Effects of Low Birth Weight in 8- to 13-Year-Old Children
Implications in Endothelial Function and Uric Acid Levels

Maria C.P. Franco, Dejaldo M.J. Christofalo, Ana Lydia Sawaya, Sérgio A. Ajzen, Ricardo Sesso

Abstract—Low birth weight has been associated with an increased incidence of adult cardiovascular disease. Endothelial dysfunction and high levels of serum uric acid are associated with hypertension. In this study, we have determined whether uric acid is related to blood pressure and vascular function in children with low birth weight. We evaluated vascular function using high-resolution ultrasound, blood pressure, and uric acid levels in 78 children (35 girls, 43 boys, aged 8 to 13 years). Increasing levels of uric acid and systolic blood pressure were observed in children with low birth weight. Birth weight was inversely associated with both systolic blood pressure and uric acid; on the other hand, uric acid levels were directly correlated with systolic blood pressure in children of the entire cohort. Low birth weight was associated with reduced flow-mediated dilation ($r=0.427$, $P<0.001$). Because the children with low birth weight had elevated uric acid as well as higher systolic blood pressure levels, we evaluated the correlation between these variables. In the low birth weight group, multiple regression analysis revealed that uric acid ($B=-2.886$; $SE=1.393$; $P=0.040$) had a graded inverse relationship with flow-mediated dilation, which was not affected in a model adjusting for race and gender. We conclude that children with a history of low birth weight show impaired endothelial function and increased blood pressure and uric acid levels. These findings may be early expressions of vascular compromise, contributing to susceptibility to disease in adult life. 

Key Words: uric acid ■ children ■ hypertension

Hypertension is one of the most important causes of premature death worldwide; it is present in nearly 25% of adults and increases in prevalence with age. On the other hand, undernutrition remains among the main devastating problems in the developing world. In these countries, 30 million newborns every year are affected by fetal malnutrition, which can be characterized clinically by low birth weight (LBW). In parallel with these observations, it has been reported that LBW is an important determinant in the development of the hypertension, ischemic heart disease, obesity, and type 2 diabetes, suggesting that there are significant associations between factors present in the prenatal environment that affect fetal development and programming of adult life diseases. In addition, vascular endothelial dysfunction is a key event in the development of diseases associated with LBW. In fact, positive association between LBW and endothelial dysfunction has been demonstrated in young adults and children. These observations support the concept that deleterious alterations in fetal environment have direct effect on the vascular wall, leading to the impairment of the vascular function.

The interaction between the effect of prenatal influences and independent risk factors on vascular function is still an unsolved issue. Several clinical and laboratory observations are consistent with the hypothesis that uric acid (UA) might be an important factor in the pathogenesis of both hypertension and vascular disease. In fact, Cannon et al have demonstrated that UA levels are elevated in hypertension and are present in 25% of untreated hypertensive subjects. It has been shown that UA is positively associated with an increase in systolic blood pressure (SBP) and may be a risk factor or marker for ultrasonographically determined carotid atherosclerosis. However, to date, there is little information about the relative impact of the prenatal environment on UA levels and development of the cardiovascular disease. The purpose of this study was to investigate if alterations in serum UA are present in young children with LBW and to determine whether there is a relationship between UA concentration, vascular function, and SBP levels.

Methods
One hundred and thirteen children aged 8 to 13 years were recruited and evaluated between November 2004 and July 2005. Participants were randomly selected from the database of the Nutritional Rehabilitation Center of the Federal University of São Paulo. Personal and family medical histories (including information about the birth weight (BW)) and chronic and familial diseases) were obtained by a questionnaire interview with parents or guardians on the same day as the screening evaluation. Exclusion criteria were the presence of renal disease, chronic illness, positive family history, or clinical
signs of cardiovascular disease or endocrinopathy. Twenty-four of the 113 selected children were excluded because they had BW within the range of 2501 g to 2999 g. In addition to these, seven children were excluded because of family history of hypertension, three had laboratory tests indicative of diabetes mellitus, and one child had renal disease. Seventy-eight children remained eligible for this study. The validity of the BW data was crosschecked with hospital records. Agreement between BW (kg) data from recall and birth record sources was good (n=52; mean difference [birth record-recall]=0.067 kg; SD=0.17 kg; r=0.78; P<0.0001). Children were divided into 2 groups based on BW: the normal birth weight (NBW) group had 36 children who had been born at term with appropriate BW (BW≥3.0 kg) and the LBW group had 42 children born at term with small BW for gestational age (BW≤2.5 kg). The Ethics Committee of the Federal University of São Paulo granted approval for the study, and written informed consent was obtained from one of the parents of children enrolled in the study. The investigation conforms to the principles outlined in the Declaration of Helsinki.

