Salt Sensitivity of Children With Low Birth Weight

Giacomo D. Simonetti, Luigi Raio, Daniel Surbek, Mathias Nelle, Felix J. Frey, Markus G. Mohaupt

Abstract—Compromised intrauterine fetal growth leading to low birth weight (<2500 g) is associated with adulthood renal and cardiovascular disease. The aim of this study was to assess the effect of salt intake on blood pressure (salt sensitivity) in children with low birth weight. White children (n = 50; mean age: 11.3 ± 2.1 years) born with low (n = 35) or normal (n = 15) birth weight and being either small or appropriate for gestational age (n = 25 in each group) were investigated. The glomerular filtration rate was calculated using the Schwartz formula, and renal size was measured by ultrasound. Salt sensitivity was assigned if mean 24-hour blood pressure increased by ≥3 mm Hg on a high-salt diet as compared with a controlled-salt diet. Baseline office blood pressure was higher and glomerular filtration rate lower in children born with low birth weight as compared with children born at term with appropriate weight (P < 0.05). Salt sensitivity was present in 37% and 47% of all of the low birth weight and small for gestational age children, respectively, higher even than healthy young adults from the same region. Kidney length and volume (both P < 0.0001) were reduced in low birth weight children. Salt sensitivity inversely correlated with kidney length (r² = 0.31; P = 0.005) but not with glomerular filtration rate. We conclude that a reduced renal mass in growth-restricted children poses a risk for a lower renal function and for increased salt sensitivity. Whether the changes in renal growth are causative or are the consequence of the same abnormal “fetal programming” awaits clarification. (Hypertension. 2008;52:625-630.)

Key Words: arterial hypertension ■ Barker’s hypothesis ■ Brenner’s hypothesis ■ low birth weight ■ salt sensitivity ■ small for gestational age

In the last decades, elevated blood pressure (BP) has become increasingly recognized as a major health threat in the adult population and among adolescents. In parallel, survival of premature or small for gestational age (SGA) newborns because of intrauterine growth restriction has improved, resulting in an expanding group of infants with low birth weight (LBW; ie, <2500 g). Evidence is growing of the consequences of prenatal (intrauterine) programming on organ function. Therefore, it is reasonable to speculate that an undisturbed full-length intrauterine period is a prerequisite for normal organ function in humans. LBW is frequently associated with a disproportionately high incidence of cardiovascular diseases, hypertension, diabetes mellitus, and kidney diseases in adulthood. Several epidemiological studies have identified an inverse association between LBW or SGA and an increased BP in infancy and childhood or even overt hypertension in adulthood. Various animal models have confirmed an association of LBW with subsequent arterial hypertension. Among other mechanisms, a congenital nephron deficit postulated by Brenner et al supporting salt and water retention might contribute to this relationship, an assumption further supported by observations of an association between LBW and a reduced kidney volume, as measured by ultrasound-based morphometry.

Salt sensitivity is defined as an augmentation of mean arterial pressure on 24-hour ambulatory BP monitoring (ABPM) during increased salt intake. Several mechanisms promoting salt sensitivity have been considered in adults, including a nephron deficit (reduced renal mass). In a rat model, Woods et al demonstrated that severe maternal dietary protein restriction during pregnancy reduced the number of glomeruli and programmed salt-sensitive hypertension in both female and male offspring in adult life. Of interest, an inverse relationship between birth weight and salt sensitivity has been documented recently in adult individuals.

Here, we hypothesize that an inverse relationship between salt sensitivity and renal mass is detectable early in life, whereby a reduced renal mass is associated with an increase in BP in response to an augmented salt intake. Thus, we aimed to investigate prepubertal or adolescent children exposed to a risk for a reduction in renal mass by LBW and to measure their BP response to changes in dietary salt intake.

