Renal volume of five-year-old preterm children are not different than full-term controls

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Received 26 February 2021; accepted 14 June 2021
Available online 8 September 2021

Abstract

Objective: In previous studies, smaller renal volumes were reported in prematurely born infants, however, these renal volumes were not corrected for body surface area, the main determinant of renal size. Given the rapid growth of the renal cortex after premature birth, the authors hypothesized that corrected volumes would not differ from healthy controls.

Methods: Ambispective cohort study with prospective follow-up of prematurely born babies in a large specialized center and retrospectively recruited healthy control group. Children were assessed for renal length and renal volumes at age 5 by three independent ultrasonographers. Detailed anthropometry, blood pressure and renal function were also obtained. Age independent z-scores were calculated for all parameters and compared using descriptive statistics.

Results: Eighty-nine premature study participants (median 32 weeks gestational age) and 33 healthy controls (median 38 weeks gestational age) were studied. Study participants did not differ in age, sex, Afro-Colombian descent, height, blood pressure, serum creatinine, or new Schwartz eGFR. Premature study participants had a significantly lower weight (17.65 ± 2.93 kg) than controls (19.05 ± 2.81 kg, p = 0.0072) and lower body surface area. The right renal volumes were significantly smaller (39.4 vs 43.4 mL), but after correction for body surface area, the renal volumes of premature and full-term controls were similar.

Keywords:
Renal volume; Renal volume z-scores; Renal length; Renal function; Low birth weight; Blood pressure

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https://doi.org/10.1016/j.jped.2021.06.008
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volume and renal length z-scores were identical for both kidneys (mean right kidney -0.707 vs -0.507; mean left kidney -0.498 vs -0.524, respectively).

Conclusion: Renal volumes need to be corrected to body surface area. After correction for body surface area, 5-year-old healthy and prematurely born children have comparable renal volumes.

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Introduction

Many metazoan organs are comprised of highly branched tubular structures, for instance, the lungs and the kidney. They are developed through a process called branching morphogenesis. Branching organs have a finite endowment of organoids at a given developmental age, and as for the kidneys, this process is largely completed by 36 weeks of gestation in humans. Genetic factors such as Adams18 metalloprotease and many others as well as environmental factors modify nephron endowment. Prematurity is known to affect nephron endowment. It is believed that premature delivery results in an interruption or at least an alteration of the normal nephrogenesis which would normally continue to the 36th week of gestation. A recent study suggests that some nephrogenesis can still occur after premature delivery, but the resulting glomeruli are far fewer than normal and abnormal. A key feature of prematurity is the low birth weight (LBW). Research in England and Wales showed the impact of LBW on mortality in later childhood and adolescence. In Colombia, 1 of 10 newborns have a preterm birth. LBW accounts for 7.7% of all newborns of which 50% are preterm newborns. Such, LBW is a key feature of preterm birth. Low birth weight is defined as a birth weight < 2,500 g.

Unfortunately, there is currently no reliable methodology to measure nephron endowment. Serum creatinine, the most widely used biomarker of glomerular function, has many pitfalls and is affected by maternal renal function for at least one week. Abitbol et al. suggested using renal volume instead. It is known that after premature delivery, renal cortex volume and thus total renal volume increases rapidly. This is believed to occur due to glomerular hyperfiltration as a consequence of nephron underdosing. On the other hand, it has been shown that renal volumes are decreased later in life when compared to healthy age-matched controls, at ages 7 and 11 and 20. Unfortunately, these studies did not correct renal volume for the body surface area. In a recent paper on the renal volume of prematurely born infants, the difference in the renal volumes no longer was significant after correcting for body surface area. As this fact would invalidate the previously reported lower renal volumes as a consequence of prematurity, the authors analyzed the question in a prospective cohort study of prematurely born infants and healthy controls. The authors hypothesized that renal volumes would not be different between prematurely and healthy born infants.

Methods

Setting and study population

Cali is a large city of 2.3 million inhabitants and the capital of the Valle del Cauca Department in Southwestern Colombia. Cali’s natality rate was 12 per 1000 habitants in 2017 with an infant mortality rate of 9 per 1000 life newborns, and 11% LBW. Kangaroo Mother House Alfa is a comprehensive program of medical care for preterm children in Cali. This program follows children during their first year of life. Mother baby dyads are referred after hospital discharge and receive a comprehensive follow-up which is led by nurses. Fundación Valle del Lili is a tertiary care university hospital with a large catchment area covering all of Southwestern Colombia. The pediatric nephrology program is mid-size with approximately 10 renal transplants and 3000 clinic visits per annum.

