Original Article

Kidney Size, Renal Function, Ang (Angiotensin) Peptides, and Blood Pressure in Young Adults Born Preterm

The HAPI Study

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Abstract—Preterm birth incurs a higher risk for adult cardiovascular diseases, including hypertension. Because preterm birth may impact nephrogenesis, study objectives were to assess renal size and function of adults born preterm versus full term and to examine their relationship with blood pressure (BP; 24-hour ambulatory BP monitoring) and circulating renin-Ang (angiotensin) system peptides. The study included 92 young adults born (1987–1997) preterm (≤29 weeks of gestation) and term (n=92) matched for age, sex, and race. Young adults born preterm had smaller kidneys (80±17 versus 90±18 cm^3/m^2; $P<0.001$), higher urine albumin-to-creatinine ratio (0.70; interquartile range, 0.47–1.14 versus 0.58, interquartile range 0.42 to 0.78 mg/mmol, $P=0.007$), higher 24-hour systolic (121±9 versus 116±8 mm Hg; $P=0.001$) and diastolic (69±5 versus 66±6 mm Hg; $P=0.004$) BP, but similar estimated glomerular filtration rate. BP was inversely correlated with kidney size in preterm participants. Plasma Ang I was higher in preterm versus term participants (36.3; interquartile range, 13.2–62.3 versus 19.4; interquartile range, 9.9–28.1 pg/mL; $P<0.001$). There was no group difference in renin, Ang II, Ang (1–7), and alamandine. In the preterm, but not in the term group, higher BP was significantly associated with higher renin and alamandine and lower birth weight and gestational age with smaller adult kidney size. Young adults born preterm have smaller kidneys, higher urine albumin-to-creatinine ratio, higher BP, and higher circulating Ang I levels compared with term controls. Preterm young adults with smaller kidneys have higher BP.

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The Developmental Origins of Health and Disease theory suggests that abnormalities in the fetal environment predispose individuals to pathology in later life.[1] There exists a complex interplay between organogenesis, the stressors associated with preterm birth, and the development of cardiovascular and renal sequelae throughout life.

An estimated 10% of neonates are born preterm (<37 weeks of gestation), 1.5% are born preterm at ≤29 weeks of gestation, and almost 90% of these preterm infants survive with appropriate care in developed countries.[2] Human nephrogenesis occurs from 9 to 34 to 36 weeks of gestation,[3] with the most glomerular development occurring in the third trimester.[4] As a result, the total nephron number and architecture are usually determined during fetal life. Clinical data suggest that low birth weight (usually defined as birth weight <2500 g) is associated with an increased risk of chronic kidney disease (CKD).[5–7] However, most studies lack power to stratify for preterm and even more so preterm birth. Evidence from animal studies, human autopsy findings, and observational cohorts indicates that prematurity, independent of birth weight, results in abnormal renal development,[8–11] including glomerular paucity, hypertrophy, and structural malformations.[9,12,13] In parallel, reduced renal volume on ultrasound is a consistent finding in preterm individuals.[12,14–16] These abnormalities can result in abnormal glomerular filtration rates, tubular dysfunction, and hypertension in childhood[10,16,17]; however, these long-term consequences associated with impaired renal growth have not been confirmed in adult subjects who were born preterm.

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Reports consistently reveal that preterm-born adults have higher blood pressure (BP) than their term counterparts[18–20] and could be at increased risk of death secondary to cardiovascular diseases.[21] It is unclear whether this hypertensive trend is associated with underlying renal parenchymal pathology, renal vascular abnormalities, hormonal disruptions (such as the renin-Ang [angiotensin]-aldosterone system [RAAS]), or a combination thereof. Because the first preterm cohorts are currently entering their third and fourth decades of life, we now have the opportunity to evaluate prematurity as an important risk factor for developing renal and cardiovascular diseases and to identify patients who would benefit from primary preventative measures.

We hypothesize that prematurity is a risk factor for reduced kidney size and abnormal function and that this reduced renal volume is associated with increased BP. Our primary objective was thus to assess and correlate renal size and function with BP in young adults born preterm at ≤29 weeks of gestation. Secondary objectives included the assessment of renovascular, hormonal (RAAS), and neonatal factors that may potentially impact renal function, size, and BP in this patient population.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population and Design

The data were obtained from the HAPI (Health of Adults Born Preterm Investigation) project—a cross-sectional observational study assessing the health of young adults (18–29 years of age) born preterm at ≤29 weeks of gestation between 1987 and 1997 and admitted at 1 of the 3 main neonatal intensive care units (NICUs) in Montreal, Quebec: Sainte-Justine University Hospital and the McGill University-affiliated Royal Victoria Hospital and Sir Mortimer B. Davis Jewish General Hospital. Term controls (1:1) were recruited among friends and siblings of preterm participants and were matched for age (±2 years), sex, and race. For all participants, exclusion criteria included severe neurocognitive impairment and pregnancy. The study took place between December 2011 and December 2016.

Data Collection

Perinatal and neonatal data were obtained from written hospital records. Interval health data were obtained via patient questionnaires and corroborated with physician records as needed.

Paired subjects were assessed on the same day, during which they answered health and lifestyle questionnaires, underwent anthropomorphic and vital sign measurements, morning (after overnight fast) blood and urine sampling, renal ultrasonography, and departed with a 24-hour ambulatory BP monitor (ABPM). Healthcare providers participating in clinical data collection were blinded to the exposure status (preterm versus term).