Methods

Subjects

The protocol was approved by both the local ethical review board and the pediatric ethics committee and fulfilled the criteria of the...
Declaration of Helsinki. All of the participating children and their parents gave informed consent. Healthy children born term or preterm with LBW (ie, <2500 g) or with normal birth weight between October 1991 and January 1998 at the University of Bern Women’s Hospital, currently aged 7 to 15 years and living within the Berne area, were eligible to enter the study. Children with LBW because of congenital infections, such as cytomegalovirus, dysmorphism, twins, severe cerebral palsy, congenital heart disease, or with a history of urinary tract infections, urologic problems, or renal problems were excluded.

Fetal and maternal data were carefully recovered from the hospital records using standard criteria to identify pregnancy-induced hypertension, preeclampsia, and birth weight as related to the gestational age. Gestational age was determined by a recollection of the last menstrual period and confirmed or corrected by an ultrasonographic examination before the 20th week of gestation using the crown-rump length. Correction of the gestational age using the measured length was made when a difference of ≥5 days from the menstrual age was recognized. Birth weight was defined as SGA when more than 2 standard deviation scores (SDS) below the mean for the local population and as appropriate for gestational age (AGA) prematurely or at term with a birth weight greater than the 10th percentile.

Clinical Measurements
All of the participants attended the University Children’s Hospital, Inselspital, during afternoon hours. Height and weight were measured, and body mass index was calculated; percentiles were computed according to the Swiss national growth charts,20 and obesity was diagnosed in accordance with the definition by Cole et al.21 A physical examination was performed, including assessment of puberty stage (Tanner stages), and office BP and heart rate were measured supine on the right arm with an oscillometric automated device (Dinamap) using an appropriate cuff size after 10 minutes of rest in a quiet room. The mean of 3 independent measurements was calculated, as proposed by current guidelines.4

Assessment of Salt Sensitivity
During the first week (7 days), each subject maintained a regular diet, omitting food enriched with sodium (controlled-salt diet, standardized dietary counseling to avoid peak salt intakes with food containing high levels of salt). At the end of this week (day 6 to day 7), a 24-hour ABPM (model Profilomat, Disetronic) and a 24-hour urine collection were obtained. During the second week (7 days), each subject continued the regular diet now enriched with sodium (high-salt diet; salt given as tablets, 0.12 g/kg of body weight per day). At the end of this week (day 6 to day 7), a second 24-hour ABPM and a 24-hour urine collection were performed. Comparable salt sensitivity testing protocols have already been applied to children by other groups.22,23 “Salt sensitivity” was defined as a change in the mean arterial pressure of ≥3 mm Hg on 24-hour ABPM in response to an increased salt intake, as reported elsewhere.16 Sodium excretion in the 24-hour urine collection was used to estimate salt intake and to reassure compliance with the intake of the sodium tablets. All of the measurements were performed on corresponding days of the 2 study weeks with the same ABPM device and the same appropriate cuff. Arterial hypertension during the ABPM recordings was defined according to Wuhl et al.24 Subjects were not allowed to take any medication, including oral contraceptives.

Assessment of Kidney Length and Volume by Ultrasound
All of the examinations were performed by the same experienced ultrasonographer. The maximal longitudinal extension of the kidney was determined at the level of the renal hilum. The maximal width and depth (thickness) were measured in orthogonal planes at the level of the renal hilum using a transverse plane perpendicular to the longitudinal axis of the kidney. These standardized planes in renal biometry are similar to those published previously.23,26 Measurements were made on freeze-frame images during real-time examination by manually positioning electronic calipers in the image.

Mean length, width, and depth were calculated as the average of 3 independent measurements. Imaging was performed with a Siemens Sonoline G60S and curved array 6.0-MHz transducer (Siemens). Data for right and left kidneys were analyzed separately. Kidney volume was calculated in cubic centimeters using the equation of an ellipsoid: volume = mean length × mean width × mean depth × 0.523.23,26 Kidney length was corrected for healthy white children of the same height and kidney volume for healthy children of the same weight.25

Biochemical Measurements
Serum creatinine, sodium, and potassium were measured. A urinary dipstick was performed in spot urine. Glomerular filtration rate (GFR) was estimated with a modified Schwartz formula27: [enzymatic method, 54 × height (cm)/[serum creatinine (μmol/L) + 25]] and in reliable children with the 24-hour creatinine clearance.