Measurements of Anthropometric and Biochemical Variables

Body weight and height measurements were made in light clothing without shoes during home visit. Weight was measured using an electronic scale (SD-150, Country Technologies) with 10-g precision. Height was determined using a portable stadiometer accurate to the nearest 0.1 cm. The anthropometric indicators used to assess child nutritional status were height-for-age, weight-for-age, and body mass index (BMI). The values were compared with the standards of the National Center for Health Statistics and expressed as Z score.17 These scores were obtained through the Epi Info Software Program (CDC–2000 Reference; Version 3.3.2, Center for Disease Control and Prevention). All children provided a blood sample, which was collected in the morning after an overnight fast. Glucose, cholesterol, high-density-lipoprotein (HDL) cholesterol, triglycerides (TG), UA, creatinine, and insulin were measured by routine methods at the Clinical Laboratory of the São Paulo Hospital. Low-density-lipoprotein (LDL) cholesterol concentration was determined with the Friedewald equation, insulin resistance was calculated by the homeostasis model assessment (HOMA) method, and estimated glomerular filtration rate (GFR) was calculated by the Schwartz formula.20 Urinalysis (microscopic examination of the urine sediment, pH, glucose, protein, ketones, bilirubin, and urobilinogen) was conducted for all participants and did not reveal any significant finding.

Diagnosis of Hypertension

Hypertension was defined in accordance with the Fourth National Task Force on High Blood Pressure in Children and Adolescents as systolic or diastolic blood pressure ≥95th percentile for age, height, and gender.21 Blood pressure was measured twice in the right arm with the child in supine position at the beginning of the ultrasound measurements by use of a Dinamap automated blood pressure recorder with an appropriate cuff size. The blood pressure value used in the analysis was the average of 2 measurements made at 2-minute intervals. All measurements were made by the same nurse and none of the children had their blood pressure previously measured.

Ultrasound Study Measurements

A noninvasive ultrasound technique was used to assess the ability of the brachial artery to dilate in response to increased blood flow (induced by forearm cuff occlusion and release), an endothelium-dependent response as previously described.22 After 30 minutes of supine rest, the left brachial artery was assessed in basal conditions and during reactive hyperemia, a procedure that promotes flow-mediated dilation (FMD) of the vessel. The FMD was expressed as the percentage change in diameter compared with basal measurements (%FMD). The equipment used for ultrasound was a digital, 2-dimensional HDI-3000 model, equipped with a 7- to 9-MHz linear transducer and manufactured by ATL Ultrasound, Inc. Examinations were performed in an air-conditioned room at an ambient temperature of ~22°C. To avoid circadian variations, all examinations took place during the morning between 8:00 and 9:30 AM. In addition, the same ultrasonographer, blinded to clinical data, examined and evaluated all the children in this survey. To assess intraobserver variation, 19 studies of brachial artery reactivity were randomly selected for a second analysis, and the measurements of FMD were highly correlated (r=0.820; P<0.001).

Statistical Analysis

Categorical variables were compared using the χ² test. Student t test was used to compare mean values of continuous variables between the 2 groups. Correlations were assessed by Pearson’s correlation coefficient. Multivariate analysis in the LBW and NBW groups was performed to evaluate the association between potential risk factors with %FMD (dependent variable). Additionally, multiple linear regression analysis of the overall cohort was used to investigate the association between SBP or %FMD (dependent variables) and the following variables: birth weight, age, gender, race, BMI (Z score), cholesterol, HDL, LDL, TG, HOMA, and UA. No violations in the assumptions in multiple linear regression analysis were detected in normal plot of residuals of regression models. Values of continuous variables are expressed as mean±SEM. Statistical tests were 2-tailed, and the significance level was set at P<0.05.

Results

Baseline Characteristics—Uric Acid Levels

Clinical, anthropometric, and metabolic characteristics of the children are shown in Table 1. The distributions of gestational

