Postnatal Kidney Function in Children Born Very Low Birth Weight

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Introduction. There are scarce data on estimating the time of completing kidney maturation in very-low-birth-weight (VLBW) infants. The aim of this study was to determine whether different aspects of kidney function differ between VLBW infants and normal babies at 18 to 30 months postconceptional age.

Materials and Methods. This study was carried on 23 VLBW infants and 21 normal-birth-weight infants at 18 to 30 months corrected postconceptional age, who were born between June 2007 and June 2008 at Alzahra Hospital and Shahid Beheshti Hospital, in Isfahan, Iran. Very low birth weight was defined as a birth weight between 1000 g and 1500 g, while gestational age is less than 32 weeks. In both groups, children with a history of sepsis, asphyxia, intubation, hypoxic ischemic encephalopathy, and pyelonephritis were excluded.

Results. The mean of systolic, diastolic, and mean arterial blood pressure were not significantly different between the two groups. Urine calcium-creatinine ratio, fraction excretion of magnesium, and renal threshold for phosphate were significantly higher in the VLBW children compared with the control group. Glomerular filtration rate was higher in the control group than in the VLBW group.

Conclusions. Our results demonstrated that in VLBW children at the corrected age of 24 ± 6 months, some aspects of tubular and glomerular functions are still impaired. Longer longitudinal cohort studies on VLBW are required to determine the time of completing kidney function maturation in these children.

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INTRODUCTION

In human beings, glomerulogenesis begins at 5 weeks gestational age and develops and peaks at the second trimester. In the fetus, glomerular filtration rate (GFR) has a correlation with both age and body weight. Prenatal GFR, even corrected for body weight is lower in neonates than in adults. However, nephronogenesis stops after 34 to 36 weeks after conception. Furthermore, renal blood flow (RBF) is low in human neonates. The clearance of para aminohippurate, as a measurement of renal blood flow, correlates with gestational age. Although with a delay in premature neonates, RBF and GFR increases and reaches the mature level by 2 years of age in normal infants.[1-6]

Increasing in tubular transport and balancing with GFR occurs concomitantly in the neonatal period.[7-9] However, glomerular tubular balance is impaired in immature nephrons, especially those with short proximal tubules.[10] This imbalance results in glucosuria and salt wasting in very premature newborns.[11] The combination of physiologic lag in

maturation and pathological processes involving kidneys in premature newborns results in delayed tubular-glomerular function comparing with full-term babies. Irrespective of published data on different aspects of kidney function in preterm neonates, there is scarcity of data on the time of completing kidney maturation in premature babies. The aim of this study was to determine whether various aspects of kidney function differ between very-low-birth-weight infants and normal babies at 18 to 30 months postconceptional age.

MATERIALS AND METHODS

This historical cohort study was carried on 23 very-low-birth-weight (VLBW) infants and 21 infants with normal birth weight. The infants were at 18 to 30 months postconceptional age. The postconceptional age was corrected for premature infants. The VLBW infants were selected after revising the hospital-recorded birth charts of 670 infants born VLBW between June 2007 and June 2008 at Alzahra Hospital and Shahid Beheshti Hospital, Isfahan, Iran. The study was performed in accordance with the ethical standards of the Helsinki Declaration and approved by the Ethics Committee of the Research Department of Isfahan University of Medical Sciences. The informed written consent was obtained from the parents.

The participants in the control group were recruited from healthy children referred to private clinics for routine examination. The inclusion criteria for the VLBW group were a birth weight between 1000 g and 1500 g, a gestational age less than 32 weeks, and age at the time of entering the study of 18 to 30 months (corrected for gestational age). Infants with a history of pyelonephritis, sepsis, asphyxia, and hypoxic ischemic encephalopathy; history of administration of nephrotoxic medications during neonatal period (such as aminoglycosides and ibuprofen); urinary tract infection at the time of sampling; and hydroureteronephrosis or anatomical abnormality on prenatal ultrasonographic assessments were excluded.