Study design, inclusion criteria and data collection

This is an ambispective (retrospective and prospective) study. The exposed cohort was five-year-old children with a gestational age < 36 weeks who were included in the kangaroo program when they were infants less than 2 months of age. The authors excluded children with major congenital or renal abnormalities and/or loss of contact. The enrolled children had their first visit to the kangaroo program between 2006 and 2012. Follow-up was collected at 5 years of age (±3 months). The authors obtained a non-exposed (NE) cohort (healthy children with birth weight greater than 2500 grams and gestational age > 36 weeks) from different schools around the city. This study is in accordance with the Declaration of Helsinki and was approved by the Fundación Valle del Lili ethics board committee. Informed written consent was obtained from parents in each case.

Exposure variables

Weight at birth and gestational age were recorded from the clinical chart of the child, as well as when he/she entered the Kangaroo program. The estimated gestational age (GA) was determined from an ultrasound (US) during the first 20 weeks of gestation. If that was not available, the GA was calculated from the most recent US prenatal ultrasound. Finally, if no prenatal ultrasound was performed, the GA was estimated using the last menstrual period and neonatal examination. Both weights at birth and gestational age were captured in the Kangaroo program administrative database, with other demographical and clinical variables.

Outcome variables

The main outcome variables were renal ultrasound dimensions at 5 years of age. Each child had one renal US study for renal dimensions (with a General Electric, LOGIQ E9) using an age-appropriate 9–12 mHz curved array transducer. The US was done by three independent radiologists with the
subject lying in the supine position and scanned in the para-coronal view with the transducer positioned to obtain the longest kidney dimension. Then a transverse image was obtained at a 90° angle to the longest axis where the width (transverse dimension) and thickness (anteroposterior) dimensions of the kidney were measured. Each radiologist obtained 3 measurements of all three dimensions for a total of 27 measurements of each kidney per participant. Kidney volume was calculated using the ellipsoid formula: \( V = \frac{4}{3} \pi abc \) where \( a, b, c \) are the major, intermediate, and minor axes of the ellipsoid, respectively. 

Results

Demographics and clinical variables

Fig. 1 shows the flow and distribution of the study participants included. Thirty-three study participants comprised the control group whereas 89 study participants comprised the premature group. Table 1 summarizes the anthropometric and renal measurements of the two participant groups.

The control group \((n = 33)\) had a mean birth weight of \(3237 \text{ g}\), whereas the premature group had a significantly lower mean birth weight of \(1478 \text{ g}\) \((p < 0.0001)\). The median gestational age was 32 weeks in the premature group and 38 weeks in the control group \((p < 0.001)\). There were no significant statistical differences with regards to sex or Afro-Colombian origin.

Anthropometry differed among both groups. While study participants had an identical age and height, the weight of the prematurely born children was significantly lower. The mean weight was 17.65 kg in the premature cohort and 19.05 kg in the control cohort \((p = 0.0072)\). There was a trend towards a lower weight \(z\)-score \((-0.2570\) in the premature \& the control \((p = 0.0402,\) one-sided \(t\)-test). Subsequently, the body surface area was significantly lower in the premature group.

There was no difference in the systolic and diastolic blood pressure \(z\)-scores. The average systolic blood pressure in the premature group was \(100.7(\pm 6.7)\) mm Hg, not significantly different from the control group \((99.3(\pm 8.2)\) mm Hg \((p = 0.3539)\). The average diastolic blood pressure in the premature group was \(62.1(\pm 6.5)\) mmHg, not significantly different from the control group \((61.5(\pm 7.7)\) mmHg \((p = 0.6933)\). The average systolic blood pressure \(z\)-score in the premature group was \(+0.62(\pm 0.72)\), not significantly different from the control group \((0.44(\pm 0.77)\) \((p = 0.2336)\). The average diastolic blood pressure \(z\)-score in the premature group was \(+0.43(\pm 0.68)\), not significantly different from the control group \((0.38(\pm 0.69)\) \((p = 0.6921)\).

Renal function measured by biomarkers was not different among groups. Mean serum creatinine and Schwartz eGFR were similar among both groups, with a mean eGFR of \(102.6 \text{ mL}/\text{min}/1.73 \text{ m}^2\) in the premature group and \(102.2 \text{ mL}/\text{min}/1.73 \text{ m}^2\) in the control group.

The kidney volume of the right kidney was significantly smaller in the premature group \((39.4 \text{ mL})\) as compared to the control group \((43.37 \text{ mL},\) \(p = 0.0306)\). However, after correcting the renal volume to body surface area and expressing the measurements as \(z\)-scores, there was no significant difference between groups. The left renal volume and the left renal volume \(z\)-score did not differ among groups \((Table 1)\). The authors also found no differences between groups for the right or left kidney length or the right or left kidney length \(z\)-score \((Table 1)\).
The authors also calculated the total renal volumes and the total renal volumes per body surface area (TKV/m²). The mean TKV/m² of the preterm group was 112.5 ± 18.8 mL, not significantly different from the control group (114.5 ± 19.1 mL, p = 0.6034, unpaired t-test). There was also no significant correlation between the renal volume z-score and the TKV/m².

