Endothelial dysfunction in children with low birth weight, born at term

Normal zamanında düşük doğum ağırlığı ile doğan çocuklarda endotel disfonksiyonu

Aydın Akyüz[1], Şeref Alpsoy[1], Dursun Çayan Akkoyun[1], Burçin Nalbantoğlu[2], Birol Topçu[3], Feti Tülübaş[4], Burcu Özdilek[2], Mustafa Metin Donma[2]

[1]Namık Kemal University, Faculty of Medicine, Department of Cardiology, Tekirdağ, Turkey
[2]Namık Kemal University, Faculty of Medicine, Department of Pediatrics, Tekirdağ, Turkey
[3]Namık Kemal University, Faculty of Medicine, Department of Biostatistics, Tekirdağ, Turkey
[4]Namık Kemal University, Faculty of Medicine, Department of Biochemistry, Tekirdağ, Turkey

Abstract
The aim of our study was to assess whether endothelial function of the brachial artery is normal or impaired in children born at term with low birth weight (LBW) compared with their normal birth weight (NBW) peers, because there are still few data on this subject in children born at term with LBW. We compared brachial artery flow mediated dilatation (FMD) in children with LBW (n= 55, 30 male) and NBW (n= 45, 24 male) who were born at term. Age, gender, weight, height, waist and hip circumference, body mass index, body mass Z score, fasting glucose, total cholesterol, triglycerides, low density lipoprotein-cholesterol, high density lipoprotein- cholesterol, calcium, C-reactive protein, hemoglobin, serum insulin concentration, homeostatic model assessment index, creatinine values, brachial artery baseline diameter and brachial artery post dilatation diameter were similar in both groups (all p values >0.05). Compared with the NBW group, the LBW group had lower FMD (%) (6.68 ± 2.1 vs. 7.8 ± 1.9, p = 0.004). Brachial artery FMD was negatively correlated with waist circumferences (r = - 0.521, p < 0.001). A general linear analysis model, FMD as the dependent variable revealed significant effect of waist circumference (β ± SE:- 0.07±0.02, p<0.001) and LBW controlling for age (β ± SE: -0.028±0.01, p = 0.004). LBW closely affects to FMD. Therefore, the children with LBW born at term may be potentially at risk for early atherosclerosis compared with their peers.
Keywords: Atherosclerosis; birth weight; childhood; flow mediated dilatation.

Özet
Normal zamanında doğan düşük doğum ağırlıklı (NZDDDA) çocuklarda endoteliyal fonksiyonları ile ilgili veriler azdır. Bu çalışmamızda NZDDDA'lı çocukların brakiyal arter (BA) endoteliyal fonksiyonlarında normal doğum ağırlıklı (NDA) akranlarına göre fark olup olmadığını değerlendirmeyi amaçladık. BA'nın akım aracılı dilatasyonunu (AAD) NZDDDA'lı (30'u erkek 55 çocuk) ve NDA'lı (24 ü erkek 45 çocuk) çocuklarda karşılaştırdık. Yaş, cinsiyet, kilo, boy, bel ve kalça çevresi, vücut kile indeksi, vücut kitle Z skoru, açlık kan şekeri, total kolesterol, trigliserid, düşük yoğunluklu kolesterol, yüksek yoğunluklu kolesterol, kalsiyum, C-reaktif protein, hemoglobin, serum insulin düzeyi, hemostatik model değerlendirme indeksi, kreatinin ve BA bazal ve dilatasyon sonrası çapı her iki grupta benzerdi (tüm p değerleri >0.05). Her iki grup karşılaştırıldığında, DDA'lı grup daha düşük AAD (%) (6.68 ± 2.1'e karşı 7.8 ± 1.9, p < 0.004) sahipti. AAD bel çevresiyle ters korelasyona sahipti (r = - 0.521, p < 0.001). AAD, DDA'nın varlığı (β ± SE: -0.028±0.01, p = 0.004) ve bel çevresi (β ± SE: 0.07±0.002, p<0.001) ile ilişkili idi. DDA, AAD'yi yakın olarak etkiler, bu nedenle normal zamanında doğan DDA'lı çocuklar akranlarına kıyasla potansiyel olarak erken ateroskleroz riski altında olabilirler.
Anahtar kelimeler: Ateroskleroz; doğum ağırlığı; çocukluk; akım aracılı dilatasyon.

