Reduced renal length and volume 20 years after very preterm birth

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Abstract Intrauterine growth retardation is presumed to be associated with decreased renal size and impaired renal function as a result of stunted kidney development and nephron deficit. To study whether very preterm birth also affects renal size at young adulthood, we sonographically measured bipolar kidney length and volume in 51 very premature individuals (<32 weeks of gestation), either small (SGA) or appropriate (AGA) for gestational age (22 SGA and 29 AGA), and 30 full-term controls 20 years after birth. Relative kidney length and volume were calculated. Both absolute and relative left kidney length and volume were significantly lower in SGA and AGA individuals, notably in women. Renal size did not differ between SGA and AGA individuals. In 70% of controls, the left kidney was larger than the right one compared with 40.9% in SGA [relative risk (RR) 1.7; 95% confidence interval (CI) 1.0 −3.0] and 48.3% in AGA (RR 1.5; 95% CI 0.9 −2.3) individuals. Renal structural anomalies were present in eight prematurely born participants only. Our data suggest that kidney growth is stunted after preterm birth, especially on the left side, and in the female gender.

Keywords Renal growth · Kidney development · Developmental origins of health and disease · Renal ultrasound · Preterm birth · Intrauterine growth retardation

Introduction

An increasing number of studies show an association between intrauterine growth retardation (IUGR) and underdevelopment of the fetal kidneys, with limited nephron number and decreased renal size [1–4]. Furthermore, birth weight appears to be a strong determinant of renal size, nephron number, glomerular volume, albuminuria and systolic blood pressure [5, 6]. These findings add weight to the hypothesis that IUGR carries a risk of renal function loss as a result of nephron deficit, loss of filtration surface area, hyperfiltration, glomerular hypertension, and glomerular damage [7]. As nephrogenesis continues until 36 weeks of gestation, very preterm babies (gestational age <32 weeks) are likely to show a nephron deficit at birth [8]. In addition, preterm birth is known to be associated with impaired nephrogenesis [9, 10] and limited postnatal kidney growth until the age of 18–24 months [11, 12]. Whether adult renal size is also impaired after premature birth compared with full-term birth or whether renal catch-up growth during childhood is present has not yet been studied.

We report reduced renal size (length and volume) in 20-year-old individuals born very prematurely [13]. Renal...
size was correlated with glomerular filtration rate (GFR) (ml/min/1.73 m²) and effective renal plasma flow (ml/min/1.73 m²). The data reported here documents an additional analysis on renal size in the same cohort.

Methods

Study population

We recruited three groups of 20-year-olds: (1) Those born very prematurely (<32 weeks) and small for gestational age (SGA), (2) those born very prematurely and appropriate for gestational age (AGA), and (3) those born full term (37–42 weeks) and AGA (controls). The SGA and AGA groups participated in a follow-up study of almost all (94%) of live-born individuals in the Netherlands with a gestational age <32 weeks and/or a birth weight <1,500 g. This is the POPS cohort: Project on Prematures and Small for Gestational Age infants. Participants in the our study had participated in the most recent POPS 19 study (N=422) [14]. Recruitment of SGA individuals started with the lowest birth weight adjusted for gestational age [≤−2 standard deviation scores (SDS) N=29] and that of AGA individuals with the highest birth weight adjusted for gestational age (0–2 SDS N=205). Controls born between 1 January 1982 and 31 December 1984 were recruited by advertisement posted in the Erasmus Medical Center, Rotterdam, The Netherlands.