Demographic data, systolic and diastolic blood pressure, height and body weight, and paraclinical results were collected for all participants. Height was measured at the standing position by a Seca height-measuring instrument (Seca, Birmingham, UK). The weight was measured by Seca scale (Seca, Birmingham, UK) at the same visit. Blood pressure was determined two times in the sitting position by auscultatory method. The mean blood pressure was calculated based on the following formula:

Mean arterial blood pressure = (systolic blood pressure + 2 × diastolic blood pressure)/3

Fasting serum and spot urine were collected to measure serum creatinine, sodium (Na), potassium, magnesium, phosphate, cyctatin C, and calcium and urinary Na, potassium, phosphate, calcium, magnesium, and albumin. Microalbumin was measured by an enzyme-linked immunosorbent assay method and was normalized according to serum creatinine. An albumin-creatinine ratio more than 20 mg/g was considered abnormally high. Cystatin C of serum was measured by nephelometry with a Nephstarsystem instrument (TSTLAB Co, Isfahan, Iran) and turbidometry with an auto-analyzer instrument method. Renal threshold for phosphate (Tp/GFR), an indicator of proximal tubular function, was calculated by the following formula:

Tp/GFR (mg/dL) = plasma phosphate - (urine phosphate × plasma creatinine/urine creatinine)

Glomerular filtration rate was determined by the Schwartz formula and a cystatin C-based formula[12]:

GFR (mL/min/1.73 m^2) = 0.55 × height/plasma creatinine

log(GFR) = 1.962 + [1.23× log(1/cystatin C)]

Fraction excretion (FE) of magnesium (Mg) and calcium were measured as indicators of the function of the thick ascending limb of Henle and the distal nephron, respectively. Fraction excretion of each electrolyte, except for FE of magnesium, was measured as follows:

FE = (urine electrolyte × plasma creatinine)/(plasma electrolyte × urine creatinine)

Fraction excretion of magnesium, as an indicator of function of the thick ascending limb of Henle, was calculated using the following formula[13]:

FE Mg = (urine Mg × plasma creatinine)/(0.7 × plasma Mg × urine creatinine)

The SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA) was used for statistical analyses. The chi-square test and the independent *t* test were used for comparisons. A *P* value less than .05 was considered significant.

RESULTS

Twenty-three children born premature and VLBW

were studied and compared with 21children with normal birth weight. The male-female ratio was 0.57. The mean gestational age of the infants with VLBW and normal birth weight was 29.21 ± 2.04 weeks and 36.57 ± 1.74 weeks, and the mean age of the two groups were 24.77 ± 3.25 months and 25.09 ± 3.38 months, respectively. The age of the VLBW group was adjusted for the gestational age. The mean birth weight was 1278.26 ± 117.70 g in the infants with VLBW and 3224.28 ± 416.60 g in the controls. However, the significant difference in body weight had not continued until the time of the study; the mean body weight at the time of the study was 12545.45 ± 1448.71 g in the VLBW group and 12433.33 ± 1677.86 g in the control group. In addition, the mean heights were not significantly different between the two groups at the time of the assessment.

The mean values for systolic, diastolic, and mean arterial blood pressure were not notably different between the two groups (Table 1). Glomerular filtration rate measured using the Schwartz formula and serum cystatin C level were higher in the control group compared with the VLBW group (Table 2). As a marker of proximal tubule function Tp/GFR and urine microalbumin levels were significantly higher in the infants with VLBW than in the controls (Table 2). However, the urinary levels of microalbumin in both groups were in normal range. Fraction excretion of magnesium was significantly lower in the control group compared with that in the VLBW infants. Urine calcium-creatinine ratio was significantly higher in the VLBW infants than in the control group (Table 2).

Table 1. Blood Pressure in Infants With Normal and Very Low Birth Weight

	Infants By Birth Weight		
Blood Pressure	Very Low	Normal	*P*
Systolic, mm Hg	99 ± 3	100 ± 4	.26
Diastolic, mm Hg	58 ± 4	59 ± 5	.45
Mean arterial, mm Hg	71.5 ± 4.0	73.0 ± 3.0	.35

DISCUSSION

We evaluated GFR and serum and urine electrolytes and their fraction excretions in addition to blood pressure in children born VLBW in comparison with children with normal birth weight at the same postconceptional age. We found that at the age of 24 ± 6 months, many aspects of kidney function were still immature. Considering these results, GFR was higher in the control group compared with the VLBW group. Nonetheless, urine microalbumin, FE Mg, urine calcium-creatinine ratio, and Tp/GFR were significantly higher in the VLBW group in comparison with the control group.

