Evaluation of renal function and ambulatory blood pressure monitoring in children and adolescents: The role of birthweight

Nergis Karayel1, Ferah Sönmez2, İlknur Girişgen3, Alparslan Ünsal4, Çiğdem Yenisey5, Mete Önde6

1İnegöl State Hospital, Department of Pediatrics, Bursa, Türkiye
2Bezmialem University, Department of Pediatric Nephrology, İstanbul, Türkiye
3Pamukkale University, Department of Pediatric Nephrology, Denizli, Türkiye
4Adnan Menderes University, Department of Radiology, Aydın, Türkiye
5Adnan Menderes University, Department of Biochemistry, Aydın, Türkiye
6Kemalpaşa Health Directorate, Department of Biostatistics, Antalya, Türkiye


ABSTRACT

Objective: A marked relationship is known between low birth weight and reduced nephron number. In this study, it was aimed to investigate the effects of low birth weight on renal function and blood pressure in healthy children and adolescents.

Methods: This study was carried out on 33 children (7 to 18 years) who were born with a birth weight under 2500 g. The control group was composed of 30 children born at term with a birth weight appropriate for gestational age. Urine microalbumin, N-Acetyl-β-D Glucosaminidase, sodium levels and blood urea nitrogen, creatinine, and cystatin-C levels were investigated in patients and the control group. The sizes of kidneys in both groups were examined by ultrasonography. Blood pressure was monitored for 24 hours as ambulatory blood pressure.

Results: The study group had higher levels of blood cystatin-C, urinary sodium, and N-Acetyl-β-D-Glucosaminidase than the control group. Kidney volumes were smaller in the study group than in the controls.

Conclusion: In our study, we observed that some glomerular and tubular functions were affected in children with low birth weight and in children born preterm. These effects were not observed in children with normal birth weight for gestational age. Considering that nephron formation is completed at the 37th week, gestational age (prematurity) was thought to affect glomerular maturation more than intrauterine growth retardation. Our findings did not demonstrate hypertension in children born with low birth weight in childhood. We suggest that low birth weight children should be followed carefully for renal functions and blood pressure.

Keywords: Children, cystatin-C, low birth weight, renal function tests
INTRODUCTION

The fetal origins hypothesis proposes that an early life environment has significant impacts on health in later life. Especially, low birth weight (LBW) has been shown to have a relationship with renal diseases and hypertension at different ages in later life.

A marked relationship has been reported between LBW and reduced nephron numbers. Brenner et al. showed that the filtration area in kidneys with low nephron numbers is reduced compared to healthy individuals with normal nephron numbers. This was confirmed by human postmortem and animal studies, in which LBW was associated with fewer nephrons and thereby a reduced kidney weight/volume. It is important to identify early signs of kidney disease before the damage is done. Laboratory tests showing early structural and functional changes should be performed at regular intervals to detect patients at elevated risk of developing kidney damage. A variety of tests are used clinically to measure renal function. Glomerular filtration rate (GFR) is the finest measurement of kidney function in children and has a major role in the diagnosis of acute and chronic kidney damage. Creatinine clearance-based evaluation of GFR is frequently used in pediatrics. The inaccuracy of creatinine-based estimates of GFR, particularly in children with reduced muscle mass, is well known. Recently, studies have declaimed the use of serum cystatin C as a new marker for the evaluation of early renal impairment. Another method for evaluating glomerular kidney function is the assessment of albuminuria and proteinuria. N-acetyl-beta-D-glucosaminidase (NAG), which cannot be filtered by the glomerulus, is a well-known early marker of proximal tubular injury.

Birth weight and hypertension are known to be negatively associated. Ambulatory blood pressure monitoring (ABPM) for the evaluation of pediatric hypertension has been used in children and adolescents over the past 25-30 years. ABPM, which can more precisely characterize changes in BP throughout daily activities, has been found to be superior to office BPM (OBPM) in predicting cardiovascular morbidity and mortality.

Estimation of renal size by ultrasonography (US) may be used as a surrogate measure for nephron number and as an indirect indicator of renal growth under different clinical conditions.

The aim of the study was to examine the effects of LBW on kidney function, kidney dimensions, and blood pressure levels in healthy children and adolescents.

MATERIAL AND METHODS

Patients

The study group consisted of children who had been born with LBW and had no history of diseases or drug treatment during the study period. LBW was defined as birth weight under 2500 grams. LBW is further classified as very low birth weight (VLBW<1500 g) and extremely low birth weight (ELBW<1000 g). Prematurity was described as babies born before 37 completed weeks of gestation. Sub-classes of preterm birth are extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), and late preterm (32 to 37 weeks). Children were classified as small for gestational age (SGA) and appropriate for gestational age (AGA) based on Lubchenco’s charts.