Introduction

The prevalence of low birth weight (LBW) is about 10% (1). It is known that LBW <2500 g at birth is associated with the risk of developing late-onset diseases such as hypertension, chronic kidney disease, insulin resistance in adult life (2-4). Although some publications in the past demonstrated that LBW is not a cause of endothelial dysfunction (5,6), these findings have largely been buried beneath a wealth of data on the relationship between cardiovascular risk and LBW associated with preterm (7-12).

The unfavorable effect of prenatal influences on endothelial function in childhood has been documented (7,13), and several clinical observations are consistent with the loss of nitric oxide bioavailability playing a central role in the pathogenesis between LBW and dysfunction of the

Correspondence: Aydın Akyüz, Namık Kemal University, Faculty of Medicine, Department of Cardiology, Tekirdağ, Turkey
Tel:+90 542 4116550 *ayakyuzq5@gmail.com*

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endothelium (14,15). However, it is still unclear whether LBW is a causative factor for early atherosclerosis in childhood. In the case of presence of early atherosclerosis findings in childhood, earlier intervention in other atherosclerosis risk factors, such as hypertension, dyslipidemia, diabetes, and smoking would be a more of a necessity to prevent adult cardiovascular disease.

Assessment of brachial artery FMD by high-resolution ultrasound to detect early atherosclerosis is non-invasive and easy (16-17). To date, even though there is enough data from two-dimensional ultrasound measurement on endothelial function by using the FMD method (7,9), there is still disagreement about the effect of LBW associated with term on endothelial dysfunction in childhood.

The main goal of this study was to investigate whether there are endothelial dysfunction findings in children with LBW who had been born at term.

Methods

Study design and study population

This study is a cross-sectional, observational study.

Study population and protocol

Between October 2012 to May 2013, 128 consecutive children who had been born at term were enrolled from our pediatric clinics and examined in our cardiology and pediatric clinics, and categorized into two groups. The first group, the LBW group, was composed of 55 LBW children [25 female and 30 male, between 65 and 168 months old, mean birth weight 2.1 (1.5-2.4) kg]. The second group, the NBW group, was composed of 45 normal born weight (NBW) peers [21 female and 24 male, between 66 and 176 months old, mean birth weight 3.3 (3.0-3.8) kg]. All parents were clinically healthy and nonsmokers. Baseline characteristics such as anthropometric, biochemical and hormonal parameters and clinical features of the two groups are shown in Table 1. All children were weighed and their heights were measured; then BMI Z score were calculated, as described previously (18).

The inclusion criteria for acceptance in the LBW group were birth at ≥38 weeks gestation with born weight ≤2500 grams and for the NBW group ≥3000 grams. The following exclusion criteria were defined for the 2 groups: Children with born postterm or >4 kg (macrosomic), obesity, moderate-to-severe valvular disease, left ventricle ejection fraction <45%, electrolyte disorders, history of heart disease, active or passive smoking, hypertension, diabetes mellitus or any systemic disease, hormonal disorders or any medication.

Clinical and laboratory examinations, including anthropometric measurements and routine blood tests, were obtained from all subjects during morning hours in a quiet, temperature-controlled room after ≤10 hours fasting. All participants were examined in the outpatient ultrasonography room after obtaining their blood. Measurements of brachial artery FMD were performed on all study participants. The committee for research Ethics at our institution approved the study, and informed consent was obtained from each subject's parents.

