Adiponectin in Human Cord Blood: Relation to Fetal Birth Weight and Gender

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Adiponectin is an adipocyte-derived plasma protein with insulin-sensitizing and antiatherosclerotic properties. The aim of this study was to examine whether adiponectin is present in human fetal blood, to define its association with fetal birth weight, and to evaluate whether dynamic changes in adiponectin levels occur during the early neonatal period. Cord blood adiponectin levels were extremely high (71.0 ± 21.0 μg/ml; n = 51) compared with serum levels in children and adults and positively correlated with fetal birth weights (r = 0.4; P < 0.01). No significant differences in adiponectin levels were found between female and male neonates. In addition, there was no correlation between cord adiponectin levels and maternal body mass index, cord leptin, or insulin levels. Cord adiponectin levels were significantly higher compared with maternal levels at birth (61.1 ± 19.0 vs. 17.6 ± 4.9 μg/ml; P < 0.001; n = 17), and no correlation was found between cord and maternal adiponectin levels. There were no significant differences between adiponectin levels at birth and 4 d postpartum (61.1 ± 19.0 vs. 63.8 ± 22.0 μg/ml; n = 17). These findings indicate that adiponectin in cord blood is derived from fetal and not from placental or maternal tissues. The high adiponectin levels in newborns compared with adults may be due to lack of negative feedback on adiponectin production resulting from lack of adipocyte hypertrophy, low percentage of body fat, or a different distribution of fat depots in the newborns. (J Clin Endocrinol Metab 88: 5656–5660, 2003)

A DIPONECTIN IS A plasma protein that has been discovered a few years ago (1–4). It is produced exclusively and abundantly in adipose tissue and circulates at relatively high (micrograms per milliliter) concentrations (1–5). Recent findings have indicated that adiponectin has antiatherogenic properties (6–8). Other studies have demonstrated that it has antiinflammatory effects like inhibition of endothelial NF-κB signaling (8) and suppression of phagocytic activity and TNF-α production in macrophages (9).

Adiponectin is a member of the growing group of adipose secreted proteins, sometimes described as adipocytokines. As opposed to other members in this group like leptin, TNF-α, and IL-6, adiponectin plasma levels in obese subjects are, paradoxically, lower than in nonobese subjects (5). Consistent with these data, adiponectin gene transcription is decreased in adipocytes from obese subjects (10). Conversely, weight reduction in obese individuals is accompanied by an increase in plasma adiponectin concentrations (11, 12), suggesting that fat mass may exert a negative feedback on adiponectin production. Increasing evidence supports the notion that adiponectin is an important regulator of insulin sensitivity. In humans, an inverse relationship between insulin resistance and plasma adiponectin levels has been observed (13, 14). Furthermore, linkage studies have demonstrated a strong association between insulin resistance and a site at chromosome 3q27, where the adiponectin-encoding gene is located (15). Moreover, genetic variations in the adiponectin gene are associated with increased risk of type 2 diabetes (16). Finally, administration of adiponectin to normal or obese mice improved glucose tolerance and insulin sensitivity (17–19).

In addition to regulation of whole-body metabolism, numerous studies have explored the role of adipocytokines and particularly leptin in intrauterine growth. The findings that leptin is present in cord blood and its levels are positively correlated with the neonate’s birth weight (20–22), as well as the high levels of expression of both leptin and leptin receptors in the placenta and fetus, suggest that leptin plays a key role in fetal development (23, 24).

At the present, no information is available in respect to adiponectin in intrauterine growth. In this view the aim of the present study was to examine whether adiponectin is present in cord blood and to define the association between this protein and fetal birth weight, gender, leptin, and insulin. In addition, we have studied whether dynamic changes of adiponectin levels occur in healthy neonates during early neonatal life.

Subjects and Methods

Subjects

The present study was comprised of two sub-studies.