Statistics
Subject characteristics and results are presented as means ± SEMs. Relations between variables were assessed by using a best-fit linear regression analysis. Mann-Whitney test or Fisher’s exact test were used to analyze the subgroups, as appropriate. Wilcoxon matched-pairs tests were used to compare the same subjects with a controlled-salt diet versus a high-salt diet.

Using the prevalence of salt-sensitive individuals indicated by Lovati et al,28 we expected to differentiate salt-sensitive from salt-resistant individuals by their mean BP response as related to salt intake with ≥11 individuals in each group, with α = 0.05 providing a power of 80%. Because we did not reduce salt intake to a severe low-salt diet, we might have missed borderline salt-sensitive children but expected to retain very sensitive individuals.

All of the statistical analyses were performed using SYSTAT version 10 for Windows (SYSTAT Software Inc). Significance was assigned at P < 0.05.

Results
Clinical Characteristics
We recruited 50 white children. Of those, 25 in each group were either born SGA or AGA preterm or term, respectively, during the period May 2006 to April 2007. Of these, 17 were born with LBW at term SGA (term SGA), 8 with LBW preterm and SGA (preterm SGA), 10 with LBW preterm and AGA (preterm AGA), and 15 children born at term with AGA (term AGA), respectively.

The mean birth weight of the 35 children born with LBW was 1852 g (range: 690 to 2499 g) at a mean gestational age of 35 weeks (range: 25.7 to 40.9 weeks). Fourteen of these children (40%) were treated with betamethasone to enhance lung maturation. The mean age of the mother at delivery was 31 years (range: 19.9 to 40.4). Maternal pregnancy-induced hypertension was present in 6 (17%) pregnancies, preeclampsia in 5 (14%), and chronic maternal arterial hypertension in 2 (6%). Nicotine abuse during pregnancy was documented in 9 (26%) of the pregnancies.

The children born term with AGA (term AGA; weight range: 2730 to 4890 g; gestational age range: 38.0 to 41.4 weeks) had uneventful maternal and fetal pregnancies with no betamethasone treatment. Chronic or pregnancy-induced maternal arterial hypertension, preeclampsia, or maternal perigestational nicotine abuse was absent.

The main characteristics of the children at the time of recruitment are given in Table 1 dichotomized for those with LBW and with normal birth weight. Puberty stage was comparable in all of the groups of children. Dipstick urine analysis was normal in all of the children.

626 Hypertension October 2008
In this cohort of children we noted no significant gender differences for the studied parameters of birth weight, systolic and diastolic BP, and renal mass. Also, no gender disparity was encountered comparing preterm versus term individuals. Consequently, the parameters were analyzed without differentiation with respect to gender. In the groups with LBW, 7 children with LBW who complied with the study protocol. The mean 24-hour urinary sodium excretion was 15.7±6.5 mmol of Na/mmol of creatinine during the high-salt diet (P<0.0001). A significant increase in body weight was observed during the high-salt diet compared with the controlled-salt diet (mean increase: 0.4±0.11 kg; P=0.004).

Nine (37%) of 24 children born with LBW were salt sensitive. Eight (89%) of these 9 children were born SGA (5 children at term SGA and 3 preterm SGA), and the other was born prematurely AGA. In contrast, of the 15 salt-resistant children, only 9 (60%) were born SGA (6 children at term SGA and 3 preterm SGA) with the remaining 6 (40%) being born preterm AGA. If we only consider the 17 children who were born SGA (11 children at term SGA and 6 as preterm SGA), 8 (47%) were salt sensitive.