The control group consisted of children who were all born at term with a birth weight appropriate for their gestational age. Both groups were selected from the pediatric outpatient clinics and were seen because of minor illnesses.

Birth weight data, personal (including information about birth weight, neonatal intensive care hospitalizations, and risk factors for hypertension or impaired kidney functions during the neonatal period) and family medical histories were obtained by a questionary with parents. Exclusion criteria were the presence of chronic illness, renal disease, drug use, or any of the above-mentioned risk factors that could affect renal function. Anthropometric measurements were made for each child. BMI was calculated as weight (kg)/height (m²).

Biochemical analyses

Blood samples were measured by a routine biochemistry analyzer to determine serum urea and creatinine levels. Serum cystatin C levels were measured with an enzyme-linked immunosorbent assay (ELISA) method, and the results were recorded as ng/ml. GFR was calculated from the serum creatinine, the child’s height, and a proportionality constant using the original Schwartz method.

The 24-hour urine protein, microalbumin, and Na levels were measured by a routine biochemistry analyzer. The urinary NAG levels were measured by a spectrophotometric method with a colorimetric kit (Diazyme Laboratories, 12889 Gregg Court Poway, CA 92064, USA). NAG levels in the samples were calculated using the following equation and given as IU/L.

\[
\text{Sample Absorbance - blank solution absorbance/Standard Absorbance - blank solution absorbance = IU/L.}
\]
Ultrasonographic assessment

Kidneys were measured by the same radiologist using the same ultrasound system. Kidney dimensions (length, thickness, width), anterior-posterior diameter (AP), and cortical thickness were measured. Kidney measurements were assessed with respect to the reference values defined by Rosenblum et al. Kidney volume was calculated by the formula for an ellipsoid (length × thickness × width × 0.5233). The measurements were assessed with respect to the reference values defined by Oswald et al.

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) was performed using the oscillometric Welch Allyn 24-hour ABP Monitor, version 12, combined with an appropriate-sized cuff placed on the non-dominant hand during a hospital stay. The ABPM records were analyzed for mean systolic (SBP) and diastolic (DBP) arterial blood pressure during sleep (nighttime) or when awake (daytime) over the 24-h period. The BP loads for systolic and diastolic pressure were also recorded. The results of ABPM were assessed using the method of Soergel et al. Non-dipping was defined as a fall in average sleeping systolic or diastolic BP < 10% from baseline. Blood pressure loads were considered as the percentage of systolic and diastolic BP readings greater than the 95th percentile. Loads in excess of 25% were considered elevated. Loads in excess of 50% were considered severely elevated.

Statistical analyses

All statistical analyses were performed using the SPSS version 14 software package. The normal distribution of numeric variables was tested with the Kolmogorov-Smirnov test. Independent sample t-test was used for the comparison of normally distributed numeric variables. Mann-Whitney U test was used for the comparison of non-normally distributed variables. Pearson’s or Spearman’s correlation tests were used to determine the correlations between various measurements. P values less than 0.05 were considered statistically significant.

RESULTS

The study group was composed of 33 children: 20 girls and 13 boys with a mean age of 10.0±2.3 years. The mean birth weight of the study group was 2000.6±387.6 g (1100-2450 g); 81.8% of the children were LBW, and 18.2% of the children were VLBW. Twenty-three of the LBW neonates were preterm birth and ten were term birth. Ten of the LBW neonates were SGA. The control group was composed of 30 healthy children (15 girls, 15 boys).

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<tr>
<th>Table 1. Anthropometric parameters of the LBW and the control groups</th>
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<td>Gender (Girl/Boy)</td>
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LBW: Low birth weight
with a mean age of 11.1±2.8 years. The mean birth weight of the control group was 3451.6±473.8g (2550-4300g). The study group consisted of 15 (45.5%) children admitted to the NICU during the neonatal period. Of these, 6 (18.2%) received mechanical ventilation, 2 (6.1%) had an umbilical vein catheterization, and 9 (27.3%) used drugs in that period. The control group consisted of 4 (13.3%) children admitted to the NICU during the neonatal period, none of whom needed invasive procedures or drug therapy. The age, gender, weight, height, and BMI percentiles of the patients were not statistically different between the LBW and control groups (Table 1). The renal functions of the LBW group and the control group are shown in Table 2. The GFR in the LBW group was not significantly different compared to the control group (Table 2). There was a significant correlation between GFR and current weight in the LBW group (r=0.486, p=0.004). The mean urea levels were significantly higher in the children-with-LBW group compared to the control group (Table 2). The mean serum creatinine levels were significantly lower in the children-with-LBW group compared to the control group (p=0.022). Serum creatinine levels were positively associated with the current weight of the children (r=0.471, p=0.006), but there was no significant correlation between serum creatinine levels and birth weight. The mean urea, serum creatinine levels, and GFR were similar between the children born preterm and term. Also, the mean serum creatinine levels and GFR were similar between the children born SGA and AGA. The mean serum urea levels were significantly higher in the SGA group than in the AGA group (Table 3).