BP was measured by a trained clinical nurse per the Canadian Hypertension Education Program guidelines.[22] Measurements were taken with an automated oscillometric device (DINAMAP model DPC300M-CF; GE Medical Systems Information Technologies, Inc, Milwaukee, WI), in triplicate after seated rest for 5 minutes and the last 2 measures averaged and included in the analyses. Each pair received an appropriately sized 24-hour ABPM (Spacelabs model 902007; Spacelabs Medical, Inc, Redmond, WA) to be used on their nondominant arm. Measures were taken every 20 minutes for the duration of the assessment period, during which participants charted a diary detailing waking activities, sleep (time at which they went to bed and got up the next day), symptoms, and any medications, food, beverage, or other substances taken. The accuracy of the sleep log was inspected against the raw BP and heart rate data. The ABPM data were interpreted by a single clinician and in accordance with the Canadian Hypertension Education Program guidelines.[23] Specifically, a subject was considered hypertensive if the mean 24-hour systolic BP (SBP) was ≥130 mm Hg, mean 24-hour diastolic BP (DBP) was ≥80 mm Hg, mean awake SBP was ≥135 mm Hg, or the mean awake DBP was ≥85 mm Hg. Twenty four-hour awake and asleep mean BPs, their respective SDs, the percentage of measurements above hypertensive loads, and the rate of BP dipping with sleep (percentage decrease in mean awake versus asleep SBP and DBP) were analyzed. Subjects were excluded from BP analysis if they had <20 BP measurements awake, <7 BP measurements asleep, or <70% of readings successfully measured, per the Canadian Hypertension Education Program guidelines.[23] Overall, 24-hour ABPM recordings retained for analysis provided 63±17 readings for preterm-born and 63±14 for term-born subjects.

Blood and urine were collected on the morning of assessment. Blood was collected for electrolytes, urea, creatinine, cystatin-C, renin, aldosterone, and Ang peptides (Ang I, Ang II, Ang [1–7], and alamandine) after patients had been resting supine for 30 minutes. Measure of Ang peptides was an amendment to initial study protocol, so measures were not obtained for all study subjects.

Cystatin-C—a low molecular weight serum protein independent of age, sex, and muscle mass[24]—was assessed because of its higher sensitivity than conventional markers for the detection of kidney disease[17,25–27] and its positive association with adverse cardiovascular outcomes. Cystatin-C was measured per recent standardization practices to the international calibrator,[28] using a particle-enhanced turbidimetric immunoassay (Architech c8000; Abbott Laboratories, Taguig City, Philippines).

Components of the RAAS were assessed for their known critical role in hypertension, especially in the presence of renal dysfunction. Renin and aldosterone were measured by chemiluminescence using iSYS (IDS-Intermédico model IS310400, 2009). For Ang peptides, 1 mL of blood was collected in a tube containing 50 µL inhibitor cocktail solution (1 mmol/L p-hydroxymercuribenzoate, 30 mmol/L 1,10-phenantroline, 1 mmol/L pepistatin-A, 1 mmol/L phenylmethylsulfonyl fluoride, and 7.5% EDTA),[29] immediately centrifuged and plasma frozen at −80°C. Ang peptides were measured using reversed-phase ultraperformance liquid chromatography (ACQUITY UPLC I-Class System [SM-FTN]; Waters, Dublin, Ireland) coupled to electrospray ionization tandem mass spectrometry (LC-ESI-MS-MS; XEVO TQ-S, Waters, Dublin, Ireland). The chromatography separation was performed with an ACQUITY UPLC BEH C18 Column, 1.7 µm, 2.1×100 mm Waters (Milford, MA, Ireland). Detection was in multiple reactions monitoring mode, using an electrospray positive ionization. The calibration curve was prepared using a stock solution containing all the synthetic standards (Bachem, Inc, Torrance, CA). The applied calibration curve model y=ax+b proved to be accurate over the concentration range 0.025 to 1 ng/mL, with a correlation coefficient 0.99. The interassay and intra-assay variability was ≤15%. The sensitivity of the assay was in the low picogram range (2–10 pg per sample [300 µL plasma]).

All other urine and serum markers were measured at the Sainte-Justine University Hospital clinical biochemistry laboratory per routine practice. Blood glucose levels were measured after a 12-hour fasting and 2 hours after a 75-g oral glucose load. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI 2009 formula using serum creatinine (eGFR Scr), CKD-EPI 2012 formula using serum cystatin-C (eGFR Scys), and the CKD-EPI 2012 formula using both cystatin-C and creatinine (eGFR Scr-Scys; see Appendix for formulae).[30,31]

Renal ultrasonography was performed by 2 trained radiology technicians (8 and 6 years, respectively) and interpreted by a staff radiologist (R.E.-J) who was blinded to the patient groups. Measurements were taken in the prone position on a scanner (AplioXG, 2009; Toshiba) using a curvilinear 3.75 MHz (6C1) transducer. Bilateral measures of maximal bipolar length and axial laterolateral and anteroposterior dimensions at the level of the renal hilum were taken. Kidney volume was calculated using the equation diameter×lengt h×π/6.[32] Because of the known relationship between renal volume and body mass, mean kidney volume was divided by the patient's

estimated BSA (BSA=√([body height (m)×weight (kg)]/3600). The mean of 4 Doppler measurements of resistive index obtained intrarenally (superior, mid, and inferior poles) and at the renal hilum was computed for each kidney. Any anomalies noted on ultrasonography were also reported.

Data Analysis

Data were analyzed using SPSS 24 (IBM SPSS Statistics for Windows, version 24; Armonk, New York). Descriptive statistics were summarized as means with SDs, medians with interquartile range, and proportions. To compare renal size, renal function, and BP, we performed paired *t* tests for continuous variables with normal distribution, Wilcoxon signed-ranked tests for skewed variables, and McNemar tests for categorical variables. We used the Hodges-Lehmann estimator to calculate the magnitude of the differences in medians between pairs. Paired analyses were used given our recruitment methodology (matched pairs), which allowed to account for environmental factors, such as socioeconomic status and lifestyle habits, including smoking, likely to confound renal health. In our analyses, we further corrected renal size for BSA to account for possible differences in adult size as reported in the literature.[33,34] To examine the relationship between renal size, function, and BP, Pearson correlation was used for parametric data and Spearman correlation for nonparametric data and categorical variables. We conservatively used a Bonferroni correction to account for multiple comparisons within each domain of interest, namely kidney volume (2 comparisons; $P<0.025$), kidney function (7 comparisons; $P\leq0.007$), ABPM (6 comparisons for SBP or DBP; $P\leq0.008$), and heart rate (3 comparisons; $P\leq0.02$). As for our secondary objective, comparisons in renovascular and RAAS measures were completed as described above. We further explored the relationship between neonatal factors and renal and RAAS measures stratifying by preterm birth status using correlational analyses. Because these analyses were hypothesis generating, as opposed to hypothesis proving, we did not adjust *P* values for multiple testing.