Study 1. This study was designed to evaluate adiponectin levels in cord blood and to determine its relation to birth weight, gender, leptin, and insulin. Cord blood was obtained from 51 neonates at the time of delivery and before the separation of the placenta. Mean (±sd) maternal age, body mass index (BMI) and gestational week of delivery were 31.5 ± 5.3 yr, 28.0 ± 4.0 kg/m², and 39.5 ± 1.6, respectively. Gestational age at delivery was calculated according to the last menstrual period and confirmed by ultrasound examination during the first trimester or early second trimester. All women delivered at term for three women that delivered between 34 and 36 completed weeks of gestation. All the mothers were healthy and their pregnancies were without complications

Abbreviations: BAT, Brown adipose tissue; BMI, body mass index; CV, coefficient of variation.
such as gestational diabetes or pregnancy-induced hypertension. Thirty-eight (74.5%) neonates were born by normal vaginal delivery, four by vacuum extraction (7.8%), one by forceps extraction (1.9%), and eight by elective cesarean section (15.6%). The indications for cesarean section were either maternal request or history of previous cesarean section. Twenty-eight of the neonates were females (54.9%), and 23 (45.1%) were males. Mean birth weight of the newborns was 3269 ± 675 g. Birth weight percentiles were calculated according to published standards (25). Six of the neonates (11.7%) were above the 90th percentile defined as large for gestational age; all weighed more than 4000 g. Eight of the neonates (15.6%) were below the 10th percentile defined as small for gestational age; all weighed less than 2750 g. All neonates were normal and did not suffer from any complication.

Study 2. This study was designed to compare maternal and newborn adiponectin levels and to assess the alterations in newborns’ adiponectin levels during the first days after birth. Seventeen healthy newborns, delivered by cesarean section, and their mothers were included in the study; nine of the neonates were females, and eight were males. Mean birth weight was 3194 ± 519 g. Mean maternal age, BMI, and gestational week of delivery were 31.2 ± 4.0 yr, 28.2 ± 4.8 kg/m², and 39.3 ± 0.7, respectively. All women were healthy; none had pregestational or gestational diabetes in this or any previous pregnancies. The women were invited for elective cesarean section; the indications for the operation were maternal request, breech presentation, or previous cesarean section. All mothers had an uneventful operation and a postoperative period without complications. All neonates were healthy without any complication during and after delivery. Blood samples were obtained from the mothers 1 d before the operation. Immediately after the delivery of the newborn, a blood sample was taken from the cord blood before the separation of the placenta. A second blood sample was taken from the newborns on the fourth day after birth.

The Ethical Committee of the Sheba Medical Center approved the protocols of both studies. Informed consent was obtained from all mothers before their inclusion in the study.

Adiponectin, leptin, and insulin measurements

Serum samples, obtained by centrifugation of cord blood or maternal and newborn venous blood, were immediately frozen and stored at −30 C until further analysis. Adiponectin and leptin were determined using RIA kits (Linco Research, Inc., St. Charles, MO). The sensitivity of the adiponectin assay was 1 ng/ml, and the interassay coefficient of variation (CV) ranged from 6.9–9.3%. The sensitivity of the leptin assay was 0.5 ng/ml, and the interassay CV ranged from 3–6%. Insulin was measured by a chemiluminescent immunometric method (Immuliite 2000, Diagnostic Products Corp., Los Angeles, CA). The sensitivity of the assay was 2 mU/liter, and the interassay CV ranged from 4–5%.

Statistical analysis

The data are expressed as means ± sd. Mean serum adiponectin concentrations and other measures of the groups were compared by Kruskal-Wallis one-way ANOVA on ranks. Pearson’s correlation coefficient was used to determine the relationship between continuous variables.