The mean blood cystatin-C levels were found to be significantly higher in the children-with-LBW group compared to the control group (Table 2). The mean blood cystatin-C levels were also significantly higher in children born preterm compared to the children born term (p=0.002). Blood cystatin-C levels were similar in children born SGA and AGA (p=0.23). A negative relationship was found between blood cystatin-C levels and birth weight in the study group (Figure 1). No significant association was found between blood cystatin-C levels and current weight in either group.

Urine Na and NAG levels were significantly increased, and microalbumin levels were significantly decreased in the children-with-LBW group in comparison to the control group.

![Figure 1. Correlation between blood cystatin C and birth weight](image-url)
Urine NAG levels were significantly increased in children born preterm compared to the term group (Table 3, p=0.043). Urine Na and NAG levels were similar between the children born SGA and AGA (Table 3).

A mean of three manual blood pressure measurements was normal in all children. According to the ABPM results, a small number of children in the study group (3.4% of them had daytime systolic blood pressure, 12.9% had nocturnal systolic and 6.5% had nocturnal diastolic blood pressure) had high blood pressure. However, the two groups (LBW and control) did not differ in terms of systolic and diastolic blood pressures and blood pressure loads (Table 4). The ratio of non-dipping was found to be 77.4% and 63% in the LBW children and the control groups respectively, but there was no significant difference between the groups. Additionally, mean BP levels and BP loads were similar in children born SGA and AGA.
The low-birth-weight group had smaller kidney size (width x length x depth) in comparison to the control group. However, no significant difference was found between the groups (Table 5). Left kidney volumes were smaller in the LBW group compared to controls, despite the fact that all kidneys were anatomically normal (p=0.04). Kidney volumes were positively associated with the current weight of the children, but there was no significant correlation between kidney volumes and birth weight. Renal sizes were not statistically significantly different between the groups compared with age-adjusted normal values.

**DISCUSSION**

In 2017, the Low Birth Weight and Nephron Number Working Group issued a consensus document emphasizing the relationship between preterm birth, low birth weight, IUGR, and reduced nephron number. LBW could be due to prematurity (AGA) or secondary to intrauterine growth restriction (IUGR-SGA). This study investigated the effects of LBW, preterm birth, and SGA on renal function and blood pressure. We found that LBW and preterm birth affected some glomerular and tubular functions in childhood.

In the fetus, GFR parallels the gestational age and body weight. GFR increases after birth and come to adult levels in humans by the age of two years. Vanpee et al. assessed kidney function in VLBW infants and the GFR remained lower at nine months of age compared to term infants. At eight years of age, the GFR was not different from that of healthy children. Another study showed that the mean GFR was the same in both the SGA and AGA groups. Our results were also similar to these findings. The GFR values were normal in all groups, and we found no significant difference between children-with-LBW and control groups. The mean GFR was similar in both the SGA and AGA groups.

Serum creatinine level is often used to evaluate renal function. However, serum creatinine level is not only detected by its renal excretion but also by its production in muscular tissue, which is dependent on gender, weight, age, and protein intake. Two studies showed similar serum creatinine values in both the SGA and AGA groups, and there were no signs of tubular or glomerular damage in the SGA children. On the contrary, Keijzer-Veen et al. showed that subjects born SGA had lower GFR and higher serum creatinine concentration at the age of 19. In our study, we found increased levels of serum urea and decreased levels of serum creatinine in LBW children. Both serum urea and serum creatinine levels were in the normal range in all groups. These conflicting results suggest that serum urea and creatinine levels cannot be used as early markers of kidney damage in these children. Although there was no overall association between birth weight and serum creatinine levels, a significant positive correlation was found between current body weight and serum creatinine levels. The major reason for this variability is thought to be the fact that creatinine is a protein produced in muscle tissue.