Ethics

Ethics approval was obtained from the Sainte-Justine University Hospital and Research Center, the Royal Victoria Hospital, and the Sir Mortimer B. Davis Jewish General Hospital Research Ethics Boards. All participants provided written informed consent.

Results

Study Population

Of the 95 subject pairs recruited, 92 were retained for analysis. Three term-preterm pairs were excluded: 1 control was born at 36.3 weeks, another had previously diagnosed severe renal abnormalities with CKD and hypertension under treatment, and 1 preterm was under β-blocker treatment for arrhythmia.

Baseline characteristics of the study participants are shown in Table 1. Mean gestational age (GA) and weight at birth were 27.1 weeks and 955 g in preterm-born subjects and 39.5 weeks and 3401 g in term-born subjects. A significantly higher proportion of preterm was born to mother with pregnancy-induced hypertension. Of the 92 individuals born preterm, 52 had at least 1 major in-hospital morbidity, including 36 with bronchopulmonary dysplasia.

Both preterm and term participants were evaluated at an average age of 23.2 years. Eighty-four pairs (>90%) were white (mostly French Canadians). Seven pairs were siblings. Body mass index and BSA were significantly lower in preterm. Smoking status and alcohol consumption rates were similar between groups. Overall, between-pair correlations were high for life habits and socioeconomic factors, including smoking (84%), education level <12 years (86%), and mother's education level <12 years (71%). Five preterm and 3 term-born subjects were known to be hypertensive but not medicated. Two preterm and 4 term participants were known to have noninsulin-dependent diabetes mellitus, whereas 1 preterm and 3 term-born subjects had been diagnosed with untreated mild hypercholesterolemia. Blood lipid profile did not differ between the groups, and the glycemia 2 hours after oral glucose challenge was slightly but significantly higher in preterm subjects (Table S1 in the online-only Data Supplement).

Descriptive statistics of outcome measure differences between preterm and term participants are found in Table 2. Kidney volume assessment was available for 85 pairs; their neonatal and adult characteristics were similar to the 92 pairs enrolled (data not shown). Neonatal and adult characteristics and outcome measures for women and men preterm versus term participants are presented in Table S2.

Kidney Volume and Markers of Renal Function

Preterm-born subjects had smaller kidneys than their term counterparts (mean kidney volume per BSA, 80 versus 90 cm^3/m^2; $P<0.0001$) and comparable renal artery resistance index. No significant differences were found in markers of renal function, including eGFR measured by creatinine, cystatin-C, and by both markers combined. Using a cutoff glomerular filtration rate of 125 to assess for hyperfiltration,[35] a similar proportion of subjects (8 preterm and 7 term) showed hyperfiltration. Median values of urine albumin-to-creatinine ratio (ACR)—a marker of altered glomerular endothelial barrier integrity[36]—were within normal limits but were significantly higher in preterms (0.70 versus 0.58 mg/mmol in term; $P=0.007$), with a median for differences of 0.16 mg/mmol (95% CI, 0.04–0.29).

24-Hour ABPM

Twenty-four-hour ABPM recordings were obtained for 47 pairs, and awake ABPM recordings were obtained for 58 pairs. Neonatal and adult characteristics, as well as outcome measures of participants with complete 24-hour ABPM recordings and those without, are presented Table S3.

Twenty-four-hour SBP (121 versus 116 mm Hg) and DBP (69 versus 66 mm Hg), as well as awake SBP (126 versus 121 mm Hg), were significantly higher in preterm-born subjects (Table 2). Awake and asleep DBP did not differ significantly between groups. Regarding the proportion of high BP readings (>135 mm Hg SBP and >85 mm Hg DBP), the median 24-hour SBP (14% versus 6%) and DBP loads (6% versus 4%), as well as awake SBP (10% versus 6%) and DBP loads (11% versus 5%), were higher in preterm-born subjects, but this was only statistically significant for SBP. No differences were observed in BP sleep dipping (Table 2).

RAAS Markers

Most participants had measured aldosterone values inferior to 103 pmol/L—our laboratory cutoff value; we, therefore, chose not to retain this marker for the analysis. Renin, Ang II, Ang (1–7), and alamandine did not differ between the groups (Table 2). Ang I values were significantly higher in preterm

Table 1. Neonatal and Adult Characteristics of Young Adults Born Preterm ≤29 wk and Full Term

Clinical Characteristics	Preterm	Term	*P* Value
Neonatal characteristics			
n	92	92	…
Male sex, n (%)	41 (44%)		…
GA, wk	27.1±1.3	39.5±1.1	…
Birth weight, g	955±223	3401±376	…
Small for GA,* n (%)	6 (7%)	6 (7%)	1.000
Maternal PIH, n (%)	26 (29%)	12/91 (13%)	0.034†
Antenatal steroids, n (%)	40 (44%)	0	…
Postnatal NSAID, n (%)	41 (45%)	0	…
Major neonatal morbidities,‡ n (%)	52 (57%)	0	…
BPD, n (%)	36 (38%)	0	…
Severe brain injury, n (%)	5 (5%)	0	…
Retinopathy of prematurity stage ≥3, n (%)	9 (10%)	0	…
Patent ductus arteriosus surgical ligation, n (%)	9 (10%)	0	…
Necrotizing enterocolitis, n (%)	5 (6%)	0	…
Confirmed sepsis, n (%)	14 (15%)	0	…
Adult characteristics			
Age, y	23.2±2.2	23.2±2.3	0.787
Body mass index, kg/m^2	22.6±3.8	23.7±4.4	0.029†
BSA, m^2	1.68±0.20	1.81±0.23	<0.001†
Current tobacco smoking, n (%)	21 (23%)	16 (18%)	0.302
Alcohol consumption,§ n (%)	12 (13%)	17 (19%)	0.332
Diabetes mellitus (as per reported prior diagnosis), n (%)	2 (2%)	4 (4%)	0.687
Hypercholesterolemia (as per reported prior diagnosis), n (%)	1 (1%)	3 (3%)	0.625
Hypertension (as per reported prior diagnosis), n (%)	5 (5%)	3 (3%)	1.000
SBP on study day, mm Hg	119±13	116±13	0.207
DBP on study day, mm Hg	71±8	68±8	0.013†
Hypertension in participants' parents‖			
Mothers	19/86 (22%)	11/80 (13%)	0.163
Fathers	26/80 (33%)	22/77 (29%)	0.593

