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The effect of low birth weight on endothelial dysfunction in young adults: a retrospective cohort study

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ABSTRACT

Aim. To investigate the effect of low birth weight (LBW) on endothelial function, and to determine the role of plasma adiponectin in endothelial dysfunction by conducting flow mediated brachial artery (FMBA) test or vasodilation response (VR) and by measuring plasma asymmetrical dimethylarginine (ADMA) in young adults born with LBW.

Methods. In a retrospective cohort study, subjects were randomly selected from the Growth Study Cohort of Tanjungsari in the Sumedang district of West Java. They consisted of 67 LBW and 67 NBW (normal birth weight) young adults.

Results. The relative risk for LBW to have low brachialis artery vasodilation response was 2.94, 95% confidence interval (CI): 1.91–4.53, and to have low plasma adiponectin concentration 1.53, (95% CI: 1.07–2.18). Multivariate analysis via Hotelling's trace showed a statistically significant difference ($p < 0.001$) for all variables studied (FMBA, plasma ADMA, and plasma adiponectin concentrations) but simultaneous confidence interval measurements indicated that the value of FMBA and the concentration of plasma adiponectin were significantly lower, respectively $p < 0.001$, 95% CI: –4.409–(–2.114), and $p = 0.015$, 95% CI: –1.083–(–0.082) in LBW compared to NBW subjects. The correlation between plasma adiponectin concentration and plasma ADMA concentration ($r = –0.16$, $p = 0.176$), and FMBA ($r = 0.13$, $p = 0.281$) in LBW subjects were not significant.

Conclusions. There is an effect of LBW on endothelial function. Plasma adiponectin's action in endothelial dysfunction in young adults with LBW has a potential role which is yet to be defined.

Key words: low birth weight, adiponectin, ADMA, FMBA test

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Introduction

Low birth weight (LBW) may increase the risk of cardiovascular diseases during adulthood. Intrauterine growth restriction can lead to alteration of organs, functions, and metabolisms and also to persistent endocrine disorders [1]. Adiponectin is a protein that is synthesised by fat cells, and plays an important role in foetal growth [2, 3]. In LBW, low adiponectin concentration persists through childhood and adulthood [4, 5]. Apart from an insulin sensitising effect, adiponectin has also antithrombotic and antisclerotic properties that directly influence the endothelial function [6].

Endothelial dysfunction is a foundation for atherosclerosis. One of the first endothelial functions to be disturbed is the vasodilation / vasoconstriction balance. Nitric oxide (NO), one of the vasodilators which is produced by the endothelial cells, has a very short half-life of 3–5 seconds, and clinically can be detected as a vasodilatation response (VR) on a flow mediated brachial artery (FMBA) test [7–9]. Asymmetric dimethylarginine (ADMA) is a laboratory marker of endothelial dysfunction that acts as an endogenous inhibitor of endothelial nitric oxide synthase (eNOS), an enzyme that competes with arginine, which is a NO precursor [10].

The incidence of LBW in Indonesia is still high, at about 11.5% [11], therefore the aim of this study was to define the effect of LBW on endothelial function and to determine the role of adiponectin in endothelial dysfunction, by addressing the following issues: 1) What is the relative risk of LBW to have endothelial dysfunction?; 2) Do young adults born with LBW have a lower plasma adiponectin concentration, a higher plasma ADMA concentration, and a lower VR value compared to NBW?; 3) Is there a negative correlation between plasma adiponectin and plasma ADMA concentrations, and a positive correlation between plasma adiponectin concentration and VR value, in young adults born with LBW?

Methods

This was a clinical epidemiological study conducted in a retrospective fashion from November 2009 until January 2010. Subjects were obtained from the Growth Study Cohort of Tanjungsari, Sumedang District, West Java [12] who fulfilled the inclusion criteria (Fig. 1). LBW as a risk or independent variable was compared to a control group born with NBW, identified 19–21 years earlier. The effect of selected dependent variables i.e. plasma adiponectin, plasma ADMA, and brachial artery VR, were examined.

Inclusion criteria were: male or female; ranging in age from 19 to 21; with birth weight and birth length data available; had taken part in a previous risk factor study; and had been previously randomised. Patients were excluded in cases of: chronic renal failure; liver disease; heart failure; or consumption of antidiabetic drugs, nitrate drugs, steroid drugs or multivitamins.