| TABLE 1. Clinical, Anthropometric, and Metabolic Characteristics |
|---------------------------------|-------|-------|-------|
| Characteristics               | NBW   | LBW   | P Value |
| Gender                         |       |       |        |
| % Male                         | 64     | 48    | 0.089  |
| % Female                       | 36     | 52    |        |
| Race                           | 42     | 33    | 0.448  |
| % White                        | 58     | 67    |        |
| % Black                        |        |       |        |
| BW (kg)                        | 3.21±0.04 | 2.38±0.03 | <0.001 |
| Gestational age (wk)           | 39.4±0.2 | 39.1±0.2 | 0.422  |
| Age (years)                    | 9.47±0.3 | 9.79±0.3 | 0.476  |
| Weight (kg)                    | 38.7±1.3 | 29.6±1.4 | 0.661  |
| Height (cm)                    | 133.7±2.0 | 134.9±1.9 | 0.672  |
| WAZ                            | −0.97±0.16 | −0.95±0.15 | 0.926  |
| HAZ                            | −0.72±0.15 | −0.76±0.14 | 0.862  |
| BMI (kg/m²)                    | 22.9±0.7 | 23.6±0.7 | 0.690  |
| Glucose (mg/dL)                | 84.0±1.3 | 83.2±1.3 | 0.636  |
| Insulin fasting (µU/mL)        | 4.8±0.5  | 5.9±0.5  | 0.125  |
| HOMA                           | 2.9±0.3  | 3.0±0.3  | 0.838  |
| Uric acid (mg/dL)              | 3.2±0.1  | 4.2±0.1  | <0.001 |
| Serum creatinine (mg/dL)       | 0.7±0.01 | 0.7±0.02 | 0.749  |
| GFR (ml/min per 1.73 m²)       | 102.6±1.6 | 103.4±1.9 | 0.769  |

Values expressed as means±SEM or percentage. WAZ indicates weight-for-age Z score; HAZ, height-for-age Z score; BMIZ, body mass index Z score; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
age, gender, race, and age were similar in both groups. In addition, no difference was observed in the anthropometric evaluation, and the groups did not differ significantly with respect to the laboratory parameters, except for the serum level of UA. The mean UA value was significantly greater in LBW compared with NBW children (Table 1), and no ethnic \( (P=0.091) \) or gender \( (P=0.759) \) differences for the UA levels were observed for the entire cohort. Renal insufficiency can lead to hyperuricemia, due to increased urate reabsorption and a subsequent elevation in serum UA, however, decreased renal function did not account for the differences between children with NBW and LBW in this study. The mean GFR was the same for both groups (Table 1), and no correlation existed between GFR and serum LBW.

\[ \text{UA} \text{value was significantly greater in LBW compared with NBW children (Table 1), and no differences in race (} P=0.814) \text{ or gender (} P=0.340 \text{) were observed for the entire cohort. In our sample of LBW children, 38.1\% (} n=16 \text{) had hypertension, and 9.5\% had prehypertension, whereas only 1 child (2.8\%) in the NBW group had hypertension. High BP classification was driven more by systolic than diastolic BP. In addition, there were no significant ethnic (} P=0.330 \text{) or gender (} P=0.104 \text{) differences in the mean SBP levels on the whole study group.}

\begin{table}[h!]
\centering
\caption{Blood Pressure and Ultrasound Assessment of the Endothelial Function}
\begin{tabular}{lccc}
\hline
Variables & NBW & LBW & \( P \) Value \\
\hline
Mean systolic BP (mm Hg) & 98.3\pm2.0 & 107.9\pm1.9 & 0.001 \\
Mean diastolic BP (mm Hg) & 63.5\pm2.0 & 67.7\pm1.8 & 0.122 \\
Baseline vascular diameter (mm) & 2.0\pm0.8 & 2.2\pm0.7 & 0.573 \\
Flow-mediated dilation (FMD\%) & 29.1\pm1.9 & 16.8\pm1.1 & <0.001 \\
Baseline blood flow (mL/min) & 12.5\pm1.6 & 15.8\pm2.0 & 0.182 \\
Blood flow (%) & 728.2\pm109.3 & 695.5\pm88.1 & 0.817 \\
\hline
\end{tabular}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{For the entire cohort, children with normal (open symbols) and low (solid symbols) birth weight groups. (A) Correlation between BW and UA \( (r=-0.498, P<0.001) \); (B) SBP \( (r=-0.320, P=0.004) \); and (C) FMD \( (r=0.427, P<0.001) \).}
\end{figure}

\textbf{Prevalence of Hypertension}
Mean SBP was higher in the LBW group compared with the NBW children (Table 2), and the mean diastolic BP levels were similar in both groups (Table 2). In our sample of LBW children, 38.1\% \( (n=16) \) had hypertension, and 9.5\% had prehypertension, whereas only 1 child (2.8\%) in the NBW group had hypertension. High BP classification was driven more by systolic than diastolic BP. In addition, there were no significant ethnic \( (P=0.330) \) or gender \( (P=0.104) \) differences in the mean SBP levels on the whole study group.