BPD indicates bronchopulmonary dysplasia; BSA, body surface area; DBP, diastolic blood pressure; GA, gestational age; PIH, pregnancy-induced hypertension (hypertension or preeclampsia); and SBP, systolic blood pressure.

*Less than the 10th percentile.

†Statistically significant differences.

‡BPD: oxygen requirement at 36 wk post-menstrual age; severe brain injury: intraventricular hemorrhage (grade 3 or 4) or cystic periventricular leukomalacia.

§Alcohol consumption: >14 consumptions per week for men and >7 consumptions per week for women.

‖Data from parents' questionnaire. Data are presented as mean±SD, median (25%–75%), or stated otherwise.

versus term-born subjects. Ang (1–7)/Ang I ratio was lower in preterm. The difference in Ang II/Ang I ratio between the groups did not reach statistical significance (P=0.052; Table 2). Correlations between renin and Ang peptide measurements within preterm and term groups are presented in Table S4. Neonatal and adult characteristics, and outcome measures of participants for whom Ang peptides were measured compared with those for whom Ang peptides were not measured, are presented in Table S5.

Correlations

Mean awake SBP and DBP obtained from ABPM and SBP measured on the day of the visit inversely correlated with the mean kidney volume adjusted to BSA in preterm-born subjects. For each 10-cm^3 decrease in kidney volume/BSA (m^2), mean SBP on the study day increased by 1.9 (95% CI, 3.7–0.1) mm Hg (Figure), mean awake SBP increased by 1.4 (95% CI, –0.1 to 2.8; P=0.067) mm Hg, and mean awake DBP increased by 1.1 (95% CI, 0.0–2.1; P=0.036) mm Hg; mean

Table 2. Kidney Volume, Renal Function, Blood Pressure, and Renin-Ang System Peptides in Young Adults Born Preterm ≤29 wk vs Full Term

Outcome Measures	Pairs, n	Preterm	Term	Mean Difference or Median of Differences (95% CI)	*P* Value
Kidney structure and function					
Kidney volume per BSA, cm^3/m^2	85	80±17	90±18	−10.3 (−14.9 to −5.7)	<0.001*
Kidney volume, cm^3	85	135±31	164±37	−28.8 (−37.7 to −20.0)	<0.001*
eGFR Scr, mL/min per 1.73 m^2	86	117.2±11.0	117.3±10.3	−0.10 (−2.8 to 2.6)	0.582
eGFR Scys, mL/min per 1.73 m^2	83	106.2±12.2	106.8±12.7	−0.58 (−4.4 to 3.2)	0.761
eGFR Scr-Scys, L/min per 1.73 m^2	82	111±10	111±9	−0.39 (−3.2 to 2.5)	0.786
eGFR Scr-Scys >125,† n (%)	92	8 (9%)	7 (8%)	…	1.000
ACR, mg/mmol	87	0.70 (0.47 to 1.14)	0.58 (0.42 to 0.78)	0.16 (0.04 to 0.29)	0.007*
Creatinine (serum, Scr), µmol/L	91	70±10	70±9	−0.06 (−2.07 to 1.93)	0.945
Cystatin-C (serum, Scys), mg/L	83	0.85±0.10	0.85±0.10	0.00 (−0.02 to 0.03)	0.822
ABPM					
24-h SBP, mm Hg	47	121±9	116±8	5.1 (2.3 to 8.0)	0.001*
24-h DBP, mm Hg	47	69±5	66±6	2.6 (0.8 to 4.4)	0.004*
24-h heart rate, bpm	47	78±10	74±11	3.6 (−0.02 to 7.3)	0.051
24-h SBP load (>130 mm Hg), %	47	14 (2 to 41)	6 (3 to 14)	12 (5 to 20)	0.001*
24-h DBP load (>80 mm Hg), %	47	6 (2 to 13)	4 (2 to 9)	3 (1 to 7)	0.015
Awake SBP, mm Hg	58	126±10	121±8	4.6 (1.8 to 7.4)	0.002*
Awake DBP, mm Hg	58	74±7	72±6	1.9 (−0.2 to 3.8)	0.079
Awake heart rate, bpm	58	83±11	79±12	4.5 (0.7 to 8.2)	0.020*
Awake SBP load (>135 mm Hg), %	58	10 (2 to 38)	6 (0 to 19)	11 (2 to 18)	0.004*
Awake DBP load (>85 mm Hg), %	58	11 (2 to 21)	5 (2 to 14)	5 (1 to 9)	0.015
Asleep SBP, mm Hg	45	111±10	107±8	3.8 (0.7 to 7.0)	0.018
Asleep DBP, mm Hg	45	60±5	58±6	1.9 (−0.4 to 4.2)	0.100
Asleep heart rate, bpm	45	68±11	65±15	3.5 (−1.0 to 8.1)	0.127
SBP sleep dipping, %	45	11.9±5.4	11.1±4.4	0.8 (−1.2 to 2.8)	0.440
DBP sleep dipping, %	45	19.5±6.7	19.4±6.8	0.1 (−2.8 to 3.0)	0.939
Kidney hemodynamic					
Renal arterial resistance index	84	0.64±0.05	0.64±0.03	−0.00 (−0.01 to 0.01)	0.786
Renin-Ang system					
Renin, pg/mL	52	14.5 (9.2 to 22.5)	12.6 (7.1 to 22.5)	1.5 (−2.8 to 5.4)	0.463
Ang I, pg/mL	49	36.3 (13.2 to 62.3)	19.4 (9.9 to 28.1)	16.4 (6.9 to 27.6)	<0.001*
Ang II, pg/mL	49	3.0 (2.3 to 4.0)	2.7 (2.3 to 3.6)	0.5 (0.0 to 1.1)	0.097
Ang (1–7), pg/mL	38	8.3 (7.7 to 10.8)	8.5 (8.0 to 9.4)	0.1 (−0.9 to 1.5)	0.741
Alamandine, pg/mL	35	6.8 (1.8 to 10.3)	3.5 (1.3 to 8.2)	1.0 (−0.4 to 2.8)	0.190
Ang (1–7)/Ang II ratio	37	2.9 (2.2 to 3.5)	2.9 (2.4 to 3.7)	0.5 (−1.0 to 0.2)	0.267
Ang II/Ang I ratio	49	0.10 (0.05 to 0.17)	0.15 (0.10 to 0.22)	−0.05 (−0.9 to 0.0)	0.052
Ang (1–7)/Ang I ratio	38	0.2 (0.1 to 0.8)	0.4 (0.3 to 1.2)	−0.2 (−0.4 to −0.0)	0.006*
Alamandine/Ang (1–7) ratio	38	0.9 (0.4 to 2.1)	0.7 (0.2 to 1.3)	0.2 (0.5 to −0.1)	0.328
Alamandine/Ang II ratio	35	1.5 (0.4 to 3.3)	1.2 (0.4 to 2.9)	0.1 (0.4 to −0.4)	0.922

