Kidney International, Vol. 68 (2005), pp. 731–740

Impaired kidney growth in low-birth-weight children: Distinct effects of maturity and weight for gestational age

IDA M. SCHMIDT, MARLA CHELLAKOOTY, KIRSTEN A. BOISEN, IDA N. DAMGAARD, CLAUDIA MAU KAI, KLAUS OLGAARD, and KATHARINA M. MAIN

University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark; and Department of Nephrology, Rigshospitalet, Copenhagen, Denmark

Impaired kidney growth in low-birth-weight children: Distinct effects of maturity and weight for gestational age.

Background. Low birth weight is an important risk factor for hypertension and unfavorable prognoses of a number of renal diseases. It is also associated with reduced kidney size and nephron number. A differentiation between the effects of low birth weight versus being born premature or small for gestational age has, however, not been addressed.

Methods. The influence of weight for gestational age (percentage deviation from expected mean), gestational age, birth weight, and early diet on kidney growth was studied in 178 children born pre- or postmature and/or small or large for gestational age, comparing them to 717 mature children, birth weight appropriate for gestational age. Kidney size was determined by bilateral ultrasonography measuring length, width and depth, using the equation of an ellipsoid for volume calculation. The examinations were performed at 0, 3, and 18 months of age together with measurements of body weight, height, and skinfold thickness.

Results. Weight for gestational age had a significant, positive effect on combined kidney volume at all three ages (0 months, $P < 0.001$; 3 months, $P < 0.001$; and 18 months, $P < 0.001$). A slight catch-up growth in kidney size was seen in the most growth-retarded infants (<10th percentile) between 0 and 18 months of age (mean Δz $\text{score}_{0-18\text{mo}} = +0.22$ SD) ($P = 0.037$). Premature children had smaller kidneys compared to mature at all ages (0 months, $P = 0.001$; 3 months, $P = 0.007$; and 18 months, $P = 0.042$), without any significant catch-up with age. Relative kidney volume was inversely correlated with weight for gestational age at birth ($P = 0.007$) but positively at 18 months ($P = 0.008$). Relative kidney growth 0 to 18 months was positively correlated to weight for gestational age ($P = 0.013$). Low birth weight was associated with impaired relative kidney growth in response to formula feeding.

Conclusion. Being small for gestational age is associated with small kidneys at birth and impaired kidney growth in early childhood. The present data suggest that intrauterine growth has a regulatory influence on nephron formation and renal function in humans reaching beyond the neonatal period.

Key words: nephrogenesis, infant, kidney size, intrauterine growth retardation, birth weight, gestational age.

Received for publication November 26, 2004
And in revised form February 7, 2005
Accepted for publication February 28, 2005

Low birth weight has been identified as an important risk factor for unfavorable course or progression of a number of renal diseases [1–6]. Likewise, an inverse association between birth weight and blood pressure in childhood and adult life is well-documented [7]. Possible underlying pathophysiologic mechanisms include renal, metabolic, and vascular changes [8]. One hypothesis is that intrauterine growth retardation may cause a reduced number of congenital nephrons [9], leading to increased single nephron glomerular filtration rate (GFR), thereby augmenting the risk of glomerulosclerosis and subsequently elevated blood pressure [10]. This hypothesis has been substantiated by several animal studies [11–14] and questioned by some [15]. In humans, low birth weight has been associated with reduced nephron number or density in autopsy studies [16–19], whereas others did not find any association between birth weight and glomerular number or the progression of diabetic nephropathy [20, 21].

As age-adjusted kidney weight is strongly positively correlated to the total number of glomeruli, kidney volume can be regarded as a proxy for nephron number [22]. Low birth weight, both pathologically low (<2.5 kg) and relatively within the normal range, has been associated with reduced kidney size in infants and adults [16, 23, 24]. However, due to lack of accurate information on gestational age distinctions between an effect of low birth weight per se versus being small for gestational age or premature could not be made. In a recent autopsy study of premature infants (gestational age <28 weeks) of extremely low birth weight (≤1000 g) radial glomerular counts were markedly decreased compared to mature infants [25]. Glomerulogenesis continued until 40 days of age but did never reach the level of mature infants. Likewise, in vivo studies of kidney size in human fetuses of known gestational age have shown that intrauterine growth retardation is accompanied by decreased fetal kidney volume compared to fetuses of appropriate weight for gestational age [26–28]. How kidney growth further evolves during infancy in small for gestational age or preterm children has not been described.

Formula feeding induces increased kidney size compared to breast feeding in 3-month-old healthy infants born at term with birth weight appropriate for gestational age [29]. Many preterm or small for gestational age infants are prone to receive infant formula. Whether they respond equally by increasing kidney size has not yet been investigated.

To investigate the influence of intrauterine growth, maturity, birth weight, and early diet on kidney growth and shape, we have followed 189 children born pre- or postmature as well as small or large for gestational age for the first 18 months of life, comparing them to a normal reference material of 717 mature, healthy singletons with birth weight appropriate for gestational age [30].

METHODS

Study design

A prospective longitudinal cohort study was performed from 1997 to 2002 at Rigshospitalet and Hvidovre Hospital, University of Copenhagen. All pregnant women of Danish origin, geographically belonging to the hospital referral area, and not referred because of expected complications in pregnancy, were consecutively asked to join the study in their first trimester of pregnancy. The children were part of an ongoing cohort study establishing reference materials for kidney size and prevalence of renal malformations, genital development and malformations, and body growth [29–33].

The children were examined within the first 5 days of life (0 months) and again at 3 and 18 months of age. In case of preterm birth, examination took place around the expected date of delivery and again 3 and 18 months later. In case of postterm birth the child was examined shortly after birth and again 3 and 18 months after the expected date of delivery. At all examinations bilateral kidney ultrasonography and anthropometric measurements were performed. At each visit the child was examined by one out of a team of eight doctors. All methods of measuring were standardized at workshops.

Inclusion and exclusion criteria

Children were included if they were born pre- or postmature and/or small or large for gestational age. Children with major congenital malformations or severe chronic diseases were excluded; however, mild hydronephrosis (pelvic anteroposterior diameter 5 to 10 mm) at one examination or coexistence of cryptorchidism or hypospadias was allowed. The normal reference ranges for kidney size, shape, and growth in mature healthy children with birth weight appropriate for gestational age have previously been published [30]. Data from these children were included as reference material in the present analysis.

