RESEARCH ARTICLE

Investigation into the relationship between cord blood adiponectin levels and aortic intima media thickness in healthy, term neonates

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ABSTRACT. ***Introduction:*** **Adiponectin has important anti-inflammatory and anti-atherogenic effects. Although adiponectin and atherosclerosis correlate inversely in children and adults, we have little information regarding this relationship in neonates.** ***Methods:*** **We measured cord blood adiponectin levels and abdominal aortic intima media thickness (aIMT) in 80 healthy, term neonates and investigated the relationship between adiponectin and total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and triglyceride, and their relationships to infant anthropometry and gender.** ***Results:*** **Mean birth weight, length, head circumference and aIMT values for male neonates were statistically significantly higher than those for female neonates. Adiponectin levels were not significantly different with respect to gender. In correlation analysis, the mean adiponectin level correlated positively with TC, HDL-C and LDL-C levels and birth weight, length and head circumference. There was no significant correlation between aIMT and any other parameters.** ***Conclusion:*** **The cord blood adiponectin and aIMT values reported here for the first time, represent reference values in the early neonatal period. The positive correlations between adiponectin levels and birth weight, length and head circumference, and TC, HDL-C and LDL-C indicate that further studies are required to demonstrate the exact relationship and clinical importance of adiponectin metabolism during the neonatal period.**

Key words: adiponectin, aortic intima media thickness, atherosclerosis, neonate

Adiponectin is a fat derived from adipocytokine that regulates glucose and lipid metabolism, positively affects birth weight and length, and skinfold thickness, and differs with respect to gender [1-4]. Adiponectin has important anti-inflammatory and anti-atherogenic effects. Studies with adiponectin-deficient mice have demonstrated the acceleration of neointimal thickening and proliferation of smooth muscle cells in response to damaged arteries [5]. In addition, adiponectin reduced the progression of the atherosclerotic process in apolipoprotein E-deficient mice in an animal model of atherosclerosis [6]. Adiponectin had an inverse relationship to carotid intima media thickness (cIMT), and low levels of this molecule had a predictive value for the detection of early (or subclinical) atherosclerosis in obese children [7, 8].

Regarding the radiological detection of early atherosclerosis, measurement of the thickness of the carotid/aortic intima media complex has been suggested to be an excellent marker of subclinical atherosclerosis [9-11]. In the literature however, there are very limited studies about aortic intima media thickness (aIMT) and its measurement in newborns [12, 13].

Although there is growing evidence that adiponectin levels and atherosclerosis correlate inversely in children and adults, this relationship is not well understood in neonates. To our knowledge the relationship between adiponectin levels and intima media thickness, measured by ultrasound, has not previously been studied; therefore, we aimed to investigate the correlation between serum concentrations of adiponectin and early atherosclerosis in healthy, term neonates and to measure aIMT.

PATIENTS AND MATERIALS

We measured serum concentrations of adiponectin and abdominal aIMT in healthy, term neonates, and investigated the relationship between serum adiponectin and total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and triglyceride in umbilical cord blood to infant anthropometry and gender. All mother-infant pairs born at the Department of Obstetrics of Erciyes University Faculty of Medicine between January 01 and October 31, 2010 were included in the study.

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All mothers had had healthy pregnancies with no chronic, maternal diseases or complications (pregnancies with complications such as preeclampsia/eclampsia, preterm rupture of membranes, multiple pregnancies and gestational diabetes mellitus were excluded from the cohort). All newborns were full-term (≥38 gestational weeks); those with prematurity, intrauterine growth retardation, multiple congenital anomalies, intrauterine/congenital infection or neonatal sepsis, and perinatal asphyxia were not included in the study. As the blood samples of newborns were obtained from cord blood, and as this blood type may be affected by maternal factors and characteristics, the most important obesity-related measure, maternal pregestational body mass index (BMI) was also considered and compared between female and male neonates. The study was approved by the local Ethics Committee, and all women provided written, informed consent before enrollment.

Biochemical analysis

Adiponectin and plasma lipid levels were measured in umbilical venous blood from 80 healthy newborns (43 males and 37 females), born at between 38 and 42 weeks gestation at the Gevher Nesibe Hospital, Erciyes University Faculty of Medicine. Blood samples were immediately transferred into glass tubes and centrifuged at 3500 rpm for four minutes. Serum samples were separated immediately by centrifugation and kept at -80°C until analysis. Adiponectin was measured using the AssayMax Human Adiponectin ELİSA kit in the BioTEK ELx50. The lower limit of detection was 0.5 ng/mL, and the intra- and inter-assay coefficients of variation were 4.1 and 7.2%, respectively. Serum concentrations of TC, HDL-C, LDL-C, and TG were measured using a photometric method adapted to an autoanalyzer (Architect® C16000, Abbott Diagnostics, Illinois, USA). LDL-C was measured directly, as fasting blood samples could not be collected.