Very preterm infants are at a higher risk for evolving kidney function impairment. It has been assumed that born prematurely, by decreasing renal size and nephron deficit, may result in delaying kidney function.[14-17] Decreased number in nephrons in VLBW infants leads to less number of nephrons in adulthood through affecting metanephron phase.[15,18] The highest rate of congenital chronic kidney diseases has been reported in premature and low-birth-weight infants.[19] Nyengaard and Bendtsen showed that GFR of VLBW infants was less than that of term infants.[20] Although levels of GFR in VLBW infants remained low even at infancy, these amounts reached normal levels when

Table 2. Laboratory Studies in Infants With Normal and Very Low Birth Weight*

	Infants By Birth Weight		
Parameter	Very Low	Normal	*P*
GFR			
Shwartz, mL/min/1.73 m^2	107.90 ± 9.98	128.05 ± 9.21	< .001
Cystatin C, mL/min/1.73 m^2	99.23 ± 10.45	113.34 ± 8.45	.04
Threshold for phosphate/GFR, mg/dL	4.41 ± 0.86	3.55 ± 0.52	< .001
Serum creatinine, mg/dL	0.51 ± 0.09	0.44 ± 0.08	.24
Fractional excretion of sodium	63.39 ± 42.04	87.45 ± 42.25	.07
Fractional excretion of potassium	15.26 ± 10.95	17.95 ± 10.93	.42
Fractional excretion of magnesium	12.47 ± 1.59	5.38 ± 1.80	< .001
Urine calcium-creatinine ratio, mg/mg	17.78 ± 7.12	12.38 ± 5.11	.007
Urine creatinine, mg/dL	80.78 ± 20.17	89.47 ± 25.54	.34
Urine microalbumin, mg/g	18.24 ± 2.25	15.50 ± 2.34	< .001

*GFR indicates glomerular filtration rate.

they turned 8 years.[6,21] The study by Rakow and colleagues on children aged 9 to 12 years, who were born prematurely, demonstrated normal estimated GFR comparing with normal children.[22] However, Rodriguez-Soriano and colleagues demonstrated that extremely LBW infants (birth weight < 1000 g) could not have normal creatinine clearance even when they were studied at the age of 6 to 12 years.[23] In our study infants at the age of 24 ± 6 months postconceptional age, the possible age for reaching adult kidney function were evaluated. In concert with many studies, we could not show normal levels of GFR in VLBW infants when they reached 24 months postconceptional age in comparison with normal infants.

While in fetal life, FE Na is 20%, in term neonates it reaches about 0.2%. However, in VLBW newborns FE Na remains even at the similar levels to fetal life during early post conceptional days. FE Na is affected by numerous factors. Among these factors; rennin-angiotensin-aldosteron system, circulatory cathecolamines, atrial- natriuretic peptide and prostaglandins have important roles. It has been suggested that increased tubular absorption of Na after birth, mostly relates to distal tubule development.[24] Gallini and colleagues showed an inverse correlation between FE Na and gestational age. Furthermore, the velocity of decrease FE Na was determined directly correlated to gestational age.[25] Rodriguez-Soriano and colleagues demonstrated non- significant difference between FE Na of extremely LBW infants and normal control group at the school age.[23] In our study, at the post-conceptional age of 24 ± 6 months, VLBW infants did not have higher FE Na than control group.

Extremely LBW infants have been shown to have lesser FE potassium at school age when compared with normal group.[23] However, we could not show any difference in FE potassium between VLBW infants and normal subjects. The different inclusion criteria between our study and similar studies may explain the difference between results. We did not enroll any infants with a past neonatal history of receiving aminoglycosides, sepsis, and asphyxia.

The largest part of magnesium re-absorption occurs in thick ascending limb of Henle, an energy-dependent and highly ischemia-sensitive portion of tubules. It has been determined that increased FE Mg may be an early reflection of tubulointerstitial injury.[26,27] Rodriguez-Soriano and colleagues did not demonstrated significant difference in urine magnesium-creatinine ratio between extremely LBW infants and normal subjects.[23] Our study subjects born VLBW had higher amounts of FE Mg at the postconceptional age of 24 ± 6 months. It may be due to a functional developmental delay in the most sensitive part of tubules comparing with normal infants.

Cuzzolin and colleagues showed no difference in serum creatinine concentration among LBW, VLBW and normal neonates at birth. However, between 3rd and 21st days of life, significant differences were observed.[28] This difference was correlated with maternal administration of nonsteriod anti-inflammatory drugs during pregnancy, intubation at birth, low APGAR score, and ibuprofen treatment of the neonates. In our investigation, both VLBW and normal infants had similar levels of serum creatinine concentration at the time of the study. We excluded infants with a proven history of sepsis, low APGAR score and or consumption of ibuprofen.