\textbf{Relationship Between SBP, BW, and UA}
For the entire cohort, BW was inversely correlated with SBP \( (r=-0.320, P=0.004) \) (Figure B), whereas the adjustment for age, gender, race, and BMI did not modify the strength of this association \( (r=-0.363; P=0.001) \). In addition, the correlation between SBP and BMI was not statistically significant \( (r=-0.118, P=0.302) \).

Because the children with LBW had no identifiable etiology for their elevated BP and they tended to have greater serum UA levels, consistent with the hypothesis of an independent link, we evaluated the correlation between SBP and serum UA concentration. In univariate analysis of the entire cohort, UA was significantly associated with SBP \( (r=0.229; P=0.040) \). This correlation of serum UA with SBP is continuous and linear, with a change in UA of 1.0 mg/dL corresponding to an increase of 3 mm Hg in SBP. However, when age, gender, race, birth weight, BMI, cholesterol, HDL, LDL, TG, HOMA, and UA were included as covariates in a multiple regression analysis of factors related to SBP, only birth weight \( (\beta=-1.069; SE=0.004; P=0.012) \) and age \( (\beta=1.750; SE=0.828; P=0.039) \) remained significantly associated with SBP in the overall study population.

\textbf{Association Between Endothelium Function, BW, and UA}
FMD in response to hyperemia was 58\% lower in LBW children (Table 2), and no differences in race \( (P=0.814) \) or gender \( (P=0.340) \) were observed for the entire cohort. The correlation of %FMD was statistically significant with both BW \( (r=0.427, P<0.001) \) (Figure C) and UA \( (r=-0.351; P=0.002) \) on the entire study population. Because the children with LBW had elevated UA as well as higher SBP...
levels, we evaluated the correlation between these variables. Multiple regression analysis in the LBW group showed that only UA ($\beta=-2.886; \text{SE}=1.393; P=0.040$) had a graded inverse relationship with $\%\text{FMD}$, which was not affected in a model adjusting for race and gender. In NBW children, these correlations did not reach statistical significance. On the other hand, further multiple regression analysis with the entire cohort showed that only BW emerged as a significantly important factor associated with $\%\text{FMD}$ ($\beta=0.772; \text{SE}=0.400; P=0.040$), adjusting for all other demographic and laboratory variables.

**Discussion**

This study demonstrated that BW was related to endothelial function of the brachial arteries of children in their first decade of life. Traditional cardiovascular risk factors showed little relationship with this measure, and adjustment for them had no effect on the correlation between BW and endothelial function, which was solid and graded. In addition, the main new findings of the present study were that children with LBW had high UA levels, which significantly correlated with BW, endothelial function, and SBP.

In several studies intrauterine growth retardation has been linked to a higher risk of developing hypertension.\(^{23,24}\) The present data support this hypothesis. In our study we observed an increased mean SBP in LBW children and an inverse association between BW and SBP, which was not affected by BMI, gender, or ethnicity. Additionally, SBP was not related to BMI, suggesting that the current nutritional status was not a determinant factor for high blood pressure in our cohort. These findings are consistent with other studies. Law et al\(^{25}\) demonstrated that raised blood pressure in children was related to proportionate small size at birth, independently of current body size. In addition, the authors also found this same correlation among children in China, Guatemala, and Chile.\(^{26}\) Although the fetal programming theory that BW influences blood pressure later in life has been recognized, some studies do not support this theory and suggest that childhood factors have a greater effect on adolescent blood pressure than intrauterine factors.\(^{27-29}\)

The present data disclosed that children with LBW also presented increase of serum UA concentration. This was accompanied by an inverse correlation between UA and BW, suggesting that LBW may predict increased UA levels in infancy. Additionally, differences in GFR have not been found when we compared the NBW and LBW groups, indicating that the association between BW and UA cannot be explained by decreased renal function. Our findings relating BW and high UA levels at infancy confirm previous reports. Feig et al\(^{30}\) demonstrated a significant correlation between elevated UA levels and BW. Pulzer et al\(^{31}\) showed an elevated UA concentration in children with LBW; however, this correlation was only observed in children with glucose intolerance. It has also been reported that the UA level in the fetal cord blood of preeclamptic infants is inversely correlated with BW.\(^{32}\) In addition, children of preeclamptic mothers have an increased risk of presenting LBW and later development of hypertension.\(^{30}\) Our observations, combined with the literature data, provide further evidence of the link between LBW and UA and may have implications in the development of adult diseases.