Gestational age and anthropometry

Gestational age (days) was determined by routine ultrasonography in pregnancy week 18 to 20. In 2.8% gestational age was determined by last menstrual period. Prematurity was defined as gestational age below 259 days (<37 weeks), and postmaturity as gestational age above 294 days (>42 weeks). Birth weight (kg) was obtained from birth records. Weight for gestational age was expressed as the percentage deviation from the expected mean weight for gestational age. For this calculation a gender-specific fourth-degree polynomial equation was used [34]. Small or large for gestational age was defined as weight for gestational age below −22% or above +22% of expected weight for gestational age approximate to −2 SD and +2 SD. Weight for gestational age was additionally stratified into six classes according to percentiles: 0 to 9.9, 10 to 24.9, 25 to 49.9, 50 to 74.9, 75 to 89.9, and 90 to100 percentiles.

Body weight was measured on a digital scale (BabyScale Model) (Solotop Oy, Helsinki, Finland) to the nearest 0.005 kg. Body length was measured supine with a Kiddimeter (Raven Equipment LTD, Essex, UK) to the nearest 0.1 cm. Body fatness was estimated measuring subscapular skinfold thickness to the nearest 0.1 mm using a skinfold calliper (Harpenden, British Indicators LTD, London, UK). All anthropometric measurements were registered as the mean of three measurements.

Ultrasonography

Kidney size was determined by ultrasonography using a 5 MHz sector probe with an accuracy of 0.1 mm (Aloka SSD 500) (Aloka Co., Ltd. Tokyo, Japan). The probe was placed on the back of the child, at the neonatal examination with the child lying on the contralateral side in a ventrally curved position, and at 3 and 18 months of age in a supported sitting position. The kidney was identified in the sagittal plane along its longitudinal axis. In this position three longitudinal anteroposterior measurements of the largest length and width were performed. The probe was then rotated 90 degrees and three cross-sectional anteroposterior measurements of the width and depth at the hilar level were performed. All dimensions were measured to nearest 0.1 cm in both kidneys.

Mean length and depth were calculated as the average of three measurements and mean width as the average of six. Maximum pelvic anteroposterior diameter was measured to nearest 0.1 mm and renal malformations classified. Kidney volume was calculated in cubic centimeters using the equation of an ellipsoid: volume = mean length ∗ mean width ∗ mean depth ∗ 0.523 [35]. Left and right kidney volumes were added for the combined kidney volume (cm^3). Relative kidney volume was calculated as combined kidney volume/body weight (cm^3/kg). Kidney shape was described by the ratio mean length/[(mean width + mean depth) ∗ 0.5]. Relative kidney growth was calculated as volume increase/weight increase (Δ cm^3/Δ kg) over the two intervals 0 to 3 months and 0 to 18 months of age. Body weight and combined kidney volume are linearly correlated at this age [30]. Details on intra- and interobserver variation of kidney size have been reported previously [30]

Feeding classification at 3 months of age

No intervention was made concerning early nutrition. If the child had received any kind of infant formula, the name of the product was registered, as was the age (weeks) at which formula feeding had started and, if relevant, the age at which breast-feeding had stopped. The children were stratified into three feeding categories according to the type of feeding during the last month prior to the 3-month examination: (*1*) fully breast fed (nothing but breast feeding since birth), (*2*) partially breast fed (combined breast and formula feeding), and (*3*) fully formula fed (no breast milk since 2 months of age).

Statistics

Descriptives are given as mean (SD), mean (standard error of the mean) or median (95% CI). Parameters that were not normally distributed were log transformed prior to analysis: kidney shape, combined and relative kidney volume. Log transformed combined and relative kidney volumes were converted into age and gender specific z scores [(Xn − Xmean)/SD)] where Xn is the value of the individual child, Xmean is the mean value for age and gender, and SD is the standard deviation at the same age and gender. This enables pooling of all data from girls and boys at separate ages for analysis. The Xmean and SD values were derived from the reference material of mature, healthy singletons born appropriate for gestational age [30].

To differentiate the effect of weight for gestational age and gestational age data was split: (*1*) the influence of weight for gestational age was analyzed in the group of children born at term ($N = 782$), and (*2*) the influence of gestational age was analyzed in children with birth weight appropriate for gestational age ($N = 821$). Differences between classes of weight for gestational age or gestational age were tested with one sample *t* test (between two groups) or one-way analysis of variance (ANOVA) (between more than two groups). Differences between z scores at two different ages were tested with paired samples *t* test for individual groups of weight for gestational age and gestational age.

General linear models including all children were applied to analyze the influence of gender, gestational age, weight for gestational age, birth weight, current weight, current subscapular skinfold thickness, and diet at 3 months of age on the following dependent variables: log-transformed combined kidney volume, log-transformed relative kidney volume, log-transformed kidney shape, and kidney volume increase per weight increase over two time periods (0 to 3 months and 0 to 18 months of age). Each model was carefully controlled by evaluation of residual plots.

Results were considered significant if $P < 0.05$. The statistical analyses were performed in SPSS 11.0 for Windows.

Ethical approval

The study was performed according to the Helsinki II declaration and approved by the local ethics committee [j.no. (KF) 01-030/97] and the Danish Data Protection Agency (no. 1997-1200-074). Informed written consent was given by the parents.

RESULTS

Participants

Of 189 eligible children being pre- or postmature and/or small or large for gestational age 11 were excluded: three with unilateral renal agenesis, two with severe bilateral, and three with severe unilateral hydronephrosis (anteroposterior pelvic diameter ≥1.0 cm), one with Down syndrome and congenital heart disease, one with severe cerebral palsy, and one with gastroschisis. Thus, 178 children were included, 30 twins and 148 singletons. Mild hydronephrosis at one examination was seen in 26 children and coexistence of cryptorchidism and/or hypospadias was found in 15 boys. The reference group of healthy mature (gestational age 37 to 42 weeks), appropriate for gestational age (weight for gestational age ± 2 SD) singletons consisted of 717 children [30]. The total number of children available for analysis was 895. The distribution of boys and girls in each category of weight for gestational age and maturity is given in Table 1.

Combined kidney volume (cm^3)

Figure 1A shows the combined kidney volume (z scores) for children born at term age 0 to 18 months according to percentiles of weight for gestational age. Weight for gestational age at birth had a significant, positive effect on combined kidney volume at all three ages (0 months, $P < 0.001$; 3 months, $P < 0.001$; and 18 months, $P < 0.001$). A small, but significant catch-up in kidney size with age was seen in the most growth-retarded infants (<10th percentile) between 0 and 18 months of age (mean Δz $score_{0-18mo} = +0.22$ SD) ($P = 0.037$). No significant changes with age were found in any other weight for gestational age category.