Antropometric measurements

Infant anthropometric data, including triceps skinfold measurements, were obtained by a trained, research midwife at birth. An electronic infant scale was used to measure birth weight (grams). Birth length was measured using a standardized infant measurement board with millimeter sensitivity, the mean of three measurements being used for analysis. Systolic, diastolic and mean blood pressures of the neonates were measured using an oscillometric technique in accordance with a standardized protocol. Infants were studied at least one to one and a half hours following their last feed. An appropriate sized cuff was applied to the right upper arm, and the baby was then left undisturbed for at least 15 minutes or until the infant was sleeping or in a quiet, awake state. Three successive measurements were taken at two-minute intervals, and the calculated mean value of each measurement (systolic, diastolic and mean blood pressure) was recorded. BMI was calculated by dividing a woman's weight in kilograms (kg) by her height in meters (m) squared. The ponderal index was calculated as birth weight in kilograms divided by the cube of length in meters.

Ultrasound studies

Before beginning the ultrasound imaging for estimating aIMT, subjects were laid quietly in a dark, temperature-controlled room. The abdominal aortic artery was scanned using a Shimadzu-1200×PLUS high-resolution ultrasound mainframe with linear array probes at 7.5 and 13 MHz. Abdominal IMT was defined to be from the leading edge of the media-adventitia interface to the leading edge of the blood-intima interface. aIMT was measured in a straight, non-branched, 1-cm longitudinal segment of the distal abdominal aorta. The measurements were performed using the manual analyzing system. The dorsal arterial wall of the most distal abdominal aorta was chosen as the area of interest because postmortem studies have shown this to be the most lesion-prone site [10, 12]. The abdominal aorta was first identified in the upper abdomen using a 7.5-MHz, pediatric, phased array transducer. It was then followed distally until the aortic bifurcation was reached and was measured from these images; it was used to locate the aortic intima-media complex using a 13-MHz linear array transducer. For the assessment of aIMT, the image was focused. Five images were captured in every case. Two experienced, vascular sonographers, who were unaware of the clinical and laboratory characteristics of the neonates, performed all of the ultrasound studies.

Statistical analysis

All statistical calculations were performed using a standard, statistical package (SPSS 15.0, SPSS Inc., Chicago, IL, USA). For continuous variables, results are presented as the mean ± standard deviation. Categorical variables are presented by frequency counts. Student's -t and Mann-Whitney U tests were used to test for quantitative variables. The chi-squared test was used for testing the qualitative variables. Anthropometric parameters, aIMT, triceps skinfold and blood pressure values, and blood lipid and adiponectin levels were compared in female and male neonates in order to investigate the effect of gender on these parameters as plasma adiponectin levels have been shown to be affected by gender in some studies [1-3, 14]. Pearson correlation coefficients were used to assess the relationships among all the variables. All p values <0.05 were interpreted as statistically significant.

RESULTS

The mean gestational age of the neonates was 38.78 ± 1.01 weeks, and the mean age of the mothers was 28 (17-41) years. Pre-gestational BMI was 24.83 ± 4.6 (14.69-38.64) kg/m^2. Twenty three and 57 newborns were delivered by spontaneous vaginal delivery and Cesarean section, respectively. Gender, anthropometric, skinfold thickness characteristics, ponderal index and blood pressure values for the neonates are shown in *table 1*.

Blood lipid and adiponectin levels, and aIMT values for the neonates are given in *table 2*.

A comparison of growth parameters, triceps skinfold and blood pressure values, blood lipid and adiponectin levels in female and male neonates is shown in *table 3*. Mean birth weight, length, head circumference and aIMT values for

Table 1
Gender, anthropometric, skinfold thickness characteristics and blood pressure values of neonates

Parameter	Value
Gender (male), n (%)	43 (53.8)
Birth weight (g)*	3,279 ± 369.4
Length (cm)*	50.2 ± 1.6
Head circumference (cm)*	35 ± 1.2
Ponderal index (g/cm^3)*	2.59 ± 0.21
Triceps skinfold thickness (mm)*	5.4 ± 1.3
Systolic blood pressure (mmHg)*	63.7 ± 10.1
Diastolic blood pressure (mmHg)*	35.4 ± 11.1
Mean blood pressure (mmHg)*	44.3 ± 9.4
Maternal pre-gestational body mass index (BMI) (kg/m^2)*	24.83 ± 4.6