Results

Adiponectin, leptin, and insulin levels in cord blood

As shown in Fig. 1A, adiponectin was detectable in the cord blood of all 51 neonates in concentrations ranging from 25–118 μg/ml. The mean and median levels were 71.0 ± 21.0 μg/ml and 70.0 μg/ml, respectively. Adiponectin levels were positively correlated with birth weights (r = 0.4; P < 0.01; Fig. 1A) but were not correlated with maternal BMI or cord leptin or insulin levels. Leptin was detectable in cord blood of all neonates in concentrations ranging from 1.3–41.0 ng/ml (Fig. 1B). The mean and median levels were 10.1 ± 7.8 ng/ml and 8.1 ng/ml, respectively. As previously demonstrated (20), there was a positive correlation between leptin levels and birth weights (r = 0.3; P < 0.03; Fig. 1B), maternal BMI (r = 0.3; P < 0.02), and cord insulin serum levels (r = 0.5; P < 0.001). Insulin levels in cord blood ranged from 2–39 mU/liter. The mean and median levels were 6.4 ± 6.5 mU/liter and 4.5 mU/liter, respectively. Cord insulin levels were positively correlated with maternal BMI (r = 0.3; P < 0.02). No correlation between cord insulin levels and birth weights was found.

Comparison of adiponectin and leptin levels in female and male neonates

Adiponectin and leptin were found to be gender-dependent in adults (5, 26) and children (27). When comparing the 28 female neonates to the 23 male neonates included in this study, no significant differences were found in cord serum levels of adiponectin, leptin, and insulin (Table 1) as well as in birth weights (Table 1) or maternal parameters (data not shown).

Comparison of adiponectin and leptin levels at delivery and 4 d postpartum

Previous studies have demonstrated that the high leptin levels in cord blood are due to both fetal and placental production (21, 23, 24). To get further insight into the origin of adiponectin in cord blood, its levels were evaluated in a second group of 17 neonates at birth and 4 d postpartum. In addition, cord blood and maternal adiponectin levels were compared in this group. As depicted in Fig. 2A, cord blood adiponectin levels were significantly higher compared with maternal adiponectin levels at birth (61.1 ± 19.0 vs. 17.6 ± 4.9 μg/ml; P < 0.001), and no correlation was found between
TABLE 1. Comparison between female and male cord blood levels of adiponectin, leptin, and insulin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Females (n = 28), mean ± SD (range)</th>
<th>Males (n = 23), mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3130 ± 657 (1325–4895)</td>
<td>3438 ± 672 (1577–4280)</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>71.4 ± 20.0 (27.0–99.0)</td>
<td>70.5 ± 22.9 (25.0–118.0)</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>11.1 ± 8.7 (1.3–41.0)</td>
<td>8.7 ± 6.4 (1.6–29.0)</td>
</tr>
<tr>
<td>Insulin (mU/liter)</td>
<td>6.4 ± 5.3 (2.0–21.7)</td>
<td>6.2 ± 7.9 (2.0–39.2)</td>
</tr>
</tbody>
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![Fig. 2](https://academic.oup.com/jcem/article-abstract/88/12/5656/2661460)

The present study provides evidence that high adiponectin levels are present in cord blood at birth and correlate with fetal birth weight. The mean concentration (71 ± 21 µg/ml) and the range (25–118 µg/ml) of adiponectin levels in cord blood are severalfold higher than those reported so far in children or adults (mean concentration lower than 10 µg/ml and range between 1 and 20 µg/ml) (5, 26–28).

The source of adiponectin in cord blood is still unknown. Our findings suggest that it is derived mainly from fetal tissues and not from maternal or placental tissues. Several lines of evidence support this notion. First, no correlation was found between maternal adiponectin serum concentrations and adiponectin levels in cord blood. In addition, adiponectin levels in cord blood were significantly higher compared with maternal adiponectin levels. Therefore, the possibility that a facilitated transport of adiponectin from the maternal blood through the placenta is responsible for the high levels of the hormone in cord blood seems unlikely.

Discussion

The mechanisms of regulating plasma adiponectin levels in the fetus are not yet known. Adiponectin seems to be produced and secreted exclusively by adipocytes. However, an increase in fat mass leads to down-regulation of adiponectin (5), whereas body weight reduction in obese (11) and as well as in normal-weight subjects (31) results in elevation of adiponectin concentrations, suggesting that fat mass may exert a negative feedback on adiponectin production. The lack of such negative feedback could contribute to hyperadiponectinemia in newborns. Indeed, the percentage of body fat is significantly lower in newborns (13%) compared with children or adults (25–30%) (32).