Renal ultrasound

Participants underwent renal function testing, blood pressure measurement, and renal ultrasound study in the Erasmus MC Sophia Children’s Hospital, Rotterdam [13]. Each of the three pediatric radiologists performed renal ultrasound by standardized protocol. Renal size was measured in the prone position with a Philips ATL HDI 5000 scanner with a C5–2 curved-array transducer (Philips Nederland BV, Eindhoven, The Netherlands). Measures of maximal bipolar kidney length, width, and thickness were obtained for both kidneys. Renal width and thickness were measured at the level of the kidney hilum. Renal volume (ml) was calculated using the formula for an ellipsoid: \( \frac{\pi}{6} \times \text{length (cm)} \times \text{width (cm)} \times \text{thickness (cm)} \) [15]. Cortical thickness was defined as the distance between the external surface of the kidney and top of the medulla. As absolute renal size is known to be associated with body size, we calculated the relative kidney length length (bipolar kidney length (cm) / body height (m)) and relative kidney volume (bipolar kidney length (ml) / body surface area (BSA, m²)) [16]. Body surface area (BSA) was calculated using the equation \( \sqrt{\frac{\text{body height (m)} \times \text{weight (kg)}}{3600}} \). Any renal or ureterovesical anomalies noted were reported.

Intra- and interobserver variability

Intra- and interobserver variability for the three pediatric radiologists were calculated beforehand for measurements

| Table 1 | Subject baseline characteristics |
|---------|---------------------------------|
|         | SGA N=22                        | AGA N=29                        | Controls N=30 | ANOVA p value | Post hoc p value |
|         | Mean   | SD    | Mean   | SD    | Mean   | SD    | Mean   | SD    | Bonferroni |
| Age (years) | 20.7   | 0.2   | 20.7   | 0.4   | 20.7   | 0.8   | 20.7   | 0.8   | 1.0        |
| Males [% (number)] | 40.9   | 9     | 37.9   | 11    | 46.7   | 14    | 0.7    | (χ²)   | All<0.01   |
| BW (g)   | 860    | 129   | 1489   | 257   | 3632   | 489   | <0.001* | All<0.01 |
| GA (weeks) | 30.6   | 1.0   | 29.5   | 1.4   | 40.2   | 1.3   | <0.001* | All<0.01 |
| BW (SDS) | −2.3   | 1.0   | 0.7    | 0.5   | 0.3    | 1.0   | <0.001* | 0.09, <0.001b,c |
| Body height (cm) | 167   | 11    | 174    | 7.7   | 176    | 10    | <0.01* | <0.01b, 0.05c |
| Body height (SDS) | −1.3   | 1.1   | −0.2   | 0.9   | −0.1   | 1.1   | <0.001* | <0.001b,c |
| Body weight (kg) | 60.6   | 9.0   | 67.4   | 12.0  | 71.4   | 11.7  | <0.01* | <0.01b |
| Body weight (SDS) | −1.1   | 1.3   | −0.2   | 1.0   | 0.2    | 1.2   | <0.01* | <0.01b |
| BMI (kg/m²) | 21.7   | 2.6   | 22.1   | 2.8   | 22.9   | 2.8   | 0.2    | 0.2    |
| BSA      | 1.68   | 0.17  | 1.80   | 0.19  | 1.87   | 0.19  | <0.01* | <0.01b, 0.05c |

Data expressed by mean [standard deviation (SD)] and analysis of variance (ANOVA) p value with Bonferroni post hoc multiple testing

| SGA | small for gestational age prematurely born individuals, AGA | appropriate for gestational age prematurely born individuals, Controls | appropriate for gestational age term-born individuals, BW | birth weight, GA | gestational age, BW SDS | birth weight standard deviation score, BMI | body mass index |
|-----|----------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------|