Another important aspect to be considered was the impact of UA on blood pressure levels in our cohort. Epidemiological studies have shown a link between UA and hypertension.\(^{33,34}\) In fact, Verdecchia et al\(^{33}\) reported a strong independent association between UA and cardiovascular risk in adult subjects with essential hypertension. Franse et al\(^{34}\) also showed that UA was an independent risk factor in patients with isolated systolic hypertension. In our study, UA was correlated with SBP levels in the entire cohort. To maximize the relevance of this finding, we evaluated the relation between these variables in the presence of other risk factors. Using multivariate analysis and adjusting for age, gender, race, BW, BMI, cholesterol, HDL, LDL, TG, and HOMA, the association of UA with SBP became statistically nonsignificant, suggesting that the preceding value of this variable does not persist after considering these important confounders. In fact, some studies have demonstrated that the significance of UA can change after multivariable adjustment, and the associations may become much weaker or not significant.\(^{16,35}\) which is consistent with our results. On the other hand, we observed that BW remained significant despite these adjustments, thus emphasizing the hypothesis that blood pressure could be programmed in early life and, thereby, influences the long-term risk of cardiovascular disease.

Several studies have demonstrated that disturbance in the intrauterine growth (because of malnutrition or other factors) has a negative influence on the endothelial function. However, only a few reports investigated this relationship in cohorts of adults; moreover, the data interpretation is complicated by potential confounding factors such as smoking, diet, and lifestyle.\(^{8,9}\) On the other hand, a pioneering study carried out by Leeson et al\(^{7}\) demonstrated a positive association between LBW and endothelial dysfunction in children, thus minimizing the potential influence of the adulthood risk factors. After that, other studies also demonstrated this same correlation in children\(^{10}\) and infants.\(^{36}\) Despite the fact that reduced endothelium-dependent vasodilation has been previously observed in LBW children, as far as we know, this is the first report that focuses specifically on the relationship between UA concentration and endothelial function in children who were small at birth.

We found that LBW correlated with the lowest endothelium-dependent responses in healthy children. This association was positive and independent of gender and ethnic group, suggesting a causal relationship. Other cardiovascular risk factors, including age, systolic and diastolic BP, blood lipids, HOMA, and UA, did not appear to be responsible for the observed association between BW and $\%\text{FMD}$ in the present cohort, because incorporation of these risk factors in the multivariate model did not alter the strength of this association. Our findings are in agreement with other studies in which these risk factors showed little if any relationship with endothelium-dependent vasodilation in 9- to 11-year-old children\(^{10}\) and fit young adults.\(^{7}\)

Consistent with the hypothesis presented, the concentration of UA correlated inversely with $\%\text{FMD}$ in the entire cohort, demonstrating that increased UA, even in physiological
range, was closely linked with impaired endothelial function. Another important observation was that, in multivariate analysis, serum UA correlated significantly with %FMD only in children from the LBW group, suggesting that disproportionate intrauterine growth may have large and permanent effects on vascular function, and this is implicated in the increase of UA concentration. Not surprisingly, after adjustment for several key confounders in the entire cohort, only BW emerged as a significant factor associated with endothelial function, reinforcing the importance of an increased relationship between LBW and vascular dysfunction. However, the association of UA and %FMD in the overall group became negligible when known vascular risk factors were simultaneously considered in a multivariate analysis adjusting for gender, race, and age. In fact, there are conflicting epidemiological data about the possible causal role of UA in the development of cardiovascular disease. Some limitations of the present study are the lack of a prospective design and the relatively small number of children investigated, which may have restricted our ability to detect statistical significant associations in the analyses performed. Further studies are warranted to elucidate the precise role of the UA in the impairment of the vascular function observed in LBW children.

An important question is how to converge the increase in UA levels with the intrauterine growth retardation. First, we can infer that this is not a consequence of the decrease in renal function, because GFR was similar in both groups. Second, it is known that LBW has been associated with a reduced number of nephrons. It remains possible that the low nephron number might itself predispose to the development of hyperuricemia as a consequence of an increase in proximal tubular reabsorption, which might stimulate UA reabsorption. Finally, elevation of UA in the child could occur from genetic or environmental mechanisms.

In conclusion, our findings indicate that children who were small at birth exhibited impaired endothelial function and increased SBP and UA levels. These results contribute to a better understanding of the link between LBW and adult cardiovascular disease and have implications for lifestyle and health risks in children and adults.

**Perspectives**

Higher childhood serum UA, even within a normal range, is significantly associated with BW, SBP, and endothelial function. Given the modest effect sizes observed in our analyses, it may be argued that these findings have limited clinical significance. Nevertheless, our observations are of biological importance because they support the concept that UA may be contributing to the hypertension and endothelial dysfunction observed in LBW children. Further studies are warranted to confirm and to elucidate these observations.

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**Disclosures**

None.

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