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proliferator-activated receptor-γ agonists like troglitazone and rosiglitazone, which markedly increase the number of newly differentiated small adipocytes, in conjunction with body weight gain (29, 39). Thus, the low fat mass and the prevalence of small adipocytes in newborns’ adipose tissue may explain the extremely high levels of adiponectin in cord blood. Because both adiponectin (13, 14) and adipocyte hypertrophy (40) are negatively correlated with insulin resistance, we can speculate that the increased population of small adipocytes in fetal adipose tissue and the high levels of adiponectin may account for the high insulin sensitivity in newborns (41). Whether adiponectin plays an important role in insulin sensitivity in neonates like in adults remains to be determined. Finally, it is very well known that human infants possess, in addition to the energy-storing white adipose tissue, a specialized type of fat, the brown adipose tissue (BAT). Recently, the adiponectin gene was found to be highly expressed in BAT in rats and mice, and it is under strikingly different hormonal regulation than in white adipose tissue (42, 43). Additional studies are required to determine whether BAT adiponectin may contribute to the high levels observed in human cord blood.

Another interesting finding in this study is the positive correlation between adiponectin and neonatal birth weight. Our null hypothesis was that a negative correlation exists between adiponectin and birth weight based on the negative correlation between obesity and adiponectin, which is well established in adults (5, 11). However, we found a statistically significant positive correlation (r = 0.4; P < 0.01) between adiponectin and birth weight. This positive correlation is compatible with the suggestion that in newborns the adipose tissue is composed mainly from small newly differentiated adipocytes that lack the factors that are responsible for inhibition of adiponectin production. This situation is analogous to the increase in plasma adiponectin along with weight gain after rosiglitazone or troglitazone treatment, due to increased number of newly differentiated adipocytes (29, 39). In addition, recent studies have demonstrated that adiponectin secretion from omental but not from sc adipocytes is negatively correlated with BMI (44). As newborns, opposed to adults, have mainly sc adipose tissue, it is likely that the lack of negative correlation between adiponectin in cord blood and birth weight is due to the different distribution of adipose tissue depots in newborns compared with adults.

Adiponectin levels were found to be gender-dependent in adults (5, 26); therefore, we compared its levels between female and male neonates. We found no differences in adiponectin levels (P < 0.87) between the two groups. The difference between the sexes in adults may reflect an effect of the sex hormones (45, 46) or other mediators that are either inactive, subtle, or absent in newborns. We did not find a significant difference in leptin levels between female and male neonates, although the levels were higher in the female neonates. Previous studies have been controversial with regard to this finding (47–50).

In summary, adiponectin is present in the cord blood of human fetuses at levels that are extensively higher than measured in children or adults. Because we are just beginning to understand the physiological role of adiponectin in adults, it is rather difficult to speculate what is the role of this protein in fetuses and neonates. Nevertheless, adiponectin may have additional roles in intrauterine development, as previously described for other adipocytokines like leptin (51, 52). Data concerning the source and the regulation of this protein in the fetus, its physiological role, and its putative role in pathological processes are yet to be clarified.

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References

by increased adiponectin plasma levels and reduced nonoxidative glucose metabolism. J Clin Endocrinol Metab 58:1748–1752


38. Soriguer Escoté FJ, Esteva de Antonio I, Tinazhones FJ, Pareja A 1996 Adipose tissue fatty acids and size and number of fat cells from birth to 9 years of age: a cross-sectional study in 96 boys. Metabolism 45:1395–1401


60. Schubring C, Siebler T, Kratzsch J, Englaro P, Blum WF, Triep K, Kiese W 1999 Leptin serum concentrations in healthy neonates within the first week of life: relation to insulin and growth hormone levels, skinfold thickness, body mass index and weight. Clin Endocrinol (Oxf) 51:199–204


64. Schubring C, Siebler T, Kratzsch J, Englaro P, Blum WF, Triep K, Kiese W 1999 Leptin serum concentrations in healthy neonates within the first week of life: relation to insulin and growth hormone levels, skinfold thickness, body mass index and weight. Clin Endocrinol (Oxf) 51:199–204