Clinical characteristics and biochemical analysis

Sphygmomanometeric method using a standard 10 cm cuff with a length of 40 cm (small adult cuff, Johnson and Johnson, USA) was used for measuring the resting systolic and diastolic blood pressure. Serum glucose concentration was detected by the glucose oxidase method. Total cholesterol (TC) and triglycerides (TG) levels were analyzed by the enzymatic method, high density lipoprotein-cholesterol (HDL-C) was detected by a chromogenic substrate kit and then low-density lipoprotein cholesterol (LDL-C) calculated with Friedewald equation [LDL-C=TC - (HDL-C - (TG/5)] (19). Serum calcium levels were determined on a AU680 analyzer (Beckman Coulter, Brea CA, USA) with a chromogenic assay. A standard nephelometric method was used for the measurement of C-reactive protein (CRP) levels (Cobas 311, Roche Diagnostics, Mannheim, Germany) with a sensitivity of 0.1 mg/l. Serum insulin concentrations were measured by using the Cobas e 601 Kit (detection range: 0,2mIU/ml - 1000 mIU/ml) which was obtained from Roche Diagnostics, Mannheim, Germany. Homeostatic model assessment index (HOMA) was calculated by formula: (Fasting glucose X Fasting insulin concentration X 0.0555)/22.5, as described previously (20).

Ultrasonographic assessment

One experienced cardiologists, who was unaware of the study participants' group obtained all ultrasonographic data with an Esaote, My Lab 50 (Florence, Italy). Brachial artery FMD was carefully identified according to previously described methodology (17-19), using the ultrasound scanner, which has a functional ECG mode and an 11 MHz linear array transducer.

To obtain optimal end-diastolic baseline images with simultaneous ECG recordings, a linear transducer was placed immediately above the antecubital fossa, preventing any compression of the anterior wall of the brachial artery.

The average value of baseline diameter was calculated using three consecutive diastolic arterial diameters on the frozen m-line image. We then placed a pneumatic cuff above the right arm antecubital fossa and rapidly inflated to at least 50 mmHg above suprasystolic pressures, thereby occluding brachial artery blood flow. From 60-90 seconds after rapid deflation of the pneumatic cuff, the average of three frozen m-line images at every third diastole was accepted as the post-dilatation

diameter. FMD (%) was calculated by dividing the baseline diameter by the maximal change between the baseline and post-dilatation diameter.

To detect the visiting coefficients of variation, twelve children with LBW and 10 children with NBW were re-examined after 15 days. The Δ diastolic diameter of brachial artery for the FMD was found to be 3.7%, respectively.

Statistical analysis

We used PASW® Statistics 18 for Windows (SPSS Inc., Chicago, IL, USA) for obtaining all statistics data. A Shapiro-Wilk test was used to check continuous variables' distribution. Data were presented as mean ± standard deviation (SD) for normally distributed data, and mean (min-max) for abnormally distributed data. The student t test was used for the data fit into the normal distribution and Mann Whitney U test was performed for non-normal distribution. Gender distribution between two groups was compared with a Chi square test. Spearman's rank correlation test was used for correlation between waist circumference and FMD (%). A p value ≤ 0.05 was considered significant. Determination of the independent variables related to FMD was obtained by using a stepwise multiple linear regression analysis.

Table 1. Clinical, anthropometric, and biochemical characteristics.

	LBW group n=55	**NBW group n=45**	**p**
Birth weight, kg	2.2 (1.6-2.3)	3.3 (3.0-3.8)	0.001*
Age, month	122±31	121±26	0.624†
Male, n (%)	30 (54.5%)	24(53.3%)	0.468‡
Weight, kg	32 (17.6 - 55)	33 (18.1 - 54)	0.241*
Height, cm	136 (109 -168)	137 (113-172)	0.455*
Waist circumference, cm	61 (43 - 85)	62(40-86)	0.194*
Hip circumference, cm	72 (43-93)	73(42-95)	0.174*
Body mass index, kg/m^2	19 (16-24)	20 (16- 25)	0.544*
BMZ score	0.41 (0.3 – 0.7)	0.43 (0.3 – 0.7)	0.756*
Fasting glucose, mg/dl	82±16.3	84±6.2	0.577†
Total cholesterol, mg/dl	161±26.4	165±32.2	0.545†
Triglyceride, mg/dl	101±76	93±51	0.290†
LDL, mg/dl	96±24	101±29	0.542†
HDL, mg/dl	50±12	48±11	0.394†
Calcium, mg/dl	9.5±0.4	9.8±0.3	0.659†
C-reactive protein, mg/dl	3.3±4.8	4.4±5.6	0.593†
Hemoglobin, gram/dl	13±1.1	13±0.8	0.223†
Serum insulin, µIU/L	6.8±5.3	8.3±7.1	0.098†
HOMA	1.57±0.3	1.8±0.2	0.363†
Serum creatinine, mg /dl	0.8±0. 2	0.75±0. 1	0.648†