Table 1. Number of children grouped by maturity and weight for gestational age $N = 895$

	Gestational age weeks	Weight for gestational age			Total
		<− 2SD	± 2SD	>− 2SD	
Boys	<37	6	36		42
	37–42	16	312	15	343
	>42		33		33
Total		22	381	15	418
Girls	<37	2	22	1	25
	37–42	11	405	23	439
	>42		13		13
Total		13	440	24	477

The z-score of combined kidney volume according to gestational age among appropriate for gestational age children is presented in Figure 1B. Premature children had significantly smaller kidneys compared to mature children at all three ages (0 months, $P = 0.001$; 3 months, $P = 0.007$; and 18 months, $P = 0.042$). Some degree of catch up growth, however statistically insignificant, was noted. In postmature children combined kidney volume did not differ significantly from mature children at any age.

In a general linear model including all children, combined kidney volume at 0 and 18 months of age was significantly positively correlated to both weight for gestational age and current weight, and negatively correlated to skinfold thickness (Table 2). Additionally, boys had larger kidneys compared to girls at 0 months, but no gender difference was seen at 18 months of age. At 3 months of age a positive correlation between combined kidney volume and both birth weight and current weight was seen, in addition to increasing kidney volume with formula feeding and boys having larger kidneys than girls (Table 2).

Relative kidney volume (cm^3/kg)

The influence of weight for gestational age on relative kidney volume (cm^3/kg) in term children is shown in Figure 2A. At birth an inverse correlation between weight for gestational age and relative kidney volume was found ($P = 0.007$). At 3 months of age the pattern changed toward the opposite, reaching statistical significance at 18 months of age (3 months, $P = 0.811$; and 18 months, $P = 0.008$). Relative kidney volume decreased in the most growth-retarded group (<10th percentile) between 0 and 18 months of age (mean Δz score$_{0-18mo} = -0.50$ SD) ($P = 0.002$), while an increase was seen in the heaviest group (90th to 100th percentile) (mean Δz score$_{0-18mo} = +0.61$ SD) ($P < 0.001$). No significant changes with age were found in any other weight for gestational age category.

The relative kidney volume (cm^3/kg) according to gestational age among appropriate for gestational age children is presented in Figure 2B. At 0 months of age a negative association between gestational age and relative kidney volume was seen; however, this was not significant ($P = 0.090$). Premature children had a significant

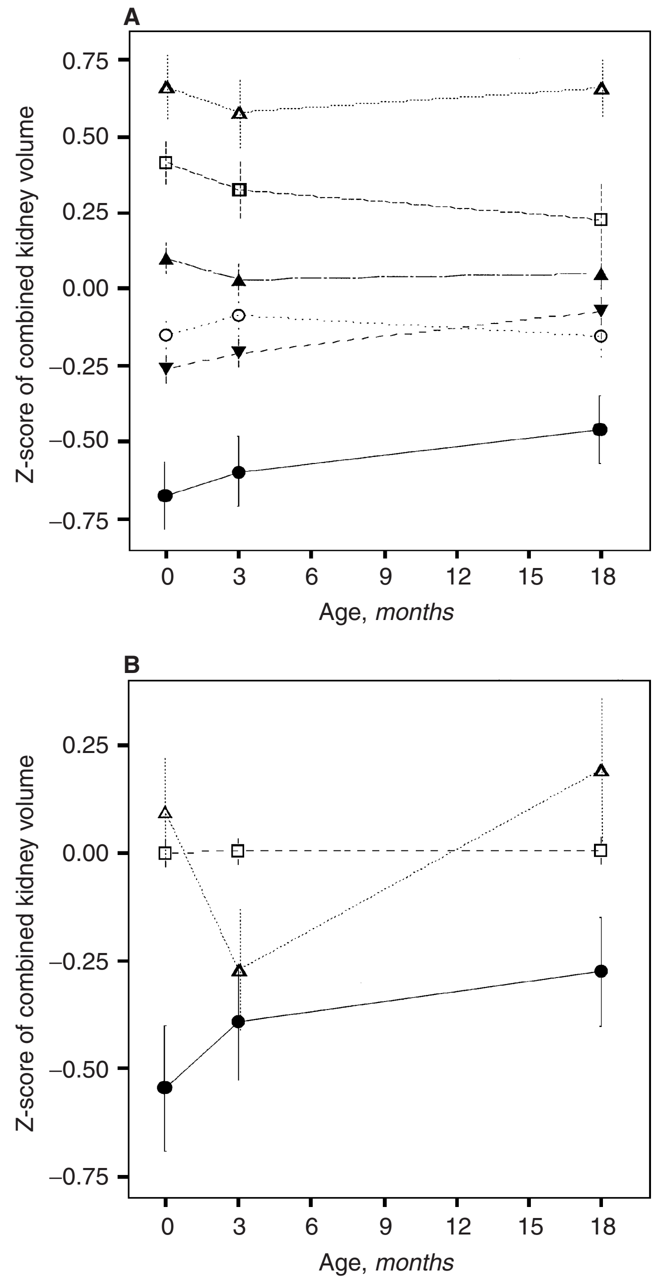

Fig. 1. Z score of combined kidney volume (cm^3) from 0 to 18 months of age. (*A*) Children born at term (gestational age 37 to 42 weeks stratified into six categories of weight for gestational age. Symbols are: (●) 0 to 9.9 percentile ($N = 80$); (▼) 10 to 24.9 percentile ($N = 135$); (○) 25 to 49.9 percentile ($N = 182$); (▲) 50 to 74.9 percentile ($N = 186$); (□) 75 to 89.9 percentile ($N = 107$); (△) 90 to 100 percentile ($N = 92$). (*B*) Children born approximately for gestational age (weight for gestational age ± 2 SD) stratified into three categories according to maturity (preterm, term, and postterm). Symbols are: (●) <37 weeks of gestation ($N = 58$); (□) 37 to 42 weeks of gestation ($N = 717$); (△) >42 weeks of gestation ($N = 46$). Dots represent means (± SEM).