* p value<0.05
Table 2 Renal size in three study groups

|                          | Males       | Females     | All         | ANOVA p value | Post hoc p value | Bonferroni |
|--------------------------|-------------|-------------|-------------|---------------|------------------|------------|
|                          | Mean  SD    | Mean  SD    | Mean  SD    |               |                  |            |
| Total absolute kidney length (cm) |             |             |             | 0.007*        | 0.007b*          |            |
| SGA (N=22)               | 20.7  1.3   | 19.9  1.5   | 20.2  1.5   |               |                  |            |
| AGA (N=29)               | 21.3  2.0   | 20.3  1.3   | 20.7  1.6   |               |                  |            |
| Controls (N=30)          | 21.9  2.5   | 21.4  1.0   | 21.7  1.8   |               |                  |            |
| Total absolute kidney volume (ml) |             |             |             | 0.005*        | 0.033b*          | 0.008b*   |
| SGA (N=22)               | 298.7 76.6  | 216.2 58.1  | 249.9 76.7  |               |                  |            |
| AGA (N=29)               | 286.8 60.3  | 248.8 35.9  | 263.2 49.3  |               |                  |            |
| Controls (N=30)          | 313.7 93.9  | 307.3 67.9  | 310.3 79.7  |               |                  |            |
| Left absolute kidney length (cm) |             |             |             | 0.001*        | 0.022a*          | 0.001b*   |
| SGA (N=22)               | 10.1  0.6   | 9.9  0.7    | 10.0  0.7   |               |                  |            |
| AGA (N=29)               | 10.6  1.4   | 10.2  0.9   | 10.4  1.1   |               |                  |            |
| Controls (N=30)          | 11.1  1.4   | 11.0  0.6   | 11.1  1.0   |               |                  |            |
| Left relative kidney length (cm/m) |             |             |             | 0.044*        | 0.059a*          |            |
| SGA (N=22)               | 5.7  0.3    | 6.2  0.4    | 6.0  0.4    |               |                  |            |
| AGA (N=29)               | 5.9  0.7    | 6.0  0.5    | 6.0  0.6    |               |                  |            |
| Controls (N=30)          | 6.1  0.7    | 6.5  0.3    | 6.3  0.6    |               |                  |            |
| Left absolute kidney volume (ml) |             |             |             | <0.001*       | 0.003a*          | 0.001b*   |
| SGA (N=22)               | 147.8 38.6  | 107.1 26.2  | 123.8 37.1  |               |                  |            |
| AGA (N=29)               | 139.0 32.4  | 123.0 19.4  | 129.1 25.8  |               |                  |            |
| Controls (N=30)          | 164.6 40.1  | 157.0 45.4  | 160.5 42.4  |               |                  |            |
| Left relative kidney volume (ml/m²) |             |             |             | 0.006*        | 0.008a*          | 0.045b*   |
| SGA (N=22)               | 82.9 22.5   | 67.0 14.2   | 73.5 19.3   |               |                  |            |
| AGA (N=29)               | 70.1 12.3   | 72.4 10.9   | 71.5 11.3   |               |                  |            |
| Controls (N=30)          | 83.3 17.1   | 88.8 26.6   | 86.2 22.4   |               |                  |            |
| Left cortical thickness (cm) |             |             |             | 0.188         |                  |            |
| SGA (N=22)               | 1.0  0.3    | 0.9  0.2    | 0.9  0.2    |               |                  |            |
| AGA (N=29)               | 0.8  0.3    | 1.0  0.3    | 0.9  0.3    |               |                  |            |
| Controls (N=30)          | 1.0  0.4    | 1.1  0.4    | 1.1  0.4    |               |                  |            |
| Right absolute kidney length (cm) |             |             |             | 0.207         |                  |            |
| SGA (N=22)               | 10.5  0.8   | 10.0  0.9   | 10.2  0.9   |               |                  |            |
| AGA (N=28)               | 10.7  0.7   | 10.1  0.7   | 10.3  0.7   |               |                  |            |
| Controls (N=30)          | 10.8  1.3   | 10.4  0.6   | 10.6  1.0   |               |                  |            |
| Right relative kidney length (cm/m) |             |             |             | 0.360         |                  |            |
| SGA (N=22)               | 6.0  0.4    | 6.2  0.5    | 6.1  0.4    |               |                  |            |
| AGA (N=29)               | 5.9  0.2    | 5.9  0.5    | 5.9  0.4    |               |                  |            |
| Controls (N=30)          | 5.9  0.6    | 6.1  0.3    | 6.0  0.5    |               |                  |            |
| Right absolute kidney volume (ml) |             |             |             | 0.103         |                  |            |
| SGA (N=22)               | 150.9 44.4  | 109.1 34.9  | 126.2 43.5  |               |                  |            |
| AGA (N=29)               | 147.9 35.1  | 125.7 22.4  | 134.1 29.4  |               |                  |            |
| Controls (N=30)          | 149.1 57.6  | 150.3 37.0  | 149.7 46.8  |               |                  |            |
| Right relative kidney volume (ml/m²) |             |             |             | 0.473         |                  |            |
| SGA (N=22)               | 84.1 24.0   | 68.0 19.4   | 74.6 22.4   |               |                  |            |
| AGA (N=29)               | 75.0 16.5   | 73.8 10.7   | 74.2 12.9   |               |                  |            |
| Controls (N=30)          | 74.7 25.1   | 84.4 18.9   | 79.9 22.2   |               |                  |            |
in seven healthy students (five females, two males). The mean (95% limits of agreement) intraobserver variability for bipolar renal length ranged between 0.0 cm (−1.1 to 1.1) and 0.1 cm (−1.0 to 1.2) for the left kidney and 0.1 cm (−0.7 to 0.9) and 0.4 cm (−0.5 to 1.4) for the right kidney. The intraclass coefficient (ICC) for intraobserver variability was 0.97 for left bipolar kidney length and 0.88 for right bipolar kidney length. The mean (95% limits of agreement) interobserver variability for bipolar renal length ranged between 0.0 cm (−1.4 to 1.5) and 0.2 cm (−1.0 to 1.5) for the left kidney and 0.1 cm (−0.1 to 0.3) and 0.2 cm (−0.4 to 0.8) for the right kidney. The ICC for interobserver variability was 0.84 for left bipolar kidney length and 0.86 for right bipolar kidney length. Renal volume estimates varied more widely, but significant systematic errors within and between observers did not occur.