*Data are presented mean ±SD, *Mann-Whitney U test, †Student t test, and ‡Chi square. HDL-high density lipoprotein, LDL-low density lipoprotein, HOMA: Homeostatic model assessment index*

Results

Baseline characteristics and biochemical measurements

Anthropometric, clinical, biochemical, FMD measurements are shown in Tables 1 and 2. There was significant difference in terms of birth weight between the two groups [2.1 (1.5-2.4) vs. 3.3 (3.0-3.8) kg, p= 0.001)]. The distributions of age, gender, fasting glucose, TC, TG, LDL-C, HDL-C, calcium, CRP, hemoglobin, serum insulin concentration, HOMA and serum creatinine values were similar in both groups. Weight, height, waist and hip circumference, and BMI, BMZ score were similar in the LBW group and the NBW group (Table 1). In addition, no difference was observed in terms of systolic and diastolic blood pressure between the two groups (Table 2).

FMD

Brachial artery baseline diameter and brachial artery post dilatation diameter were similar in the LBW group and the NBW group (2.83 ± 0.21 vs. 2.84 ± 0.19 mm, p= 0.584) and (3.01 ± 0.19 vs 3.06 ± 0.18, p = 0.143) mm, respectively. There was a difference between the LBW and NBW group in terms of FMD (%) (6.68±2.1 vs. 7.8±1.9, p = 0.004) (Table 2 and Figure 1).

Table 2. Blood pressures and ultrasound assessment of the brachial artery FMD.

	LBW group n =55	NBW group n=45	*p
Systolic blood pressure, mmHg	107±11	109±10	0.312
Diastolic blood pressure, mmHg	72±6	70±8	0.171
BA baseline diameter, mm	2.83±0.21	2.84 ±0.19	0.584
BA post dilatation diameter, mm	3.01±0.19	3.06 ±0.18	0.143
Brachial artery FMD %	6.68 ±2.1	7.8 ±1.9	0.004

*BA= brachial artery, FMD = flow mediated dilatation, *Student t test*

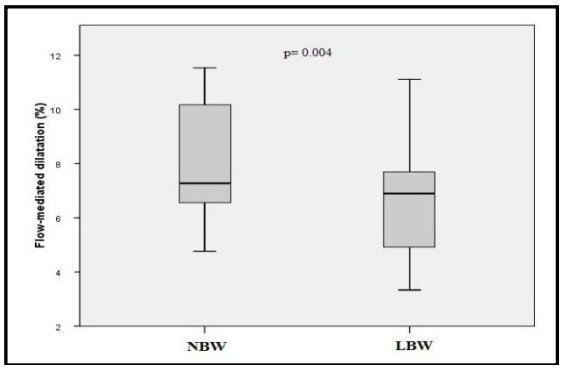

Figure 1. Variables are represented by a box and whisker plot: the thick horizontal line is the median, the filled box is the interquartile range, and the whiskers are 1.5 times the interquartile range.

In age-adjusted stepwise multiple linear regression analysis of the two groups together, brachial artery FMD was related with the presence of LBW, and FMD seemed to be influenced by waist circumference (Table 3). In addition, brachial artery FMD was negatively correlated with waist circumferences (r = - 0.521, p < 0.001) (Figure 2).