Serum cystatin C level is another marker of GFR. In children, the cystatin C levels stabilize from the second year of life, and the reference range is similar to that of adults. Moreover, cystatin C production is not influenced by age, gender, muscle

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<th>Table 5. Renal size in the LBW and the control group</th>
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*Significant difference (P<0.05) compared to controls.

LBW: Low birth weight
mass, or protein intake. Studies comparing serum cystatin C levels in LBW children and normal birth weight children are increasing. Kwinta et al. showed that serum cystatin C levels were significantly increased in the ELBW group. Our study revealed that serum cystatin C levels were significantly higher in LBW children compared to the control group, and a negative relation was found between birth weight and serum cystatin C levels. While serum cystatin C levels were significantly higher in children born preterm compared to those born term, they were similar in children born SGA and AGA. High plasma levels of cystatin C, despite normal creatinine levels and normal GFR values, are thought that plasma levels of cystatin C may be used as a better marker of kidney damage in these children.

Microalbuminuria projects an increase in glomerular vascular permeability. Many studies have shown the prevalence of microalbuminuria to be 2.7%-12.5% in children born with LBW. Some studies identified that there is an increased microalbuminuria in young adults born with LBW. In accordance with this finding, two other studies reported that urinary protein excretion was similar in children born SGA and AGA at term. In our study, urinary microalbumin excretion was found to be reduced in children with LBW compared to the control group. Urinary protein excretion was similar in the children-with-LBW and the control group. Urinary microalbumin and protein excretion were similar in children born SGA and AGA. The lack of association between birth weight and urinary microalbumin excretion suggests that renal impairment, which can be detected by urinary microalbumin excretion, had not begun in this age group yet.

Urinary NAG excretion is used as a predictor of tubular cell dysfunction and damage. Monge et al. detected higher NAG excretion in children born with LBW. Other studies showed that there was no evidence of glomerular and tubular injury in children with LBW. Our study revealed that urinary NAG excretion was increased in children with LBW and born preterm in comparison to the control group. Urinary NAG excretion was similar in children born SGA and AGA. We found that urinary microalbumin excretion was decreased in children with LBW compared to the control group, although all values were within normal ranges in both groups. The increase in NAG excretion, although a normal microalbumin excretion, confirmed that the level of NAG excretion might be an early and more accurate test to evaluate an initial malfunction or injury of the proximal tubular epithelial cells in the early phase of renal disease. Significantly elevated urinary NAG excretion in the study group also indicated proximal tubular damage in the children with LBW and born preterm.

It has been shown that the activation of the urinary renin-angiotensin system decreases the urinary excretion of sodium in LBW children and is associated with hypertension. In our study, contrary to expectations, urinary sodium excretion rates were higher in the children-with-LBW group in comparison to the control group. An increase in urinary Na excretion may be the result of tubular damage.

Many studies have shown that LBW is related to hypertension in childhood and adult life. On the contrary, Bilge et al. suggested that no difference was observed between SGA and AGA children based on clinic and ambulatory blood pressure measurements. Rakow et al. showed that blood pressure did not differ between SGA and AGA children. In our study, the mean blood pressure level was similar in children with LBW, born preterm, SGA and the control group. Our findings did not show the effect of low birth weight, prematurity, and IUGR on blood pressure in early childhood.

Many studies have demonstrated that LBW is associated with decreased kidney size in infants, children, and adults. On the other hand, some studies found no differences in mean percentiles for renal length and volume compared to healthy control children and infants born with LBW. In our study, the LBW group had an insignificantly smaller kidney size compared to the control group. Kidney volumes in these children were also strongly correlated with their current body weights.

CONCLUSION

As a result, in our study, we observed that some glomerular and tubular functions were affected in children with low birth weight and in children born preterm. These effects were not observed in children with mature SGA. Considering that nephron formation is completed at the 37th week, gestational age (prematurity) was thought to be more effective in completing maturation rather than intrauterine growth retardation. We suggest that low birth weight children should be followed for renal functions in childhood. More extensive studies of renal activity in children with low birth weight are needed in the future.

Limitations

The weaknesses of the study are the small sample size, the improper distribution of the population size, and all the data about the neonatal period was obtained by a questionnaire with the parents.
Ethical approval

The study protocol was approved by the Institutional Review Board of Adnan Menderes University Medical Faculty (Reference Number: 2010/031) and it was conducted in accordance with the World Medical Association’s Declaration of Helsinki. Informed consent was obtained from both parents for each child.

Author contribution

Concept: FS; Design: FS; Data Collection or Processing: NK, AÜ, ÇY; Analysis or Interpretation: MO; Literature Search: NK, IG; Writing: NK, IG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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