In this study, chronic renal failure was defined as chronic kidney disease stages 3, 4 and 5 with glomerular filtration rate (GFR) < 59, < 29 and < 15 mL/minute per 1.73 m^2 [13]. Liver disease was defined as liver cell injury with the elevation of alanine aminotransferase (ALT) > 1,000 U/L, at least 300 U/L [14]. The epidemiology criteria of the Framingham Study were used to consider heart failure which met two major criteria, or one major criterion plus two minor criteria [15].

A GE Logic ultrasonograph was used to obtain the diameter of brachial artery. This was measured before and within the first minute after the occlusion. The VR value (in %) is the difference in diameter of brachial artery after and before occlusion [9, 16].

Human adiponectin was performed with a sandwich enzyme-linked immunosorbent assay (ELISA) that used two kinds of anti-human adiponectin monoclonal antibodies. The specimens were pretreated, and total adiponectin and individual multimers of adiponectin were determined selectively, directly or indirectly.

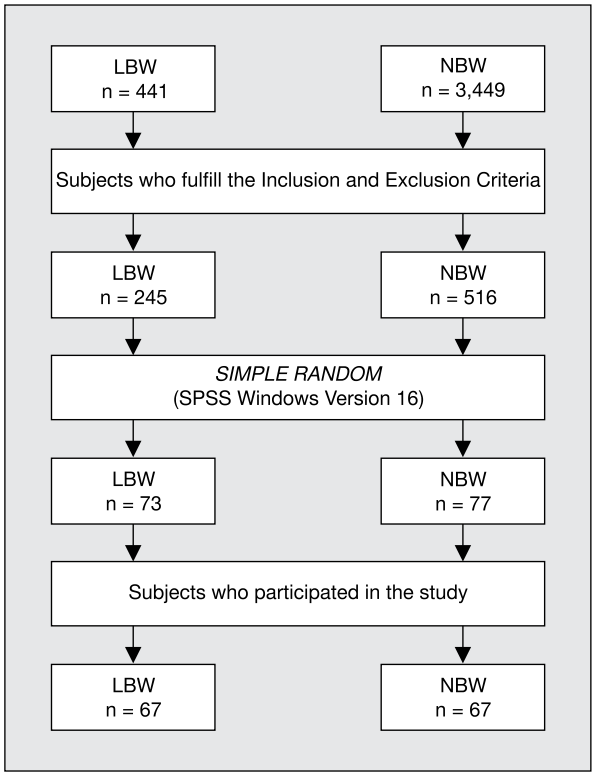

Figure 1. Subjects obtained from the Growth Study Cohort of Tanjungsari, Sumedang District, West Java

LBW — low birth weight; NBW — normal birth weight

Reference values: males 2.54–6.06 μg/mL, females 3.58–9.66 μg/mL.

ADMA was assayed by a competitive ELISA. ADMA in the samples was acylated and competed with solid phase bound ADMA for a fixed number of rabbit anti-ADMA antiserum binding sites. The expected values were 0.4–0.75 μmol/L.

This study was approved by The Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Faculty of Medicine, Universitas Padjadjaran, Bandung.

Statistical analysis

In order to determine the weight of relative risk, pre-defined cut off points were low plasma adiponectin concentration, high plasma ADMA concentration, and low brachialis artery VR value which were determined by diagnostic testing using the Receiver Operating Characteristics (ROC) curves.

Normality testing of data distribution was conducted before completing the statistical analysis using the Lilliefors significance correction. The second question was tested in two phases. In the first phase, all dependent variables were tested by multivariate statistical

Table 1. General characteristics of young adults born with LBW and NBW

Parameters	LBW (n = 67)	NBW (n = 67)
Age (years)	20.3 (0.5)	20.2 (0.58)
Male (%)	52.2	56.7
SBP [mm Hg]	117 (10)	119 (10)
DBP [mm Hg]	76 (6)	78 (7)
Haemoglobin [gr/dL]	15.0 (1.6)	15.3 (1.3)
Fasting blood glucose [mg/dL]	86.0 (6.7)	84.8 (8.7)
Total cholesterol [mg/dL]	158.5 (26.7)	161.3 (30.1)
Triglycerides [mg/dL]	84.4 (40.4)	95.10 (51.4)
HDL-C [mg/dL]	44.4 (8.8)	43.5 (8.5)
LDL-C [mg/dL]	100.1 (23.6)	101.8 (24.6)
SGOT [U/L]	21.6 (6.5)	21.5 (7.0)
SGPT [U/L]	21.5 (13.6)	20.4 (10.9)
Blood urea [mg/dL]	19.1 (5.4)	18.3 (4.5)
Creatinin [mg/dL]	0.68 (0.14)	0.71 (0.16)
Smoker [male, %]	88.6	89.5
BMI [kg/m^2]	20.1 (3.3)	20.7 (3.2)
Diabetes mellitus	None	None
Hypertension (BP ≥ 140/90 mm Hg) (n)	1	3