Table 2. Determinants of combined kidney volume at 0, 3, and 18 months of age

	0 months of age				3 months of age				18 months of age			
	Initial model		Final model		Initial model		Final model		Initial model		Final model	
Variable	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Gender (boys vs. girls)	1.112	0.000	1.086	0.000	1.046	0.028	1.051	0.000	1.024	0.205		
Diet at 3 months												
Fully formulafed					1.063	0.005	1.063	0.004				
Partially breastfed					1.033	0.067	1.033	0.065				
Fully breastfed					Ref		Ref					
Gestational age *days*	1.005	0.122			0.999	0.684			1.003	0.327		
Birth weight *kg*	0.845	0.190			1.104	0.440	1.045	0.000	0.903	0.391		
Weight for gestational age %[a]	1.008	0.079	1.002	0.034	0.998	0.668			1.005	0.252	1.001	0.017
Current weight *kg*	1.202	0.000	1.223	0.000	1.132	0.000	1.134	0.000	1.093	0.000	1.096	0.000
Skinfold thickness *mm*	0.985	0.069	0.981	0.015	1.002	0.613			0.986	0.002	0.985	0.001
Intercept cm^3[b]	5.772	0.001	13.237	0.000	16.395	0.000	13.464	0.000	14.835	0.000	24.434	0.000

[a]Weight for gestational age given in% deviation from expected mean weight for gestational age.
[b]The intercept is the initial value, which is subsequently modified by the values of the specific parameters like gender and birth weight.
Examples of interpretations Comparing two children at 0 months of age, a boy and a girl, with the same gestational age, birth weight, weight for gestational age current weight, and skinfold thickness, the boy has on the average an 8.6% larger kidney volume compared with the girl. The combined kidney volume of a 3-month-old formula, fed child is 6.3% larger than in a breast, fed child of identical gender, birth weight, and current weight. At 18 months of age, combined kidney volume increases with 0.1% per 1 percentage point increase of weight for gestational age given identical current weight and skinfold thickness.

decrease of relative kidney volume from 0 to 3 months of age (mean Δz $\text{score}_{0-3\text{mo}} = -0.49$ SD) ($P = 0.001$). At 3 months the premature group had significantly reduced relative kidney volume compared to mature children ($P = 0.010$). The apparent increase of relative kidney volume from 3 to 18 months among the premature was not significant. The postmature children did not differ from the mature at any time, and the trend of increasing relative volume with age was not significant.

In a general linear model, including all children, relative kidney volume at 0 months of age was positively correlated to male gender and negatively to birth weight and skinfold thickness (Table 3). At 3 months of age male gender and birth weight were both positively correlated to relative kidney volume, but even stronger correlated to increasing proportion of formula feeding. At 18 months of age the significant determinants were weight for gestational age and skinfold thickness, respectively, positively and negatively correlated to relative kidney volume (Table 3).

Relative kidney growth ($\Delta cm^3/\Delta kg$)

Kidney volume increase per kilogram body weight increase from 0 to 3 months of age was in a general linear model (GLM) analysis significantly correlated to diet (Table 4). Splitting the children into the three separate feeding categories no influence of gestational age, birth weight, weight for gestational age, or gender was found in the two groups receiving breast milk. However, in the fully formula fed group relative kidney growth was positively correlated to birth weight ($P = 0.032$, $r^2 = 0.06$). The model being $\Delta cm^3/\Delta kg_{0-3mo} = 2.65 +$ (birth weight $*$ 0.703). An increase of 1 kg of birth weight resulted in an increasing relative kidney growth of 0.703 cm^3/kg weight gain from 0 to 3 months of age.

Relative kidney growth from 0 to 18 months of age was significantly positively correlated to weight for gestational age ($P = 0.009$, $r^2 = 0.01$) (Table 4). The resulting model was $\Delta cm^3/\Delta kg_{0-18mo} =$ 4.86 + (weight for gestational age $*$ 0.009). An increase of 10% point of weight for gestational age resulted in a 9% increase of relative kidney growth. Thus, the difference between a child of weight for gestational age −22% (−2 SD) and +22% (+2 SD) was 39.6% (4.66 versus 5.06 $\Delta cm^3/\Delta kg$).

Kidney shape (length/[(width + depth) $*$ 0.5])

At 0 months of age a weak ($r^2 = 0.03$), but significant negative correlation between kidney shape and both weight for gestational age (β = −0.9988, $P = 0.000$) and gestational age (β = −0.9995, $P = 0.033$) was found in a GLM analysis. Mean kidney shape stratified according to weight for gestational age and gestational age is given in Table 5. Premature small for gestational age children had the slimmest kidneys (highest ratio) at 0 months. At 3 and 18 months of age no significant correlations were found.

Weight gain

Changes in z scores of body weight from 0 to 18 months of age among mature infants displayed a significant catch-up growth in the most growth retarded groups and a catch-down among the largest children. Listed from small to large for gestational age in the six weight for gestational age categories are mean Δz $\text{score}_{0-18\text{mo}}$ +1.03 SD ($P = 0.000$), +0.37 SD ($P = 0.002$), +0.04 SD (NS), −0.09 SD (NS), −0.31 SD ($P = 0.018$), and −1.10 SD ($P = 0.000$).