Table 3. Age-adjusted stepwise multiple linear regression

Dependent variable	Independent variables	β ± SE	r^2	P
FMD %	Waist Circumference	-0.07±0.002	0.263	<0.001
	The presence of LBW	-0.028±0.01	0.305	<0.04

FMD = flow-mediated dilatation, LBW= low birth weight

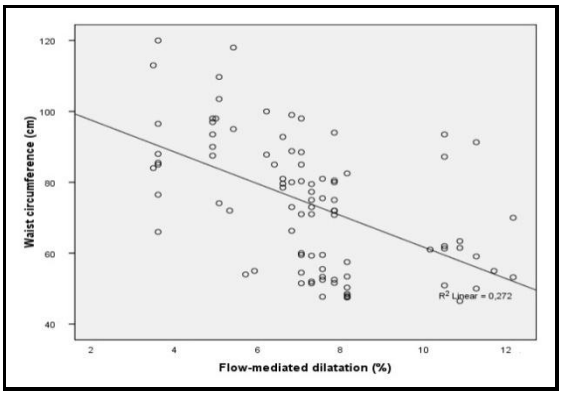

Figure 2. A negative linear relation between waist circumference and increasing flow-mediated dilatation is shown on scatter diagram. (r = - 0.521, p < 0.001).

Discussion

The present study suggests that children born at term with LBW showed abnormal endothelium, but no brachial artery vascular structure. Although there has been enough findings suggesting that LBW is associated with an increased cardiovascular risk in adults (8,10,11), there are still few data concerning subclinical early atherosclerosis in children with LBW who were born at term (9,10). We found that the brachial artery FMD in children with LBW was lower than that of peers with NBW. Our data are not different from the previous studies (8-10), and potentially suggest that LBW is a risk factor for early atherosclerosis in childhood and may be validated for young adults.

There also are enough data regarding FMD in children with LBW, but there are still some contradictions in findings relating to FMD in childhood. Hovi et al. (6) found that there was vascular structural change in terms of carotid artery intima-media thickness in adults born at LBW, but they also found that FMD was normal in the same group. Moreover, Singhal et al. (5) found that there was a normal endothelium-dependent vasodilatory capacity in adolescents born at LBW who had an accelerated neonatal growth.

The FMD measurement, a reproducible and simple technique, in the clinics with experienced ultrasound technicians have been used routinely to determine endothelial dysfunction which reflects early atherosclerosis (16,17,21). It is known that FMD is strongly related with age, systolic blood pressure, BMI, and fasting glucose as well as lipid values (22-25). BMI, systolic and diastolic blood pressures values, fasting glucose, HOMA, and lipid values were similar in our study groups. According to age-adjusted regression analysis; LBW was related with only FMD, and waist circumference was the only predictive factor affecting to FMD. Birth weight values were directly associated with FMD. However, our study does not potentially contradict Hovi et al's data (6) suggesting that preterm birth at very LBW (<1.5 kg) is associated with raised cardiovascular risk in adulthood.

Subclinical atherosclerosis might first appear in childhood (26) and occurs after endothelial dysfunction (26,27). Endothelial dysfunction associates with decreased endothelium-derived nitric oxide, impaired antiplatelet activity and increased smooth muscle cell activity and plays a role in the etiopathogenesis of coronary artery disease and its risk factors (28-30).

Birth weight and prematurity are affected substantially by maternal nutrition and health during pregnancy, and developmental programming results in hypertension and kidney disease (3). According to their study, Liew et al. (31) concluded that LBW is associated with narrower arterioles in adults. In the present study, we demonstrated impaired endothelial function in LBW children born at term compared with their NBW peers. Our findings also potentially consistent with popular opinion regarding that LBW is associated with impaired nitric oxide bioavailability (14,15).

There were third limitations in our study. First, the study population was small and did not include a very LBW group. Second, we used birth weight values according to participant' parents' information, which may be less precise. Third, we did not evaluate the subjects' neonatal growth acceleration as a variable.

According to our findings, LBW infants born weighing <2500 g and at >38 weeks of gestation are potentially at risk for early subclinical atherosclerosis in childhood. Birth weight and waist circumference assessment may help in the detection of early subclinical atherosclerosis in childhood in the absence atherosclerotic risk factors such as hypertension, dyslipidemia, and insulin resistance.

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