The authors then calculated the correlation between the renal volume z-scores and the gestational age. Interestingly, neither the right nor left renal volume z-score correlated significantly with the gestational age (Pearson r = 0.1056 and 0.006 for the right and left renal volumes, respectively). There was also no difference in kidney volume when discriminating by sex (Pearson r = 0.1097 and -0.0759 for the right and left renal volumes, respectively).

**Discussion**

In this study, the authors found normal renal length z-scores and renal volume z-scores in both the prematurely born children and the controls. Only the raw right renal volume was significantly lower in the premature group. After correcting for body surface area, this was no longer significant. The authors also found no correlation of renal length or renal volume z-scores and gestational age, suggesting that, through hyperfiltration, renal volume can be normalized by 5 years of age even in extremely premature babies. The authors also found no difference in markers of renal function. However, the children born prematurely had a significantly lower weight and a trend towards a lower weight z-score.

These findings are in keeping with the recent paper by Rakow et al. While the raw right kidney volumes were smaller in the premature group, similar to the previous reports, the authors did not find this for the left kidney volumes. As outlined in the introduction, both of these studies did not correct for body surface area. It is conceivable that the differences that were previously reported would disappear similar to the findings of Rakow and the present study’s findings. Moreover, the renal function parameters were also not different, similar to that of Miklaszewksa et al. Renal volumes correlate tightly with the body surface area, the relationship between renal volumes and body surface area never changes during childhood. The renal volume is adjusted through a complex system of hormones by increasing the diameter of the individual glomeruli.

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**Figure 1** Patient flow chart as per STROBE guidelines.

GA, gestational age.
to the body surface area, thereby making the kidney cortex grow without increasing the number of nephrons. Nonetheless, Crump et al. showed in a large national cohort study a strong inverse association between gestational age at birth and risk of chronic kidney disease from childhood into mid-adulthood. After adjustment for other perinatal and maternal factors, those born preterm or extremely preterm had nearly twofold and threefold higher risks, respectively.28 It would have been ideal to use the renal volume z-score as a surrogate for the identification of risk. However, the present study’s data would suggest that renal volumes, especially when corrected for body surface area, are not useful biomarkers for the identification of prematurely born babies at risk for CKD later in life, at least not yet at the age of five.