Microalbuminuria, low amounts of urine albumin below the level of detection by dipstick, has been demonstrated as an early marker of kidney disease and endothelial dysfunction. In VLBW infants, microalbuminuria may be a presentation of delayed maturation and decrease number of glomeruli in comparison with normal infants.

We demonstrated increased levels of urine microalbumin in VLBW infants compared with control group. However, the urinary levels of microalbumin in both groups were in normal range. Vanapee and colleagues revealed that at the early school age, there was no difference in microalbumin excretion between subjects born VLBW and normal weight.[6] Rodriguez-Soriano and colleagues showed in children born prematurely at the post conceptional age of 6 to 12 years, there was no significant difference increased in urine microalbumin excretion comparing with children born normal weight.[23] Lacobelli and colleagues demonstrated that in VLBW ex-preterms microalbumin excretion had correlation with weight z score at 12 months and with catch up growth at 6 months.[21] Some studies revealed the higher prevalence of microalbuminuria among LBW adults.[29-31] The study on 19-year-old ex-preterm adults showed negative correlation with serum creatinine and albuminuria.[31] Furthermore, many studies on LBW adults declared an increased prevalence of microalbuminuria.[29,30,32]

This finding may show the higher risk of chronic kidney disease among adult patients born small for gestational age or premature. The different methods of measuring microalbumin (enzyme-linked immunosorbent assay versus turbidometery), duration of follow-up an inclusion criteria, may explain the differences among our results and similar studies.

During nephron development, function of calcium sensing receptors becomes mature. Furthermore, their number and expression increases. Therefore, distal urinary calcium excretion changes during post conceptional age.[24] Nephrocalcinosis has been reported in premature neonates. Among the mentioned mechanisms, transient hypophosphatemia and higher urine calcium/creatinine ratio have been reported as the main possible factors.[33] It has been reported the increment in values of urine calcium-creatinie in premature infants may exist until they reach school age.[23]

In human beings; the load of consumed phosphate, parathyroid hormone, growth hormone, glucocorticoids and insulin-like growth factor-1 receptors affect renal handling of phosphate. Nephron response to the mentioned factors changes during developmental period. The high tubular maximum re-absorption of phosphate in neonatal period decreases when attaining adult age.[24] It has been reported that renal phosphate threshold tends to decrease during early days of post conceptional age in VLBW neonates [34].Furthermore, the incomplete tubular reabsorption of phosphate in school age children born premature has been discussed.[23] We demonstrated that Tp/GFR in toddlers born premature at age 24 ± 6 months post conceptional was higher than children born normal weight.

Low birth weight has been reported as a risk factor of developing impaired renal autoregulation and the risk of chronic kidney disease.[35] Hemachandra and colleagues' cohort study demonstrated that each 1 kilogram increase in birth weight rose the odds for high systolic blood pressure by 1.06 and high diastolic blood pressure by 1.11.[36] While in that cohort study small for gestational age children were not at higher risk for elevated blood pressure at 7 years of age. Nonetheless, higher level of systolic blood pressure has been reported even at 1 year of age by Duncan and colleagues.[37]

Kistner and colleagues showed higher systolic and mean arterial blood pressure but not 24- hour ambulatory blood pressure among women born premature. However, these women had more numbers of systolic blood pressure recordings over 130 mm Hg.[38] These findings suggested blood pressure regulation disturbances in women born premature. Our subjects born premature did not have higher systolic, diastolic and mean arterial blood pressure than control group.

In our study children born premature at age 24 ± 6 months post conceptional were evaluated. We excluded subjects with a history of sepsis, asphyxia, intubation and proven kidney diseases. Therefore, some different results in comparison with similar studies were expected. The limitation of the study was the low sample size due to restricted inclusion and exclusion criteria. In addition, longitudinal cohort studies are needed to determine the real time of reaching kidney maturation in VLBWs.

CONCLUSIONS

The results achieved from our study and similar studies draw our attention to prolong observation of neonates born premature. A cohort study with longer follow-up duration is necessary to evaluate different aspects of kideny function in children born premature.

CONFLICT OF INTEREST

None declared.

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