Data are presented as mean±SD, median (25%–75%), or stated otherwise. ABPM indicates ambulatory blood pressure monitoring; ACR, urine albumin-to-creatinine ratio; Ang, angiotensin; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; Scr, serum creatinine; and Scys, serum cystatin-C.

*Statistically significant differences after Bonferroni correction, see Methods.

†Hyperfiltration.

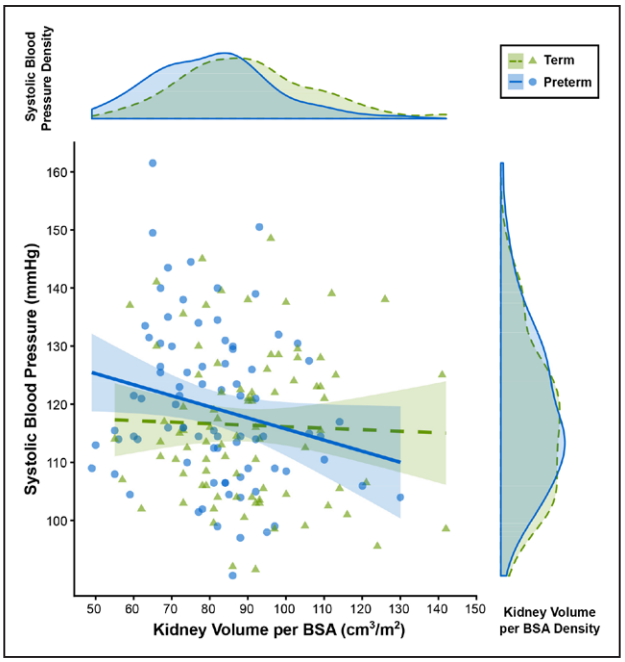

Figure. Association between kidney volume per BSA and systolic blood pressure on the study day in young adults born preterm ≤29 wk (blue dots) and full-term (green triangles). Lines represent linear regression analyses of each group (blue line for preterm and green dotted line for term), with 95% confidence level interval for predictions from the linear model in shaded area. Distribution of systolic blood pressure values and of kidney volumes/BSA for each group (preterm in blue, term in green) is presented on (**top**) and on the (**right**) side of the graph, respectively.

DBP on the study day was not significantly correlated with kidney volume (−0.7 mm Hg; 95% CI, −1.8 to 0.4). In term participants, no significant correlation between BP and kidney volume was noted.

In preterm, higher BP was significantly associated with higher renin and alamandine (Table S6). In term participants, no significant correlation was found between kidney volume, renal function (both eGFR and ACR), or BP and renin and Ang peptides (Table S6).

Impact of Perinatal Factors on Kidney Volume and Function, Renin, and Ang Peptides

In preterm, subjects with lower GA and lower birth weight had smaller kidneys (Table 3). Analyses did not identify neonatal parameters associated with eGFR in our cohort of young adults born preterm. However, subjects with lower birth weight or with major neonatal morbidities had significantly higher ACR values. In term-born subjects, none of the perinatal factors was significantly associated with adult renal measures (Table 3).

Regarding the renin-Ang peptides (Table 4), preterm participants with major neonatal morbidities and bronchopulmonary dysplasia (most frequent major prematurity-related complication) had higher adult renin levels. Higher Ang (1–7) values were found in preterm-born subjects with bronchopulmonary dysplasia and those who received neonatal NSAID. Male sex was associated with significantly higher renin values in both preterm and term groups and with higher alamandine values in preterm. Among subjects born full term, higher GA correlated with higher alamandine levels and higher birth weight correlated with lower Ang I and higher Ang (1–7) levels. Our analyses did not identify perinatal factors impacting adult Ang I levels in preterm participants, nor impacting Ang II levels in both preterm and full-term subjects.

Discussion

Renal volume corrected to BSA was 10% less in adults born preterm. We did not detect a significant difference in glomerular or tubular function between preterm individuals and matched full-term controls, but our results showed higher values of microalbuminuria in preterm. BP was significantly higher in preterm-born subjects and correlated with smaller kidney volume. Among participants born preterm, lower GA, lower birth weight, and presence of major neonatal morbidities were associated with smaller kidney volume and higher values of microalbuminuria. Ang I was increased in preterm-born subjects. Changes in renin and Ang peptides were correlated with changes in BP in preterm but not in term-born subjects. Preterm birth-associated conditions significantly impacted adult circulating renin-Ang system.