Salt-sensitive and salt-resistant subgroups of children were comparable with respect to age, weight, height, body mass index, pubertal stage, heart rate, and BP (Table 2), as well as to the mean body weight increase after the high-salt diet. If compared with salt-resistant children, salt-sensitive children had both a lower GFR estimate (98.7±2.6 ml/min per 1.73 m²; P=0.037), as provided by the Schwartz formula, and a reduced measured creatinine clearance (80±7 versus 96±3 ml/min per 1.73 m²; P<0.05; Table 2). The changes in mean 24-hour mean arterial pressure in response to salt differed, with +8.1±1.2 mm Hg in salt-sensitive children compared with −2.9±1.0 mm Hg in salt-resistant children. Heart rate was not affected by dietary control. Salt sensitivity was not correlated with intrauterine risk factors, lung maturation with betamethasone, or with birth weight, expressed in SDS adapted for gestational age.

### Kidney Length and Volume

To further assess the basis of the observed increased salt sensitivity, kidney length and volume were measured. Combined length and volume of both kidneys were of the expected size in children born at term AGA, with no size differences in accordance with observations made by other authors (left and right kidney volume of both kidneys, 96.0±3.0%, and length combined 97.0±1.5% of the expected size). In LBW children, the total kidney volume and length were reduced when compared with the expected published normal values (volume: 85.0±2.6%; length: 94.0±1.0%; P<0.0001). A comparison of children born SGA and AGA (born at term or preterm) revealed smaller and shorter (Figure 1) kidneys in children born SGA.
Table 2. Salt Responsiveness of Children Born With LBW

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Salt Sensitive</th>
<th>Salt Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>9 (37)</td>
<td>15 (63)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4 (44)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Age, y</td>
<td>10.5±0.6</td>
<td>11.8±0.6</td>
</tr>
<tr>
<td>Puberty stage &gt;2 (Tanner), n (%)</td>
<td>2 (22)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Δ24-h mean arterial pressure, mm Hg</td>
<td>+8.1±1.2*</td>
<td>-2.9±1.0*</td>
</tr>
<tr>
<td>ΔNa/crea urine, mmol/mmol</td>
<td>15.8±3.8</td>
<td>14.9±2.8</td>
</tr>
<tr>
<td>SGA, n (%)</td>
<td>8 (89)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>AGA-preterm, n (%)</td>
<td>1 (11)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1971±222</td>
<td>1763±128</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>36±1</td>
<td>35±1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>33.4±3.2</td>
<td>42.4±4.0</td>
</tr>
<tr>
<td>Age-adjusted SDS</td>
<td>-0.44±0.42</td>
<td>-0.1±0.31</td>
</tr>
<tr>
<td>Height, cm</td>
<td>138.4±3.3</td>
<td>147.6±3.7</td>
</tr>
<tr>
<td>Age-adjusted SDS</td>
<td>-0.45±0.27</td>
<td>-0.21±0.30</td>
</tr>
<tr>
<td>Short stature, n (%)</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>17.1±1.0</td>
<td>18.8±1.1</td>
</tr>
<tr>
<td>Age-adjusted SDS</td>
<td>-0.38±0.46</td>
<td>-0.03±0.31</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>1 (11.1)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Underweight, n (%)</td>
<td>1 (11.1)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Office systolic BP, mm Hg</td>
<td>103.8±2.8</td>
<td>111.5±3.8</td>
</tr>
<tr>
<td>Age- and height-adjusted z score</td>
<td>0.25±0.28</td>
<td>0.76±0.28</td>
</tr>
<tr>
<td>≥95th Percentile, n (%)</td>
<td>1 (11.1)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg</td>
<td>59.1±1.9</td>
<td>59.4±1.6</td>
</tr>
<tr>
<td>Age- and height-adjusted z score</td>
<td>-0.08±0.17</td>
<td>-0.05±0.15</td>
</tr>
<tr>
<td>≥95th Percentile, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72.0±2.6</td>
<td>75.9±3.5</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min per 1.73 m²</td>
<td>80.0±7.0*</td>
<td>96.0±3.0*</td>
</tr>
</tbody>
</table>

Values are means±SEMs unless otherwise stated. Mann-Whitney test or Fisher’s exact test was used to analyze the subgroups.

*p<0.05 between salt-sensitive and salt-resistant children.