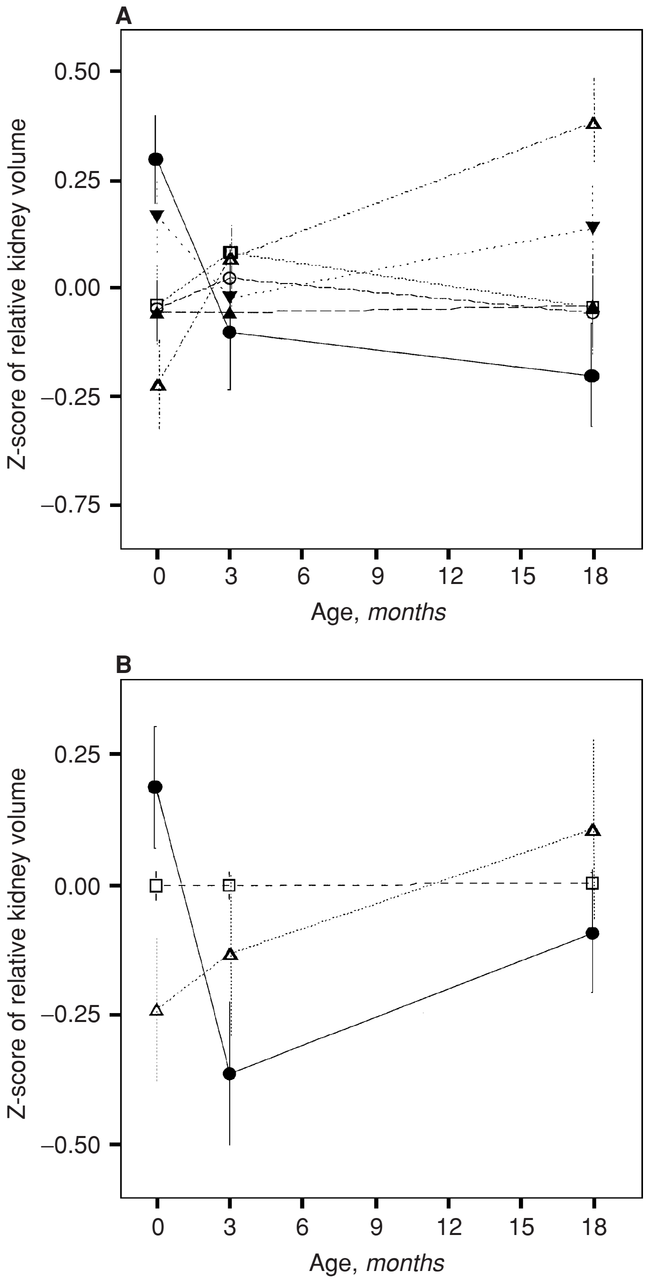

Fig. 2. Z score of relative kidney volume (cm^3/kg) for 0 to 18 month of age. (*A*) Children born at term (gestational age 37 to 42 weeks stratified into six categories of weight for gestational age. Symbols are: (●) 0 to 9.9 percentile ($N = 80$); (▼) 10 to 24.9 percentile ($N = 135$); (○) 25 to 49.9 percentile ($N = 182$); (▲) 50 to 74.9 percentile ($N = 186$); (□) 75 to 89.9 percentile ($N = 107$); (△) 90 to 100 percentile ($N = 92$). (*B*) Children born approximately for gestational age (weight for gestational age ± 2 SD) stratified into three categories according to maturity (preterm, term, and postterm). Symbols are: (●) <37 weeks of gestation ($N = 58$); (□) 37 to 42 weeks of gestation ($N = 717$); (△) >42 weeks of gestation ($N = 46$). Dots represent means (± SEM).

In children with birth weight appropriate for gestational age changes in z scores of body weight over the same age period was significantly influenced by maturity. Premature children showed catch-up growth while the postmature were catching down. The mean Δz score$_{0-18mo}$ were +0.71 SD ($P = 0.012$), −0.02 SD (NS), and−0.50 SD ($P = 0.027$) in premature, mature, and postmature, respectively.

Gender differentiated body growth during the two periods 0 to 3 months and 0 to 18 months of age did not differ between feeding categories mean Δweight$_{0-3mo}$ (SD) in boys 3.01 (0.76) kg and in girls 2.57 (0.64) kg, and mean Δweight$_{0-18mo}$ (SD) in boys 8.33 (1.17) kg and in girls 7.68 (1.10) kg.

DISCUSSION

This prospective cohort of Danish children showed that reduced weight for gestational age had a distinct impact on kidney size, different from low birth weight or prematurity. Weight for gestational age had a stronger influence than birth weight or gestational age on combined kidney volume at 0 and 18 months of age, relative kidney volume at 18 months, relative kidney growth between 0 and 18 months, and kidney shape at birth. Children born small for gestational age did in general not show any catch-up growth of combined kidney volume over the first 18 months of life, except for the most growth retarded children (<10th percentile) in whom kidney volume increased by 0.22 SD. Prematurity in children with birth weight appropriate for gestational age was associated with reduced kidney size at birth and no significant improvement was seen with age. Although formula feeding, as compared to breast feeding, led to a significant increase in relative kidney growth rate in all groups of children, children with low birth weight showed a significantly reduced response. This indicates a potential effect of fetal growth restriction on kidney size and function reaching beyond the neonatal period. Our data thus, confirm the findings from animal experiments and patient populations.

Intrauterine growth retardation has been associated with reduced kidney volume in human fetuses of known gestational age [26, 27, 36] and is well described in animal studies [12, 14, 37]. Low birth weight has also been associated with reduced kidney size in children [23, 24] and adults [24]. In autopsy studies low number and density of nephrons has been shown in individuals of low birth weight [16–19]. An inverse correlation between glomerular number and glomerular volume has been found in both individuals of low birth weight [17, 18], adult patients who had suffered from hypertension [38] and humans who had died from variable causes [39, 40]. This inverse relation between glomerular number and size has been interpreted as a sign of increased single nephron filtration rate and glomerular hypertension, potentially leading to advanced nephrosclerosis [10, 18, 38, 41]. Several experimental animal studies have confirmed these findings [10, 37].

Table 3. Determinants of relative kidney volume (cm^3/kg) at 0, 3, and 18 months of age

	0 months of age				3 months of age				18 months of age			
	Initial model		Final model		Initial model		Final model		Initial model		Final model	
Variable	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Gender (boys vs. girls)	1.087	0.000	1.074	0.000	1.024	0.224	1.035	0.008	1.022	0.217		
Diet at 3 months												
Fully formula fed					1.060	0.007	1.058	0.008				
Partially breastfed					1.041	0.025	1.040	0.029				
Fully breastfed					ref		ref					
Gestational age *days*	1.003	0.417			0.998	0.567			1.002	0.464		
Birth weight *kg*	0.869	0.280	0.975	0.063	1.125	0.359	1.025	0.022	0.931	0.546		
Weight for gestational age %[a]	1.004	0.341			0.996	0.428			1.004	0.369	1.001	0.005
Skinfold thickness *mm*	0.969	0.000	0.970	0.000	0.995	0.234			0.987	0.001	0.987	0.001
Intercept cm^3/kg[b]	6.265	0.000	8.971	0.000	6.713	0.000	5.155	0.000	1.490	0.004	6.080	0.000

[a]Weight for gestational age given in% deviation from expected mean weight for gestational age.
[b]The intercept is the initial value, which is subsequently modified by the values of the specific parameters like gender and birth weight.
Example of interpretation At 0 months of age, relative kidney volume decreases with 3.0% for each 1 mm increase of skinfold thickness given identical gender and birth weight.

Table 4. Determinants of relative kidney growth ($\Delta cm^3/\Delta kg$) between 0 to 3 months and 0 to 18 months of age

	0 to 3 months of age				0 to 18 months of age			
	Initial model		Final model		Initial model		Final model	
Variable	β	*P*	β	*P*	β	*P*	β	*P*
Gender (boys vs. girls)	−0.225	0.382			−0.085	0.555		
Diet at 3 months								
Fully formula fed	1.189	0.000	1.158	0.000	0.082	0.610		
Partially breastfed	0.304	0.210	0.271	0.259	0.112	0.408		
Fully breastfed	Ref		Ref		Ref			
Gestational age *days*	−0.067	0.137			0.012	0.629		
Birth weight *kg*	2.676	0.112			−0.451	0.640		
Weight for gestational age %[a]	−0.089	0.134			0.024	0.473	0.009	0.013
Intercept cm^3/kg[b]	13.270	0.055	3.923	0.000	3.005	0.439	4.863	0.000

[a]Weight for gestational age given in% deviation from expected mean weight for gestational age
[b]The intercept is the initial value, which is subsequently modified by the values of the specific parameters like gender and birth weight.
Example of interpretation relative kidney growth from 0 to 3 months of age in a fully breast fed child is 3.92 cm^3/kg, in a partially breast fed child, 3.92 + 0.27 = 4.19 cm^3/kg, and in a fully formula fed child, 3.92 + 1.16 = 5.08 cm^3/kg.