Informed consent and ethics committee

Informed consent was obtained from all participants after oral and written information had been given. The Erasmus MC University Medical Center ethical review board approved the study protocol.

Statistics

Statistical analysis was performed with SPSS 15.0 software. Results are presented as mean and SD. One-way analysis of

Table 2 (continued)

|                   | Males Mean | Males SD | Females Mean | Females SD | All Mean | All SD | ANOVA p value | Post hoc p value Bonferroni |
|-------------------|------------|----------|--------------|------------|----------|--------|--------------|----------------------------|
| Right cortical thickness (cm) |            |          |              |            |          |        |              |                            |
| SGA (N=22)        | 0.8        | 0.2      | 0.8          | 0.3        | 0.8      | 0.2    | 0.059        |                            |
| AGA (N=29)        | 0.8        | 0.3      | 0.8          | 0.3        | 0.8      | 0.3    |              |                            |
| Controls (N=30)   | 1.0        | 0.5      | 1.0          | 0.3        | 1.0      | 0.4    |              |                            |

Data expressed by mean [standard deviation (SD)] with analysis of variance (ANOVA) p value between groups for all individuals (males and females combined) and Bonferroni post hoc multiple testing between groups

SGA small for gestational age prematurely born individuals, AGA appropriate for gestational age prematurely born individuals, controls appropriate for gestational age term-born individuals

a AGA vs controls, b SGA vs controls

*p value < 0.05

Fig. 1 Mean kidney volume in right and left kidney in SGA, AGA and Controls

Fig. 2 Total kidney volume in the three study groups
variance (ANOVA) with post hoc multiple comparisons (Bonferroni) was used to analyze group differences in baseline characteristics. Pearson’s chi-square tests were performed to compare proportions of males between study groups; Fisher exact test was used to compare prevalences of renal anomalies. Multivariate regression analysis was used to determine regression coefficients in the association between body height or BSA and renal length and volume. Statistical significance was considered at the level of 5%.

Results

Baseline characteristics of study population

Eighty-two individuals agreed to participate: i.e. 23 SGA individuals, 29 AGA individuals, and 30 controls. However, one SGA individual suffered an unrelated allergic episode prior to study and did not undergo renal ultrasound, reducing the SGA group to 22. Baseline characteristics are shown in Table 1. Birth weight and gestational age significantly differed between the three groups. Current weight, height, and BSA of SGA individuals were lower than those of AGA individuals and controls, but body mass index (BMI) did not differ between groups.