*: Values are given as mean ± standard deviation

Table 2
Blood lipid and adiponectin levels, and aortic intima media thickness values of neonates

Parameter	Values*
Triglyceride (mg/dL)	29.9 ± 15.4
Total cholesterol (mg/dL)	60.6 ± 14
HDL cholesterol (mg/dL)	25.3 ± 6.2
LDL cholesterol (mg/dL)	29.3 ± 9.4
Adiponectin (μg/mL)	18.3 ± 4
Aortic intima media thickness (aIMT) (mm)	0.33 ± 0.03

*: Values are given as mean ± standard deviation

male neonates were statistically significantly higher than those for female neonates (*table 3*). Mean blood pressure was significantly higher in female neonates in comparison to male neonates. Values for maternal BMI, ponderal index, triceps skinfold, systolic, diastolic and mean blood pressure, and blood lipid and adiponectin levels for neonates did not differ significantly with respect to gender (*table 3*).

In correlation analyses, the mean neonatal adiponectin level correlated positively with TC (r = 0.253, p<0.05), HDL-C (r = 0.252, p<0.05) and LDL-C (r = 0.221, p<0.05) levels (*figure 1*). Additionally, there were significant positive correlations between neonatal adiponectin levels and birth weight (r = 0.257, p<0.05), length (r = 0.229, p<0.05), and head circumference (r = 0.238, p<0.05) (*figure 2*). There were no significant correlations between neonatal adiponectin levels, and ponderal index (r = -0.002, p = 0.983), triceps skinfold thickness (r = 0.129, p = 0.255), systolic blood pressure (r = -0.033, p = 0.77), diastolic blood pressure (r = 0.152, p = 0.179), mean blood pressure (r = 0.049, p = 0.669), maternal pre-gestational BMI (r = -0.040, p = 0.725), or TG (r = -0.050, p = 0.658). There were no significant correlations between aIMT, and birth weight (r = 0.092, p = 0.415), length (r = 0.116, p = 0.305), head circumference (r = -0.024, p = 0.830), ponderal index (r = -0.083, p = 0.464), triceps skinfold thickness (r = -0.064, p = 0.571), systolic blood pressure (r = -0.024, p = 0.836), diastolic blood pressure (r = -0.085, p = 0.455), mean blood pressure (r = -0.037, p = 0.743), maternal pre-gestational BMI (r = 0.079, p = 0.487), TG (r = 0.038, p = 0.737), TC (r = -0.136, p = 0.231), HDL-C (r = -0.151, p = 0.181), LDL-C (r = -0.128, p = 256) and adiponectin levels (r = -0.203, p = 0.071).

DISCUSSION

In some studies investigating the relationship between adiponectin and anthropometric parameters, a positive relationship was detected between adiponectin and birth weight [1-3], and length-at-birth and skinfold thickness

Table 3
Comparison of growth parameters, aortic intima media thickness, triceps skinfold and blood pressure values, blood lipid and adiponectin levels in female and male neonates

Parameter	Female neonates (n = 37)*	Male neonates (n = 43)*	p value
Birth weight (g)	3,166.49 ± 270.424	3,377.21 ± 415.89	**0.008**
Length (cm)	49.59 ± 1.4	50.72 ± 1.64	**0.005**
Head circumference (cm)	34.7 ± 1	35.31 ± 1.23	**0.009**
Ponderal index (g/cm^3)	2.59 ± 0.19	2.58 ± 0.22	0.710
Triceps skinfold (mm)	5.43 ± 1.12	5.42 ± 1.47	0.515
Systolic blood pressure (mmHg)	65.73 ± 10.18	62 ± 9.74	0.098
Diastolic blood pressure (mmHg)	37.19 ± 12.26	33.84 ± 9.94	0.181
Mean blood pressure (mmHg)	46.51 ± 10.26	42.4 ± 8.16	**0.049**
Maternal pre-gestational body mass index (kg/m^2)	24.15 ± 5.08	25.41 ± 4.08	0.105
Triglycerides (mg/dL)	27.76 ± 15.52	31.81 ± 15.28	0.229
Total cholesterol (mg/dL)	62.19 ± 15.86	59.14 ± 12.17	0.334
HDL cholesterol (mg/dL)	26.35 ± 5.94	24.44 ± 6.32	0.170
LDL cholesterol (mg/dL)	30.28 ± 10.92	28.46 ± 7.91	0.717
Adiponectin (μg/mL)	18.48 ± 3.83	18.08 ± 4.18	0.721
Aortic intima media thickness (mm)	0.32 ± 0.02	0.35 ± 0.04	**0.001**