Given that otherwise healthy, normotensive adults can withstand a significant loss of nephron mass before impacting glomerular filtration rate, our data suggest that sufficient nephrogenesis occurs before or after birth in preterm individuals to allow them to maintain normal renal function into early adulthood. Although this finding was previously reported in children born preterm, our data add to the current body of literature by demonstrating that normal renal function is observed in individuals who were born preterm and persists at least into the second and third decades of life.[37,38]

Even though no subject presented pathological ACR, microalbuminuria values were significantly higher in preterm-born adults. Furthermore, whereas we did not identify any relationship between perinatal factors and eGFR, higher ACR values were associated with more perinatal pathology. Microalbuminuria is considered an early sign of glomerular endothelial injury and renal dysfunction.[36] Previous studies had similarly reported absence of abnormal levels of albuminuria in children[39,40] and in young adults born <32 weeks.[37,41] Interestingly, in the latter group, Keijzer-Veen et al also noted that levels of urine albumin inversely correlated with birth weight.

We found a significant difference in BP between preterm and term-born subjects: preterm-born adults had on average a 5.1- and 2.6-mm Hg increase in SBP and DBP, respectively (24-hour ABPM), compared with term controls. The differences in BP are of similar magnitude to those reported previously.[18,42] Preterm also had >2× the number of SBP measurements noted to be in the hypertensive range; otherwise stated, SBP load was 2× greater in preterm-born people. Furthermore, BP inversely correlated with kidney size in preterm-born subjects; those with smaller kidneys had a higher BP. Our results are consistent with the current body of literature because architectural renal changes and decreased glomeruli have been demonstrated to be associated with increased BP, even in the absence of concomitant pathology.[43,44]

Experimental models of prematurity have investigated stressors encountered in the NICU and their impact on nephrogenesis. Studies have demonstrated that a hyperoxic

Table 3. Impact of Perinatal Factors on Kidney Volume and Function and on BP in Young Adults Born Preterm ≤29 wk and Term

Birth Characteristics	Renal Volume and Function						BP			
	Kidney Volume per BSA, cm^3/m^2		eGFR Scr-Scys, L/min per 1.73 m^2		ACR, mg/mmol		SBP Study Day, mm Hg		Awake SBP (ABPM), mm Hg	
	B (95% CI)	*P* Value	B (95% CI)	*P* Value	B (95% CI)	*P* Value	B (95% CI)	*P* Value	B (95% CI)	*P* Value
Preterm										
Male sex	−4.1 (−11.2 to 3.0)	0.258	−1.4 (−5.9 to 2.9)	0.502	−0.02 (−0.63 to 0.50)	0.926	11.5 (6.3 to 16.7)	<0.001*	7.2 (3.5 to 11.0)	<0.001*
Maternal PIH	−6.4 (−15.1 to 2.2)	0.145	−2.2 (−8.1 to 3.6)	0.451	0.01 (0.7 to 0.7)	0.985	−0.9 (−8.0 to 6.2)	0.801	4.9 (−1.2 to 11.1)	0.116
Antenatal corticosteroids	−1.6 (−8.7 to 5.5)	0.654	−2.3 (−6.8 to 2.2)	0.313	−0.1 (−0.7 to 0.5)	0.658	−5.4 (−11.3 to 0.3)	0.065	4.9 (−1.2 to 11.1)	0.128
GA, wk	3.3 (0.7 to 6.0)	0.012*	−0.1 (−1.7 to 1.4)	0.859	−0.05 (−0.27 to 0.17)	0.649	0.1 (−2.2 to 2.2)	0.915	0.2 (−1.6 to 2.0)	0.803
Birth weight (per 100 g)	1.62 (0.04 to 3.21)	0.044*	−0.21 (−1.20 to 0.78)	0.679	−0.13 (−0.26 to −0.00)	0.044*	0.1 (−1.2 to 1.4)	0.872	0.2 (−0.8 to 1.3)	0.649
Neonatal NSAID	−5.3 (−12.4 to 1.8)	0.142	1.9 (−2.6 to 6.5)	0.398	−0.3 (−0.9 to 0.3)	0.369	3.0 (−2.5 to 8.7)	0.279	0.9 (−3.9 to 5.8)	0.710
Major neonatal morbidity†	−5.6 (−12.7 to 1.5)	0.122	0.3 (−4.1 to 4.7)	0.879	0.7 (0.1 to 1.3)	0.015*	0.8 (−4.9 to 6.6)	0.771	−1.8 (−6.6 to 2.9)	0.436
BPD	−6.2 (−13.5 to 1.0)	0.095	1.7 (−2.8 to 6.3)	0.459	0.8 (0.2 to 1.4)	0.012*	0.1 (−5.9 to 5.9)	0.994	−0.9 (−6.0 to 4.2)	0.729
Term										
Male sex	1.8 (−5.7 to 9.3)	0.637	1.1 (−2.7 to 5.1)	0.555	−0.6 (−1.2 to 0.1)	0.111	13.5 (8.8 to 18.2)	<0.001*	8.2 (3.8 to 12.6)	<0.001*
Maternal PIH	−1.1 (−19.0 to 16.9)	0.906	3.1 (−4.6 to 10.9)	0.424	−0.3 (−1.7 to 1.0)	0.609	4.9 (−6.0 to 15.8)	0.377	5.4 (−2.0 to 12.8)	0.150
GA, wk	−1.6 (−5.1 to 1.7)	0.338	−0.3 (−2.0 to 1.4)	0.717	0.1 (−0.2 to 0.4)	0.464	−0.5 (−2.9 to 1.8)	0.659	−1.5 (−3.5 to 0.4)	0.136
Birth weight (per 100 g)	0.51 (−0.48 to 1.51)	0.309	0.26 (−0.26 to 0.78)	0.322	0.03 (−0.06 to 0.12)	0.515	0.1 (−0.8 to 0.7)	0.825	0.1 (−0.6 to 0.6)	0.977

Bivariate linear regression of perinatal factors on adult outcomes. ABPM indicates ambulatory blood pressure monitoring; ACR, urine albumin-to-creatinine ratio; B, unstandardized coefficient; BP, blood pressure; BPD, bronchopulmonary dysplasia; eGFR, estimated glomerular filtration rate; GA, gestational age; PIH, pregnancy-induced hypertension; and SBP, systolic blood pressure.