| Table 1 | Prematurely born children and control group demographics and renal volume measurements. |
|---------|--------------------------------------------------------------------------------------------------|
| Parameter | Prematurely born children, \( n = 89 \) | Control group, \( n = 33 \) | \( p \) value | Test |
| --- | --- | --- | --- | --- |
| Sex male, \( n(\%) \) | 43 (48.1%) | 22 (66.0%) | 0.102 | Fisher exact test |
| Afrodescendent, \( n(\%) \) | 9 (10.1%) | 5 (15.2%) | 0.524 | Fisher exact test |
| Gestational age, median (IQR) | 32 (30-33) | 38 (38-40) | < 0.001 | Mann-Whitney U test |
| Birthweight, mean (±SD) | 1478 (425) | 3237 (510) | < 0.0001 | Mann-Whitney U test |
| **Five years follow-up** | | | | |
| Age [years], mean (±SD) | 5.0 (1.17) | 4.96 (0.22) | 0.419 | \( t \)-test |
| Height [cm], mean (±SD) | 106.4 (4.4) | 107.6 (5.2) | 0.160 | \( t \)-test |
| Height z-score, mean (±SD) | -0.14 (0.96) | -0.15 (1.03) | 0.965 | \( t \)-test |
| Weight [kg], median (IQR) | 17.1 (15.7 - 19.2) | 18.5 (17.2 - 21.2) | 0.007 | \( t \)-test |
| Weight z-score, mean (±SD) | -0.26 (1.20) | +0.17 (1.13) | 0.080 | \( t \)-test |
| Body Surface Area \([m^2]\), mean (±SD) | 0.72 (0.07) | 0.75 (0.07) | 0.010 | \( t \)-test |
| Body mass index \([kg/m^2]\), median (IQR) | 15.4 (14.1 - 16.6) | 16.0 (15.4 - 17.6) | 0.008 | Mann-Whitney U test |
| BMI z-score, median (IQR) | 0.04 (-0.99 - +1.31) | 0.52 (-0.03 - +1.41) | 0.011 | \( t \)-test |
| **Blood Pressure (BP)** | | | | |
| Systolic BP [mmHg], mean (±SD) | 100.7 (6.7) | 99.3 (8.2) | 0.354 | \( t \)-test |
| Systolic BP z-score, mean (±SD) | 0.62 (0.72) | 0.44 (0.77) | 0.234 | \( t \)-test |
| Diastolic BP [mmHg], mean (±SD) | 62.1 (6.5) | 61.5 (7.7) | 0.693 | \( t \)-test |
| Diastolic BP z-score, mean (±SD) | 0.43 (0.68) | 0.38 (0.69) | 0.692 | \( t \)-test |
| **Renal measurements** | | | | |
| Serum creatinine [umol/L], median (IQR) | 31 (27 - 34) | 31 (28 - 36) | 0.530 | Mann-Whitney U test |
| New Schwartz eGFR [mL/min/1.73m2], mean (±SD) | 102.6 (12.0) | 102.2 (13.2) | 0.859 | \( t \)-test |
| **Renal volume** | | | | |
| Right kidney [mL], median (IQR) | 38.2 (33.5 - 44.6) | 43.8 (35.8 - 48.0) | 0.050 | Mann-Whitney U test |
| Right kidney z-score, mean (±SD) | -0.71 (0.65) | -0.5073 (0.73) | 0.147 | \( t \)-test |
| Left kidney [mL], median (IQR) | 40.4 (35.1-47.8) | 40.8 (37.7 - 49.9) | 0.413 | Mann-Whitney U test |
| Left kidney z-score, mean (±SD) | -0.50 (0.58) | -0.52 (0.64) | 0.622 | \( t \)-test |
| **Length renal size** | | | | |
| Right kidney [mm], median (IQR) | 70.1 (67.0 - 73.7) | 72.7 (68.7 - 76.0) | 0.126 | Mann-Whitney U test |
| Right kidney z-score, mean (±SD) | 0.99 (0.91) | 0.82 (0.77) | 0.163 | \( t \)-test |
| Left kidney [mm], median (IQR) | 70.7 (67.7 - 77.0) | 73.0 (69.3 - 77.2) | 0.350 | Mann-Whitney U test |
| Left kidney z-score, mean (±SD) | 0.84 (0.91) | 0.96 (0.90) | 0.521 | \( t \)-test |
years. The significantly lower weight of the prematurely born children has previously been described. This explains the lower body surface area found in the present study’s participants, which subsequently mitigates any differences between groups with regards to kidney volumes. The data presented here are in keeping with the recent description of a rapid increase of renal cortex volumes in prematurely born children by Li et al.

The present study has some limitations. The proportion of extremely premature babies was low. Only 8 study participants were under 28 weeks of gestation. The authors also did not have cystatin C measurements, which are a better tool for assessing renal function in children. The original cohort shrunk because of refusal to participate, which introduces an unknown bias. The follow-up of 5 years may be insufficient to demonstrate differences in renal volumes. The authors also faced challenges recruiting the control group due to the need for a blood test. The fact that the control group comprises only 1/3 of the prematurely born children group may have introduced bias. Moreover, the authors used German reference intervals for the calculation of the age-independent z-scores. Data from Argentina may be more representative and have been published by Bianchi et al., however, these data do not permit the calculation of age-independent z-scores. Nonetheless, the study comprises a sizeable cohort of longitudinally study participants that compares favorably to the published literature. The repeated measures of all kidney dimensions by three independent radiologists, each in triplicates, form a strength.

Taken together, the present study’s data suggest that renal volumes of 5-year old prematurely born children do not differ from healthy controls, especially after adjusting for body surface area. The authors propose to always calculate renal volume z-scores, which are easily facilitated by the Ped(z) app. The measurement of renal volume z-scores at age 5 may not identify low nephron endowment in prematurely born children and may therefore not be a useful tool to identify study participants at risk of CKD later in life.

Funding

This study was generously supported by the International Society of Nephrology with $10,000 US and Dr. Wendy Hoy from Australia with $10,000 US through the International Society of Nephrology (ISN) Sister Renal Center Program: Boston Children’s Hospital USA – Fundación Valle del Lili Cali Colombia.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

First of all, the authors thank our study participants and their caregivers. We thank the Lilibeth Caberto Kidney Clinical Research Unit, University of Western Ontario, in London Ontario, for the generous assistance with research space and infrastructure. The authors thank the Centro de investigaciones clinicas de Fundación Valle del Lili for the strong support given during the entire research process. Dra. Laura Torres-Canchala was generously supported by the International Society of Nephrology for a two-month research sabbatical at the University of Western Ontario.

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