Low birth weight has been identified as an independent risk factor of progression of several renal diseases: in childhood unfavorable course of nephrotic syndrome [2, 3] and IgA nephritis [4], multiple subclinical tubular defects predisposing to renal lithiasis [42], increased risk of renal scarring in adulthood following urinary tract infection without vesicourethral reflux in childhood [5], and increased blood pressure [7]. In adult patients low birth weight has been associated with accelerated deterioration of renal function in idiopathic membranous nephropathy [43], elevated incidence of albuminuria in high-risk populations [1, 44, 45], increased risk of end-stage renal disease, hypertension, and coronary heart disease [6, 7, 46, 47]. The limited catch-up kidney growth seen among the growth retarded children in our study may, in part, explain the link between prenatal growth retardation and later diseases. However, the associations have been questioned. In type 1 diabetic adults low birth weight (<20th centile) was not associated with the progression of established nephropathy (decline in GFR per year) [21]. Unfortunately, no information on gestational age was available, and the authors discuss relevant confounders like hypertension and maternal diabetes. A lack of association between low birth weight and glomerular number and size was indicated in non–insulin-dependent diabetic patients and age- and gender-matched controls [20]. The number of subjects, however, was limited (26 + 19), the range of birth weight was 2750 to 4500 g (none with serious intrauterine growth retardation), and gestational age was not known. In a rat study it was concluded that birth weight had no influence on glomerular number and volume [15]. The classification of low versus normal birth weight was made within each litter; the two smallest male pups were designated low birth weight and the two males closest to the mean litter weight were designated normal birth weight. By this procedure pups of identical birth

Table 5. Mean kidney shape (length/[(width + depth) × 0.5]) at 0 months of age according to gestational age and weight for gestational age.

Gestational age *weeks*	Weight for gestational age		
	<−2 SD	±2 SD	>+2 SD
<37	2.05 (1.65–2.31)	2.01 (1.64–2.53)	1.89
37–42	1.91 (1.59–2.56)	1.93 (1.62–2.34)	1.89 (1.63–2.23)
>42		1.91 (1.57–2.46)	

Results are given as median (2.5 to 97.5 percentiles).

weight but from different litters were classified differently, which may have influenced the results profoundly.

Children born premature and/or small for gestational age had slimmer kidneys than mature appropriate for gestational age children. This is in accordance with studies of kidney size in human fetuses of known gestational age showing that intrauterine growth retardation is accompanied by decreased fetal kidney volume with a sausage-like shape compared to fetuses of appropriate weight for gestational age [26, 27]. Glomerulogenesis takes place in a centripetal direction from the inner cortex and outwards with more and more generations of glomeruli added as nephrogenesis proceeds until 32 to 34 weeks of gestation. In an autopsy study of premature infants (gestational age <28 weeks) of extremely low birth weight (≤1000 g) radial glomerular counts were markedly decreased compared to mature infants [25]. Glomerulogenesis continued until 40 days of age but did never reach the level of mature infants. Assuming that the kidney has the shape of an ellipsoid, a uniformly reduced cortical thickness in all directions would result in a slimmer kidney shape. Thus, we speculate if our findings of slim kidney shape in premature small for gestational age children may be a result of impaired glomerulogenesis.

Body composition had a significant influence on relative kidney volume (cm^3/kg). Thus, in two children of same gender and weight, but different body composition the lean child (smallest skinfold) has the largest kidney volume. This result is well in line with previous data showing that kidney volume correlates slightly better with lean body mass than with height, weight, or body surface area [48, 49]. In an autopsy study of 200 children younger than 2 years of age, the relative kidney weight (percent of body weight) was negatively correlated with body weight for height [50]. A comparison between kidney weight in lean and obese adults showed lower relative kidney weight (kidney weight/body weight) in the obese [51].

Intrauterine growth retardation can be caused by numerous maternal, placental, or fetal factors. In our cohort we were not able to differentiate between those. Likewise, we were not able to establish whether the growth retardation occurred early or late in gestation. In animal studies, however, these factors have been studied separately. Placental insufficiency in rats induced by ligation of uterine arteries promoting intrauterine growth retardation leads to reduced nephron number [12, 52, 53], increased albuminuria, and impaired compensatory response to postnatal unilateral nephrectomy [52]. In sheep intrauterine growth retardation induced by umbilicoplacental embolization in the third trimester did not decrease nephron number, whereas spontaneous intrauterine growth retardation in twin pregnancies led to reduced nephron endowment. This suggests that the timing of growth restriction is very important, assuming that intrauterine growth retardation in twinning takes place in both second and third trimester [54]. Maternal protein restriction in rats has been associated with reduced kidney size and low glomerular number in the offspring [12, 37, 55–59], as well as impaired renal functions [12, 56, 60] with indications of progressive deterioration with age [55, 61]. The window of susceptibility to maternal protein restriction coincided with the period of nephrogenesis [56].

A few nutrients and hormones that are altered in case of intrauterine growth retardation have been identified as single factors with negative influence on nephrogenesis in animals [62, 63]. Vitamin A deficiency and maternal hyperglycemia have been associated with low nephron number in rats, both in a dose-response manner [64, 65], and increased levels of maternal glucocorticoids were associated with impaired nephrogenesis and hypertension in the offspring [66, 67].

In the present study, low birth weight was correlated with impaired relative kidney growth among formula-fed infants. Assuming that the normal renal response to formula feeding is increased relative kidney growth, as compared to breast-fed infants, caused by an increased renal solute load and hyperfiltration due to elevated protein intake [29], children of low birth weight are less capable of producing a corresponding appropriate adaptive response. This is in line with studies in rats showing that intrauterine growth retardation not only leads to reduced nephron number, but also impaired response to postnatal unilateral nephrectomy [52] or experimental diabetes [57].

CONCLUSION

Weight for gestational age is an important independent determinant of kidney size not only at birth, but persisting in early childhood up to at least 18 months of age. Weight for gestational age has a stronger influence than crude birth weight or gestational age. Thus, weight for gestational age rather than birth weight should be used in future analyses of the impact of fetal growth on renal size, function, and diseases in later life. Relative kidney volume decreased significantly with age in the most growth-retarded group. Whether this trend progresses after 18 months of age into a pathologic condition is, however, unknown. We also found a blunted response in relative kidney growth during formula feeding in low-birth-weight infants, suggesting that these children are less capable of producing an appropriate adaptive response. The present data suggest that intrauterine growth has a regulatory influence on nephron formation and renal function in humans reaching beyond the neonatal period.