*Statistically significant differences.

†Major neonatal morbidities: bronchopulmonary dysplasia (oxygen requirements at 36 wk post-menstrual age) or severe brain injury (intraventricular hemorrhage grade 3 or 4 or cystic periventricular leukomalacia) or retinopaty of prematurity (grade ≥3) or confirmed neonatal sepsis or patent ductus arteriosus surgical ligation or necrotizing enterocolitis.

environment,[45,46] nephrotoxic drugs,[47–53] and a decreased protein intake[54–56] during active nephrogenesis result in reduced nephron endowment and abnormal glomerular architecture. Renal pathology specimens have also revealed an increased vulnerability to neonatal acute kidney injury in preterm infants, further exacerbating glomerular paucity.[11] Thus, in the context of prolonged NICU stays with repeated nephrotoxic exposures, the renal development of preterm individuals is likely further compromised.

In addition, compelling data are accumulating that the renin-Ang system is differentially modulated in experimental models of prematurity.[46,57,58] However few studies have previously reported on the renin-Ang system in preterm-born children and adolescents,[59,60] and none, to our knowledge, in preterm-born adults. In our study, circulating Ang I was significantly higher in the preterm participants, whereas no between-group difference was detected for Ang II, Ang (1–7), and alamandine. Higher Ang I values, which had not been reported in individuals born preterm, were similarly elevated to the values reported in children with renovascular hypertension.[61] Considering Ang I has no known biological action, the physiological impact of higher levels on cardiovascular risk factors in preterm subjects remains to be further explored. Our cohort's Ang II values were lower (×10) compared with those reported by South et al[60] in a study of 14-year-old born preterm at 27.8 weeks of gestation (no full-term control group). The lower Ang II values that we found could be related to the different methodologies used to collect blood, or to measure the Ang peptides as other studies[60,62] have used radioimmunoassay in which Ang antibodies could cross react with Ang III and IV, and/or true difference which would require further investigation. Current study adult preterm plasma Ang (1–7) values were in a comparable range of values with those reported by South et al[60] and lower compared

Table 4. Correlation Between Perinatal Factors and Renin, Ang I, Ang II and Ang (1–7) and Alamandine in Young Adults Born Preterm ≤29 wk and Full Term

	Renin-Ang System									
	Renin		Ang I		Ang II		Ang (1–7)		Alamandine	
Birth Characteristics	cc	*P* Value	cc	*P* Value	cc	*P* Value	cc	*P* Value	cc	*P* Value
Preterm										
Male sex	0.713	<0.001*	0.044	0.760	0.125	0.387	0.185	0.230	0.349	0.029*
Maternal PIH	0.120	0.382	0.064	0.657	0.002	0.990	0.072	0.644	–0.035	0.834
Antenatal corticosteroids	0.000	1.000	–0.177	0.229	–0.055	0.709	–0.262	0.093	–0.042	0.807
GA	–0.068	0.621	–0.123	0.393	–0.234	0.102	–0.043	0.780	–0.313	0.053
Birth weight	–0.062	0.653	–0.245	0.086	–0.199	0.167	–0.177	0.249	–0.253	0.121
Neonatal NSAID	–0.062	0.661	–0.029	0.848	–0.091	0.541	0.321	0.041*	0.157	0.353
Major neonatal morbidities†	0.344	0.010*	0.04	0.764	0.083	0.566	0.076	0.623	0.074	0.650
BPD	0.271	0.045*	0.117	0.417	0.094	0.514	0.317	0.036*	0.175	0.287
Term										
Male sex	0.429	0.001*	–0.239	0.076	–0.120	0.379	0.010	0.946	0.260	0.081
Maternal PIH	–0.007	0.960	–0.177	0.193	–0.226	0.094	0.188	0.190	–0.185	0.217
GA	–0.062	0.661	–0.002	0.987	–0.173	0.201	0.157	0.275	0.384	0.008*
Birth weight	–0.076	0.587	–0.301	0.024*	–0.063	0.647	0.403	0.004*	–0.062	0.684

Ang indicates angiotensin; BPD, bronchopulmonary dysplasia; cc, correlation coefficient using nonparametric Spearman (2 tailed); GA, gestational age; and PIH, pregnancy-induced hypertension.

*Statistically significant differences.

†Major neonatal morbidities: BPD or severe brain injury (intraventricular hemorrhage grade 3 or 4 or cystic periventricular leukomalacia) or retinopaty of prematurity (grade ≥3) or confirmed neonatal sepsis or patent ductus arteriosus ligation or necrotizing enterocolitis.

with nonpregnant women[63] and normotensive children.[61] To our knowledge, alamandine levels had not been reported in subjects born preterm or in cohort studies.