81.0±3.0% versus 95.0±2.0%, P=0.0003; length: 92.0±1.3% versus 98.0±1%, P=0.003).

Kidney Morphology, Salt Sensitivity, and Renal Function

The group of salt-sensitive children displayed smaller kidneys than the group of salt-resistant children (P=0.02; Figure 2).

Moreover, a negative linear correlation was observed between the degree of salt sensitivity and the total kidney length (r²=0.307; P=0.005) or volume (r²=0.171; P=0.044) within the children who successfully completed the salt-sensitivity test. Of interest, salt-sensitive children displayed smaller left kidneys compared with right kidneys (P=0.02), a phenomenon not observed in salt-resistant children. In addition, a weak, but consistent, negative linear correlation was found between total kidney volume and calculated GFR (r²=0.11; P=0.02). However, a correlation between degree of salt sensitivity and GFR was absent.

Discussion

In this study that aims to explore the area of the fetal origins of adult diseases, we demonstrate a high prevalence of salt sensitivity in children with LBW affecting 37% of the children studied. This frequency of salt sensitivity exceeds the one observed in nonselected white adolescents (18%)29 and that of the nonhypertensive participants of the Dietary Approaches to Stop Hypertension (DASH)-Sodium Trial (20%),30 while not reaching statistical significance. This percentage is also higher than the 26% experienced in an ongoing study of young adults from the current study’s geographical region (n=41; 19 female; mean age: 25.9 years; age range: 20.5 to 34.4 years). We found the highest prevalence of salt sensitivity, affecting almost half of these patients (P=0.02 compared with data from the literature29), exactly in those children with the most severe growth retardation born SGA (below the second SD for birth weight). Of interest, salt sensitivity is not reflected in the baseline 24-hour ABPM, suggesting at least in part a functional response to salt at this age.

Given the limited ability and willingness of children to comply with the study requirements, we were still able to assess the group of children born with LBW who were highly motivated to participate in our study. In addition, the advantage in testing children is the reduced risk of confounding variables, such as adult lifestyle influences. This group of children was of comparable size with a very recently published cohort of adults, whose salt sensitivity had been related to their birth weight.19 Despite not performing a pure low-salt

Figure 1. Kidney length, expressed in percentage of the expected size in children born SGA (at term or preterm, n=25) and children born AGA (at term or preterm, n=25).

Figure 2. Correlation between salt sensitivity and kidney length, expressed in percentage of the expected values from the literature. Values are grouped in salt-sensitive and salt-resistant children. The difference between the 2 groups was statistically significant (P=0.02).
Perspectives

In conclusion, this study demonstrates that renal mass is reduced in children born with LBW and depends on the degree of growth retardation, which then determines lower GFR, increased salt sensitivity, and elevated BP. These findings are important because they, first, provide an initial step to better understanding of the mechanisms of later disease in children affected by an unfavorable intrauterine milieu; second, support continued surveillance of children born with LBW to early identify resulting diseases; and, third, offer an opportunity to direct prophylactic antihypertensive interventions, such, as salt restriction, by means as simple as an early onset of nutritional education for children and parental dietary counseling with respect to salt-controlled eating habits. A prospective follow-up of children born with LBW with respect to renal fate, arterial hypertension, and salt sensitivity is warranted in future studies.

Acknowledgments

We are extremely grateful to all of the families who took part in this study and to Muriel Huegli for excellent secretarial assistance.

Sources of Funding

G.D.S. was supported by the Fondazione Ettore e Valeria Rossi and the Swiss Renal Foundation and M.G.M. by the Swiss Renal Foundation and the Swiss National Foundation (3200B0-113902/1).

Disclosures

None.

References


Salt Sensitivity of Children With Low Birth Weight
Giacomo D. Simonetti, Luigi Raio, Daniel Surbek, Mathias Nelle, Felix J. Frey and Markus G. Mohaupt

Hypertension. 2008;52:625-630; originally published online August 11, 2008; doi: 10.1161/HYPERTENSIONAHA.108.114983

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/52/4/625

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/