ACKNOWLEDGMENTS

We are grateful to the participating families and to the staff of the Obstetric Departments of the University Hospital of Copenhagen for excellent cooperation and we appreciate the skilled help of our assisting nurses and students. The present study was supported by the Danish Research Council (no. 9700833), the Research Foundation of The Copenhagen Hospital Corporation (nos. 109/00 and 134), the European Commission (nos. QLK4-1999-01422 and QLRT-2001-00269), and the Ville Heise Foundation.

Reprint requests to Ida Maria Schmidt, M.D., University Department of Growth and Reproduction, GR 5064, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
E-mail: imschmidt@dadlnet.dk

REFERENCES

1. HOY WE, REES M, KILE E, *et al*: A new dimension to the Barker hypothesis: Low birthweight and susceptibility to renal disease. *Kidney Int* 56:1072–1077, 1999
2. SHEU JN, CHEN JH: Minimal change nephrotic syndrome in children with intrauterine growth retardation. *Am J Kidney Dis* 37:909–914, 2001
3. ZIDAR N, AVGUSTIN CM, KENDA RB, FERLUGA D: Unfavorable course of minimal change nephrotic syndrome in children with intrauterine growth retardation. *Kidney Int* 54:1320–1323, 1998
4. ZIDAR N, CAVIC MA, KENDA RB, *et al*: Effect of intrauterine growth retardation on the clinical course and prognosis of IgA glomerulonephritis in children. *Nephron* 79:28–32, 1998
5. HELLSTROM M, HESSEL H, JACOBSSON B, *et al*: Association between urinary tract infection, renal damage and birth size. *Acta Paediatr* 90:628–631, 2001
6. LACKLAND DT, BENDALL HE, OSMOND C, *et al*: Low birth weights contribute to high rates of early-onset chronic renal failure in the Southeastern United States. *Arch Intern Med* 160:1472–1476, 2000
7. HUXLEY RR, SHIELL AW, LAW CM: The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: A systematic review of the literature. *J Hypertens* 18:815–831, 2000
8. INGELFINGER JR: Pathogenesis of perinatal programming. *Curr Opin Nephrol Hypertens* 13:459–464, 2004
9. BRENNER BM, GARCIA DL, ANDERSON S: Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens* 1:335–347, 1988
10. BRENNER BM, CHERTOW GM: Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 23:171–175, 1994
11. WOODS LL, WEEKS DA, RASCH R: Programming of adult blood pressure by maternal protein restriction: Role of nephrogenesis. *Kidney Int* 65:1339–1348, 2004
12. MERLET-BENICHOU C, GILBERT T, MUFFAT-JOLY M, *et al*: Intrauterine growth retardation leads to a permanent nephron deficit in the rat. *Pediatr Nephrol* 8:175–180, 1994
13. MERLET-BENICHOU C: Influence of fetal environment on kidney development. *Int J Dev Biol* 43:453–456, 1999
14. BAUER R, WALTER B, BAUER K, *et al*: Intrauterine growth restriction reduces nephron number and renal excretory function in newborn piglets. *Acta Physiol Scand* 176:83–90, 2002
15. JONES SE, NYENGAARD JR, FLYVBJERG A, *et al*: Birth weight has no influence on glomerular number and volume. *Pediatr Nephrol* 16:340–345, 2001
16. HINCHLIFFE SA, LYNCH MR, SARGENT PH, *et al*: The effect of intrauterine growth retardation on the development of renal nephrons. *Br J Obstet Gynaecol* 99:296–301, 1992
17. MANALICH R, REYES L, HERRERA M, *et al*: Relationship between weight at birth and the number and size of renal glomeruli in humans: A histomorphometric study. *Kidney Int* 58:770–773, 2000
18. HUGHSON M, FARRIS AB, DOUGLAS-DENTON R, *et al*: Glomerular number and size in autopsy kidneys: The relationship to birth weight. *Kidney Int* 63:2113–2122, 2003
19. ZIDAR N, COR A, PREMRU ST, STAJER D: Is there an association between glomerular density and birth weight in healthy humans. *Nephron* 80:97–98, 1998
20. NYENGAARD JR, BENDTSEN TF, MOGENSEN CE: Low birth weight—Is it associated with few and small glomeruli in normal subjects and NIDDM patients? *Diabetologia* 39:1634–1637, 1996
21. JACOBSEN P, ROSSING P, TARNOW L, *et al*: Birth weight—A risk factor for progression in diabetic nephropathy? *J Intern Med* 253:343–350, 2003
22. NYENGAARD JR, BENDTSEN TF: Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec* 232:194–201, 1992
23. SPENCER J, WANG Z, HOY W: Low birth weight and reduced renal volume in Aboriginal children. *Am J Kidney Dis* 37:915–920, 2001
24. SINGH GR, HOY WE: Kidney volume, blood pressure, and albuminuria: Findings in an Australian aboriginal community. *Am J Kidney Dis* 43:254–259, 2004
25. RODRIGUEZ MM, GOMEZ AH, ABITBOL CL, *et al*: Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. *Pediatr Dev Pathol* 7:17–25, 2004
26. SILVER LE, DECAMPS PJ, KORST LM, *et al*: Intrauterine growth restriction is accompanied by decreased renal volume in the human fetus. *Am J Obstet Gynecol* 188:1320–1325, 2003
27. KONJE JC, OKARO CI, BELL SC, *et al*: A cross-sectional study of changes in fetal renal size with gestation in appropriate- and small-for-gestational-age fetuses. *Ultrasound Obstet Gynecol* 10:22–26, 1997
28. LAMPL M, KUZAWA CW, JEANTY P: Infants thinner at birth exhibit smaller kidneys for their size in late gestation in a sample of fetuses with appropriate growth. *Am J Human Biol* 14:398–406, 2002
29. SCHMIDT IM, DAMGAARD IN, BOISEN KA, *et al*: Increased kidney growth in formula-fed versus breast-fed healthy infants. *Pediatr Nephrol* 19:1137–1144, 2004
30. SCHMIDT IM, MAIN KM, DAMGAARD IN, *et al*: Kidney growth in 717 healthy children aged 0–18 months: A longitudinal cohort study. *Pediatr Nephrol* 19:992–1003, 2004
31. SCHMIDT IM, CHELLAKOOTY M, HAAVISTO AM, *et al*: Gender difference in breast tissue size in infancy: Correlation with serum estradiol. *Pediatr Res* 52:682–686, 2002
32. BOISEN KA, KALEVA M, MAIN KM, *et al*: Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. *Lancet* 363:1264–1269, 2004
33. CHELLAKOOTY M, SCHMIDT IM, HAAVISTO AM, *et al*: Inhibin A, inhibin B, follicle-stimulating hormone (FSH), lutenizing hormone (LH), estradiol and sex hormone-binding globulin (SHBG) levels in 473 healthy infant girls. *J Clin Endocrinol Metab* 88:3515–3520, 2003
34. LARSEN T: Intrauterine Growth restriction—Identification, correlation and causation evaluated by use of ultrasound. *Dan Med Bull* 48:256–274, 2001
35. ZENKL M, EGGHART G, MULLER M: The normal kidney size in children. An ultrasound study. *Urologe A* 29:32–38, 1990
36. KONJE JC, BELL SC, MORTON JJ, *et al*: Human fetal kidney morphometry during gestation and the relationship between weight, kidney morphometry and plasma active renin concentration at birth. *Clin Sci (Lond)* 91:169–175, 1996
37. INGELFINGER JR, WOODS LL: Perinatal programming, renal development, and adult renal function. *Am J Hypertens* 15:46S–49S, 2002
38. KELLER G, ZIMMER G, MALL G, *et al*: Nephron number in patients with primary hypertension. *N Engl J Med* 348:101–108, 2003