*: Values are given as mean ± standard deviation

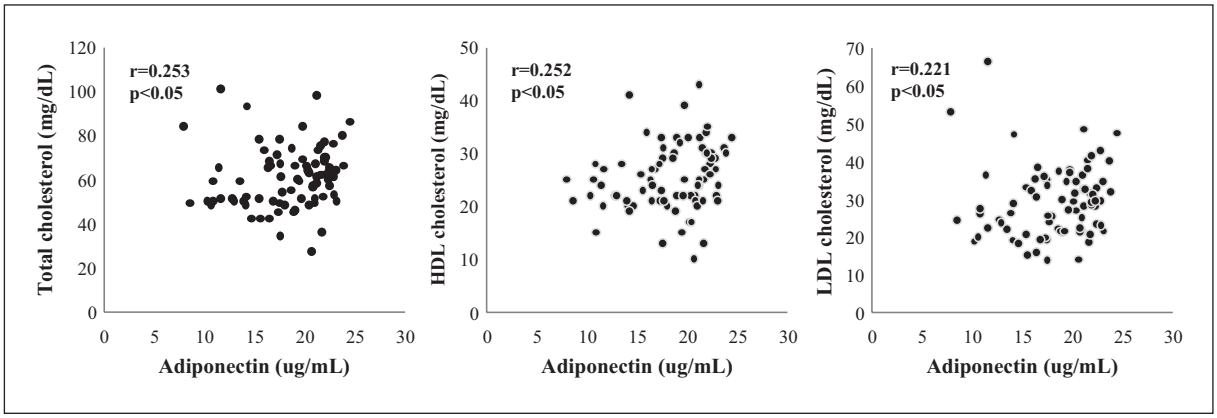

Figure 1
Significant, positive correlations between neonatal adiponectin levels and total, HDL, and LDL cholesterol levels, respectively (r = 0.253, r = 0.252, r = 0.221, p<0.05).

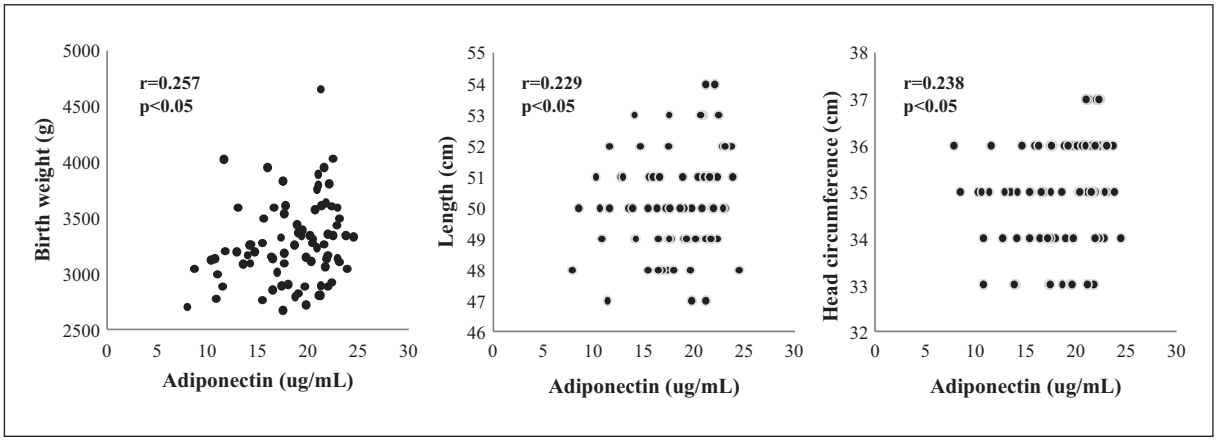

Figure 2
Significant, positive correlations between neonatal adiponectin levels and birth weight, length and head circumference, respectively (r = 0.257, r = 0.229, r = 0.238, p<0.05).

[2, 4], whereas no relationship was found between adiponectin and anthropometric parameters in others [15, 16]. A positive correlation was demonstrated between adiponectin and fetal fat mass [3]. In our study, there were significant, positive correlations between neonatal adiponectin levels and birth weight, length and head circumference.

In adults, females have significantly higher adiponectin concentrations than males. This may be a consequence of testosterone, which decreases the plasma adiponectin concentration through its effect on the secretion of adiponectin from adipocytes [14]. In newborns, no significant gender difference was observed [1-3]. In the male fetus, the testosterone level increases from the end of the second month of gestation, soon reaching a maximal value that is maintained until late in gestation, after which it decreases. At birth, testosterone levels in males are higher than those in females. Thus, the exposure to testosterone *in utero* does not influence the adiponectin level at birth [3]. In view of these data, we did not detect any significant difference between male and female neonates as regards adiponectin levels.

