinine values during their neonatal hospital stay had the smallest kidneys.

Discussion

Our study demonstrated that children born preterm had insignificantly smaller kidney volume at school age, after we had adjusted for BSA, gender and age. Children born full term but with growth restriction had a kidney size comparable to that of the children born preterm, but after adjustment for current body size, no difference was found in comparison with the control group. Renal function was similar in the three groups with different birth characteristics.

The strength of the study is that our three groups were well defined with regard to gestational age at birth and foetal growth restriction. The children born preterm are representative for extremely preterm births, with a mean gestational age of 27 weeks and a mean birth weight of 1,000 grams. Secondly, all examinations were performed by the same research nurse and all ultrasound determinations by the same physician.

The weaknesses of the study are the small sample size and that not all children could be examined for both renal function and kidney volume. The point estimate indicated a lower renal volume in children born preterm (7–13 ml). However, we were not able to show a significant difference in kidney volume when adjusting for BSA, gender and age. This could be due to limitations in power.

eGFR is only an estimate and underestimates the gold standard of inulin clearance. The value of k used to calculate eGFR is also dependent on muscle mass, which could have differed in the three groups. Another limitation is that the volumetric investigations of the kidney by ultrasound were performed 3 years after the renal function tests and blood pressure measurements were done [12.6 (0.3) years and 9.6 (0.3) years, respectively]. We cannot exclude the possibility that, at the time that we detected lower kidney volume, renal function could have deteriorated in school age children born preterm.

With regard to renal volume, our findings could not confirm those of Schmidt et al. [27], who found significantly smaller kidneys up to 18 months of age in 178 infants born with low birth weight, including preterm infants. Catch-up growth for kidney volume was significant except for the infants born preterm.

We did not find deterioration in renal function in the children born preterm as other studies have found. Keijzer-Veen et al. [28] clearly showed that preterm birth in combination with intrauterine growth restriction led to unfavourable renal function at 19 years of age in 422 subjects. Rodríguez-Soriano et al. [29] were not able either to demonstrate smaller kidney volume in 40 children born preterm at 6–12 years of age compared to estimated normal values; however, there was no volumetric estimation

performed in the control group. On the other hand they found lower creatinine clearance in the children born preterm than in the control group.

Kidney volume is thought to be directly related to the number of nephrons, and, therefore, volumetric estimation of the kidney by ultrasound is an indirect measurement of the number of functional units in the kidney [30]. Autopsy studies have shown that there is a lack of compensation in nephron number and size in infants born with foetal growth restriction [4–6] as well as in children born preterm [31, 32]. The nephrons, however, undergo glomerular hypertrophy and mesangial proliferation. Final renal size should be influenced by the nephron size. Glomerular hypertrophy and, secondarily, relative increase in renal size could partly explain the lack of significant findings in the children with foetal growth restriction. Similar kidney function in the children born preterm suggests that the smaller kidneys due to fewer nephrons are still able to compensate by a greater utilisation of the remaining functional units of the kidney, but no signs of glomerular or tubular damage is present at this time.

We speculated that children born preterm have smaller kidneys due to the compromising postnatal period, with inadequate nutrition, a stressful environment, and medical complications. These factors, as well as the administration of nephrotoxic drugs such as indomethacin and aminoglycosides, could negatively affect normal nephrogenesis [33]. However, we could not confirm those speculations in our study.

In conclusion, children born preterm or small for gestational age at term showed no significant differences in glomerular filtration and renal volume from those born with normal birth weight at term. Although the power of this conclusion is limited by the small numbers, it points to alternative explanations for the increased risk of hypertension in people who were born too small and too early. Other mechanisms, such as differences in renal sodium handling or the sympathetic nervous system, may be equally or even more important than a reduction in nephron numbers and kidney size.

In the future, it could be of value to look at flow patterns of arterial and venous vessels to and from the kidney to be able to detect increased resistance as an indicator for structural changes in the kidneys' micro-architecture. Continued follow-up of these children to a higher age is necessary, to detect eventual changes in kidney function as early as possible.

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