39. Hoy WE, Douglas-Denton RN, Hughson MD, *et al*: A stereological study of glomerular number and volume: preliminary findings in a multiracial study of kidneys at autopsy. *Kidney Int* (Suppl 83):S31–S37, 2003
40. Schmidt K, Pesce C, Liu Q *et al*: Large glomerular size in Pima Indians: Lack of change with diabetic nephropathy. *J Am Soc Nephrol* 3:229–235, 1992
41. Mcgraw M, Poucell S, Sweet J, Baumal R: The significance of focal segmental glomerulosclerosis in oligomeganephronia. *Int J Pediatr Nephrol* 5:67–72, 1984
42. Monge M, Garcia-Nieto VM, Domenech E, *et al*: Study of renal metabolic disturbances related to renal lithiasis at school age in very-low-birth-weight children. *Nephron* 79:269–273, 1998
43. Duncan RC, Bass PS, Garrett PJ, Dathan JR: Weight at birth and other factors influencing progression of idiopathic membranous nephropathy. *Nephrol Dial Transplant* 9:875, 1994
44. Hoy WE, Rees M, Kile E, *et al*: Low birthweight and renal disease in Australian aborigines. *Lancet* 352:1826–1827, 1998
45. Nelson RG, Morgenstern H, Bennett PH: Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. *Am J Epidemiol* 148:650–656, 1998
46. Fan ZJ, Lackland DT, Kenderes B, *et al*: Impact of birth weight on familial aggregation of end-stage renal disease. *Am J Nephrol* 23:117–120, 2003
47. Barker DJ, Osmond C, Golding J *et al*: Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *Br Med J* 298:564–567, 1989
48. Schmidt IM, Mølgaard C, Main KM, Michaelsen KF: Effect of gender and lean body mass on kidney size in healthy 10-year-old children. *Pediatr Nephrol* 16:366–370, 2001
49. Oswald J, Schwentner C, Lunacek A, *et al*: Age and lean body weight related growth curves of kidneys using real-time 3-dimensional ultrasound in pediatric urology. *J Urol* 172:1991–1994, 2004
50. Morrison EY, Alleyne GA: Malnutrition, kidney size and composition. *Arch Latinoam Nutr* 26:7–14, 1976
51. Kasiske BL, Umen AJ: The influence of age, sex, race, and body habitus on kidney weight in humans. *Arch Pathol Lab Med* 110:55–60, 1986
52. Adachi S, Zelenin S, Matsuo Y, Holtback U: Cellular response to renal hypoxia is different in adolescent and infant rats. *Pediatr Res* 55:485–491, 2004
53. Alexander BT: Placental insufficiency leads to development of hypertension in growth-restricted offspring. *Hypertension* 41:457–462, 2003
54. Mitchell EK, Louey S, Cock ML, *et al*: Nephron endowment and filtration surface area in the kidney after growth restriction of fetal sheep. *Pediatr Res* 55:769–773, 2004
55. Garofano A, Czernichow P, Breant B: Postnatal somatic growth and insulin contents in moderate or severe intrauterine growth retardation in the rat. *Biol Neonate* 73:89–98, 1998
56. Woods LL, Weeks DA, Rasch R: Programming of adult blood pressure by maternal protein restriction: role of nephrogenesis. *Kidney Int* 65:1339–1348, 2004
57. Jones SE, Bilous RW, Flyvbjerg A, Marshall SM: Intra-uterine environment influences glomerular number and the acute renal adaptation to experimental diabetes. *Diabetologia* 44:721–728, 2001
58. Goldstein RS, Hook JB, Bond JT: The effects of maternal protein deprivation on renal development and function in neonatal rats. *J Nutr* 109:949–957, 1979
59. Zeman FJ: Effects of maternal protein restriction on the kidney of the newborn young of rats. *J Nutr* 94:111–116, 1968
60. Hall SM, Zeman FJ: Kidney function of the progeny of rats fed a low protein diet. *J Nutr* 95:49–54, 1968
61. Nwagwu MO, Cook A, Langley-Evans SC: Evidence of progressive deterioration of renal function in rats exposed to a maternal low-protein diet in utero. *Br J Nutr* 83:79–85, 2000
62. Merlet-Benichou C, Gilbert T, Vilar J *et al*: Nephron number: Variability is the rule. Causes and consequences. *Lab Invest* 79:515–527, 1999
63. Nelson RG: Intrauterine determinants of diabetic kidney disease in disadvantaged populations. *Kidney Int* (Suppl 83):S13–S16, 2003
64. Merlet-Benichou C, Vilar J, Lelievre-Pegorier M, Gilbert T: Role of retinoids in renal development: pathophysiological implication. *Curr Opin Nephrol Hypertens* 8:39–43, 1999
65. Amri K, Freund N, Vilar J, *et al*: Adverse effects of hyperglycemia on kidney development in rats: In vivo and in vitro studies. *Diabetes* 48:2240–2245, 1999
66. Celsi G, Kistner A, Aizman R, *et al*: Prenatal dexamethasone causes oligonephronia, sodium retention, and higher blood pressure in the offspring. *Pediatr Res* 44:317–322, 1998
67. Wintour EM, Moritz K, Johnson K, *et al*: Reduced nephron number in adult sheep, hypertensive as a result of prenatal glucocorticoid treatment. *J Physiol* 15:929–935, 2003