When we compared the mean umbilical cord blood adiponectin levels in the present study with those values reported in other studies performed on newborns [1-3], two studies presented similar values [2, 3] (19 $\pm$ 7.8 μg/mL and 22.4 μg/mL, respectively), whereas one study presented higher (71.4 $\pm$ 20 μg/mL) values [1]. The discrepancies between these studies may result from ethnic differences in the populations included, and/or differing methodologies.

Adiponectin influences atherosclerosis by changing the balance between atherogenic and anti-atherogenic lipoproteins in plasma, and by modulating cellular processes involved in foam cell formation. Adiponectin has different, favorable metabolic effects (i.e. greater insulin sensitivity, reduced visceral adipose mass, reduced plasma triglycerides, and increased HDL-C). It influences plasma lipoprotein levels by altering the levels and activity of key enzymes (lipoprotein lipase and hepatic lipase) responsible for the catabolism of triglyceride-rich lipoproteins and HDL-C [17]. In children, a positive correlation was detected between adiponectin and HDL-C levels [8, 18]. Bansal *et al*. detected a negative correlation between umbilical cord adiponectin and LDL-C levels, and no correlation between adiponectin and HDL-C levels in 74 healthy neonates [16]. In another study, no relationship was detected between serum adiponectin and cholesterol levels in 54 neonates [2]. In our study, we also detected significant positive correlations between neonatal adiponectin levels and TC, HDL-C and LDL-C levels. In 252 healthy, term neonates HDL-C levels were higher in female neonates than in male neonates [7]. In our study, cholesterol and triglyceride levels did not differ with respect to gender.

Studies in adults have shown that measurement of the thickness of the carotid intima-media complex provides an excellent marker of subclinical atherosclerosis [9]. However, McGill *et al*. showed that the first atherosclerotic lesions actually begin to develop in the abdominal aorta [10]. Jarvisalo *et al*. have shown that the measurement of aIMT is equally reproducible, but is more affected by early atherosclerosis than cIMT in childhood [11]. In studies investigating atherosclerosis in children and adults, measurement of cIMT was preferred. The relationship between cIMT and aIMT was investigated during autopsy performed in a total of 88 children (16 with hypercholesterolemia, 44 with type I diabetes and 28 healthy children). Measurement of aIMT was superior to cIMT in children with hypercholesterolemia and type I diabetes, although no superiority was seen in healthy controls; it was a sensitive, noninvasive marker for detecting subclinical atherosclerosis [11]. There are very few studies concerning aIMT measurement in newborns [12, 13]. Of these studies, both were performed in newborns with intrauterine growth restriction and were compared to healthy controls: Koklu *et al.* reported similar (0.39 ± 0.04 mm) mean aIMT values [12], whereas Skilton *et al*. reported higher (0.534 ± 0.006) aIMT values [13] when compared to the mean aIMT values (0.33 ± 0.03) in the present study.

To our knowledge, there have been no studies investigating the relationship between adiponectin levels and aIMT measurement in newborns. In 176 obese and 88 normal children, a negative correlation was detected between adiponectin levels and cIMT, and low adiponectin levels were associated with a high incidence of metabolic syndrome [8]. Increases in cIMT and decreases in adiponectin levels were demonstrated in obese children, and adiponectin was highlighted as a more sensitive marker than the other known risk factors for detecting early atherosclerosis in children with obesity [7, 19].

aIMT was significantly higher and anthropometric characteristics were significantly bigger in male neonates in the present study. The relationship between aIMT measurement and gender was investigated in only one study; however, beyond the first year of life aIMT was higher in males than in females [20]. Whether the aIMT values are affected by gender and anthropometric characteristics such as birth weight, length and head circumference in newborns, should be confirmed in further studies.

In children with obesity, a significant relationship was demonstrated only between adiponectin and HDL-C levels; there were no significant relationships present between other obesity markers, insulin resistance, anthropometric parameters and cIMT values [21]. In our study we did not find any relationship between adiponectin and aIMT values.

CONCLUSION

We conclude that cord blood adiponectin and aIMT values, reported for the first time in the present study, represent reference values in the early neonatal period. Cord blood adiponectin levels did not differ with respect to either aIMT or gender of the newborns, but aIMT was higher in male neonates in comparison to female neonates. The positive correlations between cord blood adiponectin levels and anthropometric parameters including birth weight, length, and head circumference, and blood lipids including TC, HDL-C and LDL-C in the present study indicate that further studies are required to demonstrate the exact relationship and clinical importance of adiponectin metabolism during the neonatal period.

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