LBW — low birth weight; NBW — normal birth weight; SBP — systolic blood pressure; DBP — diastolic blood pressure; HDL-C — high density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; SGOT — serum glutamic oxaloacetic transaminase; SGPT — serum glutamic-pyruvic transaminase; BMI — body mass index

analysis for two independent samples. The second phase used the simultaneous confidence interval to determine which mean variable was different. The third question was examined using the correlation testing. The Pearson's correlation was used if the data had normal distribution. The subject characteristic data were stated in mean value and standard deviation (SD). Statistical analysis was conducted using the SPSS Window software version 13.0. The values of $p < 0.05$ were considered statistically significant.

Results

General characteristics

There were 67 LBW subjects and 67 NBW subjects enrolled in this study. None of the patients in either group were receiving anti diabetic, antihypertensive, nitrate, or vasoactive drugs and/or multivitamins. The general characteristics of the two groups were not significantly different (Tab. 1).

Relative risk for LBW to have low concentration of brachialis artery VR, low plasma adiponectin concentration, and high plasma ADMA concentration

Cut off point for low plasma adiponectin concentration from the Receiving Operating Characteristic (ROC) curve was ≤ 4.13 μg/mL and for low VR value was ≤ 9.5%, while for high plasma ADMA concentration it was ≥ 0.89 mmol/L. Significantly, the LBW group were prone to have lower VR and lower plasma adiponectin than the NBW group (Tab. 2).

The mean plasma adiponectin concentration, plasma ADMA concentration and VR differences in young adults born with LBW and NBW

All three variables showed very significant differences ($p < 0.001$) according to the statistical testing using the multivariate analysis for two independent samples. The next statistical testing, using the simultaneous confidence interval, found significantly different mean variables of plasma adiponectin concentration and VR value between LBW and NBW. The baseline distribution of brachial artery diameter in both groups was not statistically significantly different, but the VR value showed a significant difference between groups. The mean plasma ADMA concentration of LBW was not statistically significantly different ($p = 0.669$) compared to the NBW (Tab. 3).

Correlation between plasma adiponectin, and plasma ADMA, and brachialis artery VR in young adult subjects born with LBW

The correlation between plasma adiponectin and plasma ADMA ($r = –0.16$, $p = 0.176$), and between plasma adiponectin and VR ($r = 0.13$, $p = 0.281$), in LBW subjects were not significant. A significant correlation was found between baseline diameter of brachial artery and VR ($r = 0.27$, $p = 0.028$), with a smaller brachial artery diameter associated with a larger VR.

Discussion

The main findings of this study are that VR significantly differs between LBW and NBW groups, although the baseline diameters of brachial artery in both groups were similar.

The endothelial dysfunction was clinically more pronounced in the young adult group born with LBW compared to NBW that appeared as low VR (8.4% vs. 11.6%) on FMBA test. Leeson et al. found that low VR in LBW was a result of vascular function alteration relating to in-utero growth disturbance [16].

Table 2. Relative risk for LBW to have low VR, low plasma adiponectin concentration, and high plasma ADMA concentration

Variables	LBW (n = 67)	NBW (n = 67)	p value	RR (95% CI)
Adiponectin			0.016	1.53 (1.07–2.18)
≤ 4.13 μg/mL	41 (60.3%)	27 (39.7%)		
> 4.13 μg/mL	26 (39.4%)	40 (60.6%)		
VR			< 0.001	2.94 (1.91–4.53)
≤ 9.5%	50 (74.6)	17 (25.4)		
> 9.5%	17 (25.4)	50 (74.6)		
ADMA			0.216	1.32 (0.89–1.96)
≥ 0.89 mmol/L	12 (63.2%)	7 (36.8%)		
< 0.89 mmol/L	55 (47.8%)	60 (52.2%)		

Note : *Chi Square test*

LBW — low birth weight; NBW — normal birth weight; VR — vasodilation response; RR — relative risk for LBW; CI — confidence interval; ADMA — asymmetrical dimethylarginine

Table 3. Mean plasma adiponectin concentration, plasma ADMA concentration, and brachialis artery VR differences between young adults born with LBW and NBW