Renal size

Renal size is detailed in Table 2. Male individuals had significantly larger kidney volume than female individuals (ANOVA p value<0.05). Left kidneys were larger than right kidneys in 70% of controls, in 48.3% of AGA individuals [relative risk (RR) 1.5; 95% confidence interval (CI) 0.9–2.3], and in 40.9% of SGA individuals (RR 1.7; 95% CI 1.0–3.0) (Fig. 1). Total kidney volume in both SGA and AGA individuals was significantly smaller than that in controls (p<0.05) (Table 2, Fig. 2). Also, absolute and relative left renal length and volume in SGA and AGA individuals were smaller than in controls. Right renal size did not differ between groups. Both left and right kidney size did not differ between SGA and AGA individuals. Cortical thickness did not differ between groups. Interestingly, after stratification for sex, all the above differences proved statistically significant in the female gender only.

Male and female individuals in the control group did not differ with regard to renal size for both kidneys. Male and female individuals in both the SGA and AGA groups differed statistically significantly with regard to total kidney volume (ANOVA p value<0.05). BSA was positively related to volume \[\beta 215\text{ ml/m}^2\ (95\%\ CI 147–283); p<0.001\] as shown in Fig. 3a. Body height was positively related to renal length \[\beta 0.09\text{ cm/cm} (95\%\ CI 0.06–0.12); p<0.001\] as shown in Fig. 3b. In Fig. 4a–d, BSA and body height are plotted separately for the left and right kidney against kidney volume and length, respectively.

Renal and ureterovesical anomalies

Renal ultrasound revealed subclinical anomalies of the kidneys and ureters in eight of 51 individuals born prematurely (Table 3) and not in controls (Fisher exact test
Anomalies varied from nephrocalcinosis ($N=1$), unilateral pyelocaliceal dilatation ($N=3$), ureteropelvic junction obstruction ($N=1$), ureter dilatation ($N=1$), extrarenal pelvis ($N=1$), and ureter duplication and ureterocele ($N=1$). These were not known before the ultrasound study. Prevalences of the anomalies did not differ between SGA (3/22) and AGA (5/29) individuals. Analyses excluding these eight individuals did not affect findings.

**Discussion**

Renal ultrasound study revealed significantly smaller renal length and volume in 20-year-old female individuals born very prematurely, either SGA or AGA, compared with age-matched controls. The difference was most pronounced for the left kidney. Differences were observed for male individuals also, but statistical significance was reached...
only in female individuals. IUGR had no significant effect on renal size. These results are consistent with impaired fetal kidney development after preterm birth, with probably no more than a small effect of IUGR on renal size. Nephrogenesis starts in early pregnancy, but it peaks at the 32nd week of gestation, continues until 36 weeks of gestation, and is correlated to renal size [5]. The AGA and SGA groups, both born before a gestational age of 32 weeks, did not differ in renal size, possibly because nephrogenesis was not complete at birth. We found differences in renal size between male and female individuals in both the SGA and AGA groups. Such gender differences have only been reported in an experimental IUGR rat model, suggestive of the importance of gender in outcomes in adulthood after IUGR [17]. In our study, differences in renal size between male SGA, AGA, and control individuals seemed smaller than those between female study participants but still showed a trend for decreased absolute renal length and volume. The lack of significance might be due to insufficient power of the study.

Singh et al. described that lower renal volume in Australian Aborigines represents kidneys with reduced nephron number [5]. As there is a limited postnatal nephrogenesis in preterm individuals [9, 10], a nephron deficit after preterm birth probably persists throughout life. From a study in 56 deceased extremely premature infants and ten deceased full-term controls, it appeared that nephron number was highly correlated to gestational age and that nephrogenesis had stopped 40 days postnatally [9]. As nephron deficit predisposes to reduced renal function in the adult [5, 6], preterm individuals are at such risk. Earlier, we found higher blood pressure and poor renal function and microalbuminuria in these premature individuals [14, 18]. Furthermore, restricted postnatal growth after premature birth may impair renal function over time [19].