Regarding the impact of perinatal factors, South et al[60] reported that, contrary to current results, antenatal corticosteroids were associated with increased plasma Ang (1–7); this was predominantly observed in subjects of black race[60] and was not present in nonblack participants, who constituted the vast majority of our cohort. Taken together, current knowledge suggests that preterm birth is associated with activation of the renin-Ang system into adolescence and young adulthood and that severe prematurity-related complications can result in long-term modulation of the renin-Ang system. Systemic measures of Ang peptides cannot be presumed to reflect renal renin-Ang system, which can contribute to hypertension and was shown to be activated in experimental models with hypertension associated with deleterious intrauterine conditions.[64,65]

Higher alamandine levels were found in preterm, but not term, subjects with higher BP. Alamandine is a vasodilatory peptide regulated by the Ang-I–renin pathway, as well as through Ang-converting enzyme 2 expression and activity; the latter was not evaluated in the current study. Similarly, we found higher Ang (1–7) levels in preterm participants with a more severe NICU course. These elements suggest that the counterregulatory cardiovascular-vasodilatory and renoprotective arm of the renin-Ang system might be activated in young adults born preterm,[66] as reported in patients with CKD.[67] One may postulate that prediseased renal parenchyma, epigenetic changes in renin-Ang system regulation, and perpetuated modifications in central nervous system BP control[68–70] could contribute to long-term consequences of preterm birth on renin-Ang system expression. Activation of the renin-Ang system and of the autonomic regulation of the cardiovascular system[71] can also lead to higher heart rate that we observed in preterm subjects.

Our results are significant for the preterm population that is now in early adulthood. Indeed, a 4-mm Hg difference in BP at a population level has been associated with a 20% change in stroke mortality and a 15% change in mortality from other vascular-related diseases; these effects are the most pronounced in younger people.[72] Furthermore, because humans lose glomeruli with age,[73] preterm-born adults will become increasingly vulnerable to the deleterious effects of hypertension and the development of CKD. Of concern, because the incidence of cardiovascular risk factors increases with age,[74] this already susceptible population may be further injured by a second hit—a well-known phenomenon in the development of CKD.[75,76] Examples are already emerging, as was seen with the cumulative impact of prematurity and obesity on the deterioration of renal function in children with CKD.[77]

Prematurity is an important risk factor to consider for the risk stratification of adults for the development of renal and cardiovascular diseases. Healthcare providers, in turn, have an opportunity to identify these patients and follow them for indications to institute primary preventive measures. Because current national guidelines recommend several first-line treatment modalities for undifferentiated hypertension, consideration should be given to targeted clinical trial to establish optimal treatment for this population.

Strengths and Limitations

Our project was confronted by limitations inherent to an observational cross-sectional study design. Furthermore, we had a relatively small study population because the final analysis included 92 pairs and was not powered to stratify analysis by sex. However, this is the first study of adult individuals born ≤29 weeks of gestation of this magnitude with such closely matched controls to account for environmental factors that may confound findings. Participants also underwent a comprehensive series of renal structural, functional, and hormonal investigations unparalleled in the currently published literature. The correlational analyses examining impact of neonatal factors and Ang peptides were exploratory and were not adjusted for confounders. The low proportion of subjects born small for GA prevented analyses taking into account this specific factor; reciprocally, this strengthened the evaluation of the impact of preterm birth in itself.

All perinatal data were collected retrospectively in hospital charts. As most records by nurses and allied health professional data had been purged, we were unable to document certain NICU exposures which may have an impact on later renal function and BP. For instance, we could not document neonatal acute kidney injury because of the paucity of systematic laboratory values measured and sparse documentation of urine output. We encountered another limitation with respect to the number of participants who did not comply with the ABPM data collection; further, the preterm subjects without ABPM data had significantly smaller kidneys and lower eGFR versus those with ABPM recordings, which could have reduced the magnitude of the differences observed between groups.

Despite these limitations, we think that our study carries several strengths, beginning with the fact that we present the data from one of the largest study of adult patients born preterm at ≤29 weeks of gestation. Objective clinical and outcome data were obtained by trained clinicians blinded to subjects' exposure status. The same group of consultants partook in each assessment to minimize interobserver variability. We recruited patients born in the greater Montreal area (which comprises ≈50% of the population in the province of Quebec[78]) during a decade, which also increases our study's generalizability.

Perspectives

We show that young adults born preterm at ≤29 weeks of gestation, compared with term controls, have smaller kidneys, higher urine microalbuminuria, which nevertheless remains within normal limits, normal eGFR, as well as modulation of adult circulating Ang peptide levels by perinatal factors. Preterm young adults with smaller kidneys have higher BP. Follow-up studies of adults born preterm are required to evaluate their susceptibility to chronic renal disease on the longer term.

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Appendix

CDK-epi 2009 formula: $eGFR=141\times\min(S_{cr}/\kappa,1)^{\alpha}\times\max(S_{cr}/\kappa,1)^{-1.209}\times0.993^{Age}\times1.018$ (if woman)×(1.157 if black); α is 0.329 for women and 0.411 for men; min indicates minimum of S_{cr}/κ or 1, max indicates maximum of S_{cr}/κ or 1, S_{cr} is serum creatinine. CKD-epi 2012 formula using cystatine-c alone: $eGFR=133\times\text{minutes}(S_{cys}/0.8,1)^{-0.499}\times\max(S_{cys}/0.8,1)^{-1.328}\times0.996^{Age}\times0.932$ (if woman); Scys is serum cystatin-C. CDK-epi 2012 formula using cystatine-c and creatinine: $eGFR=135\times\min(S_{Cr}/\kappa,1)^{\alpha}\times\max(S_{Cr}/\kappa,1)^{-0.601}\times\min(S_{cys}/0.8,1)^{-0.375}\times\max(S_{cys}/0.8,1)^{-0.711}\times0.995^{Age}\times0.969$ (if woman)×1.08 (if black); where κ=0.7 (women) or 0.9 (men), α=−0.248 (women) or −0.207 (men).

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Novelty and Significance

What Is New?

- Individuals born preterm have smaller adult kidneys, which correlates with higher blood pressure and higher levels of microalbuminuria but normal renal function.
- Lower gestational age and birth weight correlated with smaller adult kidneys.
- Ang (angiotensin) I was increased in adults born preterm.

What Is Relevant?

- Considering that kidney disease is an important aggravating factor to hypertension and cardiovascular diseases, individuals born preterm could have their renal function and blood pressure monitored throughout life. Their susceptibility to renal second hits remains to be determined.

Summary

Preterm birth impacts adult kidney size, microalbuminuria, and the renin-Ang system.