Variables	LBW (n = 67)	NBW (n = 67)	p	95% CI for difference
Total (adiponectin, ADMA and brachial artery VR)*			< 0.001*	
Plasma adiponectin [μg/mL]	4.07 (1.29)	4.64 (1.61)	0.015**	–1.083–(–0.082)**
Brachialis artery VR (%)	8.40 (3.06)	11.66 (3.63)	< 0.001**	–4.409–(–2.114)**
Baseline diameter of brachialis artery [cm]	3.35 (0.47)	3.33 (0.42)	0.758***	
Plasma ADMA [μmol/L]	0.71 (0.15)	0.69 (0.15)	0.669**	–0.041–(0.064)**

LBW — low birth weight; NBW — normal; birth weight; CI — confidence interval; *Hotelling's Trace; **Simultaneous Confidence Interval; ***Independent test

Poor nutrition during foetal growth will result in alteration of organ structure and function, also in the metabolism disturbance that appears in LBW with low plasma adiponectin concentration. Adiponectin raises NO production through eNOS enzyme stimulation. Plasma adiponectin concentration in this study was significantly lower in LBW compared to the NBW group. Thiese findings are similar to those of studies by Kamoda et al. [4] and Cianfarani et al. [5]. Unlike our study, they compared a small for gestational age group (birth weight = 2.1 ± 0.4 kg) and an appropriate for gestational age group (birth weight = 3.0 ± 0.8 kg). In our study, both groups (LBW and NBW) had the same BMI (about 20 kg/m^2). We could not eliminate the possibility that low plasma adiponectin concentration in LBW was the result of fatty tissue malfunction according to Barker & Hales' study [1] and as a result of genetic factors such as single nucleotide polymorphisms 276 on adiponectin gene [6]. Therefore further studies are needed.

In this study, no significant correlation between plasma adiponectin and VR, or between plasma adiponectin and plasma ADMA, were found. Adiponectin might have some effect on endothelial dysfunction of young adults with LBW.

Other factors might have influenced the final results, and this precludes us from drawing definite conclusions before thorough evaluation.

There are a variety of vascular or endothelial functions, but the vasodilation / vasoconstriction balance is the first to be affected [17]. In addition to the NO vasodilator synthesis disturbance, the potential role of excessive vasoconstrictors in LBW subjects such as endothelin-1, angiotensin II, thromboxane A2, and prostagladin H_2 deserve further investigation.

The mean plasma ADMA concentration of the LBW group was not significantly different to the NBW group. Only a few studies have examined the protein arginine N-methyltransferase (PRMT) activity regulation. The study by Osanai et al. [18] found that ADMA concentra-

tions were influenced by shear stress. In a physiologic state, shear stress increases PRMT-1 expression and ADMA synthesis through NF-κB pathway activation. However, in the presence of shear stress, dimethylarginine dimethylamin hydrolase-II (DDAH-II) activity would also increase, resulting in ADMA degradation. In this study, the blood samples for ADMA examination were obtained before conducting an FMBA test, thus preventing any differences between the two groups. Oxidative stress that results in ADMA accumulation [19] could be eliminated only if the general characteristics of both groups were similar i.e.. smoking, systolic and diastolic blood pressure, blood glucose concentration, and blood fat concentration between the LBW and NBW groups.

One factor that could influence plasma adiponectin and ADMA is TNFα. Tumour necrosis factor α inhibits adiponectin production [20–22], but induces ADMA accumulation [23]. The possibility of fatty tissue function disturbance [1], especially in TNFα synthesis which is strictly related to adiponectin production and ADMA accumulation, cannot be ruled out.

Low plasma adiponectin concentration and endothelial dysfunction condition persist throughout childhood and adulthood. A nonsignificant correlation between plasma adiponectin and plasma ADMA concentration, and a nonsignificant correlation between plasma adiponectin concentration and VR, revealed no potential role for adiponectin in endothelial dysfunction in LBW. There are other factors at the cellular level that influence endothelial function, and this possibility needs further investigation.

Finally, beyond the small sample size, another potential limitation is the involvement of intrauterine growth retardation (IUGR), and preterm subjects in the LBW group. The findings of this report therefore deserve confirmation in future studies that are adequately powered.

Conclusion

LBW modulates endothelial function. LBW subjects, compared to NBW subjects, have lower VR and plasma adiponectin concentration. There may be a small role played by plasma adiponectin in endothelial dysfunction of young adults with LBW. However, other variables could play important roles, and further studies are needed before definite conclusions regarding plasma adiponectin can be drawn.

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