Decreased renal volume was also found in 33 low-birth-weight (LBW) Aboriginal children between 5–18 years of age [3]. Their BSA-adjusted renal volume was 78.5 ml/m² compared with 85.7 ml/m² in 141 normal birth weight (NBW) individuals (p=0.018). Renal length was equal. The authors stated that LBW resulted from IUGR, but data on gestational age were unavailable in many participants. For that matter, our study found that IUGR did not affect renal size. Renal size differences between preterms and controls were most pronounced for the left kidney, in line with findings in Aboriginal children [3]. Interestingly, hypertensive adults with chronic kidney failure showed smaller absolute left kidney volume (but not right kidney volume) compared with normotensive chronic kidney failure patients [20]. The authors did not study whether renal size in these hypertensive patients was associated with birth weight and gestational age.

Thus, from results of other studies and this study, it would seem that very preterm individuals show limited early postnatal renal growth, especially of the left kidney. Other studies reported that postnatal renal growth after preterm birth was limited until 18–24 months of age but did not mention differences in left and right kidney growth [11, 12]. To our knowledge, only one study described normal fetal kidney growth separately for the left and right kidney [21]. Sonography at several gestational ages did not reveal significant difference between left and right kidney growth between 16 and 38 weeks of gestation. We can only speculate that the left kidney grows more rapidly than the right kidney after the gestational age of 32 weeks in normal gestation, but large studies are needed to confirm this speculation.

Ultrasound revealed renal anomalies in eight very preterm participants versus none of the controls. The anomalies mainly comprised ectasia or dilatation of the ureters and pyelocaliceal system. All individuals were asymptomatic. It is not known whether the anomalies were already present at birth. They may have developed in the early postnatal period or in childhood but then remained unnoticed, as no ultrasound studies were performed. Some renal diseases, such as acute tubular necrosis and neph-

### Table 3: Characteristics of patients with renal anomalies

| Gender | SGA or AGA | Renal anomaly | Left or right side | GFR (ml/min/1.73 m²) |
|--------|------------|---------------|-------------------|---------------------|
| Female | SGA | Unilateral pyelocaliceal dilatation | Right | 118 |
| Female | SGA | Ureter dilatation | Left | 95 |
| Female | SGA | Ureteropelvic junction obstruction | Right | 119 |
| Female | AGA | Pyelocaliceal dilatation | Left and right | 115 |
| Female | AGA | Ureteroceles and double ureter | Left | 104 |
| Male   | AGA | Nephrocalcinosis | Left and right | 119 |
| Male   | AGA | Unilateral pyelocaliceal dilatation | Right | 111 |
| Male   | AGA | Extrarenal pelvis | Left and right | 127 |

*SGA* small for gestational age prematurely born individuals, *AGA* appropriate for gestational age prematurely born individuals, *GFR* glomerular filtration rate
rocalcinosis, occur more frequently in prematurely born children, but higher incidences of renal anomalies we found have not yet been reported [22, 23]. One possible biological pathway may be inferred from the observation that in-utero disturbance of the renin-angiotensin system affects normal kidney development [24, 25].

The strength of our study lies in evaluating the effect of prematurity separately from that of IUGR. The difference in renal size was most pronounced between the AGA preterm and full-term participants. The additional effect of IUGR in these very preterm subjects was small and not significant for all renal sizes. Therefore, we suggest that limited renal growth after very preterm birth predisposes to decreased renal size at adult age.

Two possible limitations of the study should be mentioned. First, selection bias may have been introduced by selecting students only as controls. Second, three different radiologists obtained the data of renal size only once. However, to minimize the variability between the three radiologists, renal measurements were made by a standardized protocol, and all radiologists measured subjects from all three groups. Inter- and intraobserver variability testing showed a slight mean error in measurement, which was comparable with other studies [26, 27]. Moreover, renal lengths measured in controls were similar to those reported by Miletic et al. [28], indicating the radiologists in our study produced accurate measurements.

In conclusion, kidney development after preterm birth is probably stunted, leading to (relatively) smaller kidneys and a higher frequency of renal structural anomalies at the age of 20 years. There is only a small, nonsignificant, additional effect of IUGR on these observations. The effects of stunted development were more obvious in left kidneys and in female individuals. Detailed measurement of renal development, in both size and histological changes, in a large epidemiological study design is required to elucidate the pathophysiological mechanism of unilaterally decreased renal growth after very preterm birth.

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No conflict of Interest

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