CLINICAL STUDY

Leptin and adiponectin concentrations in intrauterine growth restricted and appropriate for gestational age fetuses, neonates, and their mothers

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Abstract

Objective: Leptin and adiponectin are two adipocytokines that play a critical role in the control of energy balance and metabolism as well as in conditions, such as insulin resistance, inflammation, and the development of the metabolic syndrome in adult life. Leptin has been associated with asymmetric intrauterine growth restriction (IUGR). The aim of this study was to investigate the perinatal implication of leptin and adiponectin in IUGR.

Design: Leptin and adiponectin were measured in the plasma of 40 mothers, in the umbilical cord (UC) blood of their 20 appropriate for gestational age (AGA) and 20 IUGR singleton, full-term fetuses, and neonates on day 1 (d1) and day 4 (d4) of life postnatally.

Methods: Serum leptin and adiponectin levels were measured by RIA. Serum cortisol levels were measured with an electrochemiluminescence immunoassay.

Results: Leptin and adiponectin serum levels were higher and lower respectively in IUGR (mean $\pm$ S.E.M., 32.5 ± 3.8 and 5.4 ± 0.9 μ g/l respectively) compared with AGA (20.4 ± 2.1 and 11.8 ± 1.3 μ g/l respectively) mothers ($P < 0.05$), although body mass index did not differ between these two groups. Leptin levels positively correlated with adiponectin levels in the AGA ($r = 0.547$, $P < 0.05$) but not in the IUGR mothers. UC, d1, and d4 leptin and adiponectin levels did not differ between IUGR and AGA groups. UC were significantly higher than d1 leptin levels ($P < 0.05$) in the IUGR group but not in the AGA group.

Conclusions: The increased UC leptin levels compared with d1 in IUGR fetuses might be directly and/or indirectly related to the subsequent development of insulin resistance in these neonates. This pathologic situation seems to be related to a specific profile of increased leptin and decreased adiponectin levels in IUGR mothers indicating a genetic predisposition for the development of insulin resistance.

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Introduction

Leptin, a 167-amino acid protein, the product of the obese (ob) gene, is mainly produced by adipocytes (1, 2). Leptin is a satiety factor that regulates body weight by inducing a decrease in food intake and an increase in energy consumption (3, 4). Plasma leptin concentrations reflect the amount of adipose tissue and they positively correlate with the insulin resistance (5–7). Furthermore, leptin is a pleiotropic hormone and cytokine involved in a number of diverse physiological processes, such as regulation of endocrine functions, inflammation, immune response, reproduction, and angiogenesis (8, 9). Adiponectin is a recently described 244-amino acid protein highly expressed in human adipose cells (10, 11). It is found in the circulation at varying molecular weight forms resulting from multimerization (12). It modulates insulin action and

exerts anti-atherogenic and anti-inflammatory effects (12–14). The adiponectin levels are inversely proportional to body fat content and correlate negatively with the insulin resistance (12, 15, 16). Altered secretion of both adipocytokines, through their implication in obesity, insulin resistance, and inflammation, may contribute to the development of the metabolic syndrome. Furthermore, adipocytokines (and particularly leptin) have been implicated in intrauterine growth (17).

Intrauterine growth restriction (IUGR) results in significant perinatal and long-term complications, including increased neonatal mortality and morbidity (18) and higher risk for developing metabolic syndrome later in life (19–21). Adverse prenatal environment influences fetal growth and induces thrifty developmental responses in the fetus. These responses may be inappropriate for postnatal environment of nutritional

excess and they might predispose to disease (22). Animal studies demonstrated that unfriendly environments such as those related to IUGR may lead to permanent regulatory adaptation of the hypothalamic–pituitary–adrenal axis (23). In humans, low birth weight is linked to increased fasting cortisol concentrations (24).

To investigate the hypothesis that leptin and adiponectin are implicated in the IUGR condition, we studied these adipocytokines in IUGR fetuses and neonates and their mothers in comparison with appropriate for gestational age (AGA) controls and their mothers.

Subjects and methods

Subjects

The Ethics Committee of our teaching hospital approved the study protocol. All included mothers provided signed informed consent before enrollment. Forty pregnant women giving birth consecutively to either 20 AGA or 20 asymmetric IUGR full-term singleton infants with a birth weight below the 3rd customized centile were included in the study. The gestation related optimal weight (GROW) computer-generated program (25) was employed to calculate the customized centile for each pregnancy, taking into consideration significant determinants of birth weight, as maternal height and booking weight, ethnic group, parity, gestational age, and gender (26).

The asymmetric IUGR was associated with preeclampsia, gestational hypertension, and chronic diseases (severe anaemia, type I diabetes mellitus, hepatitis B, and rheumatoid arthritis) in 5, 10, and 5 cases respectively. All IUGR cases were accompanied by small and infarcted placentas of small weight ranging from 255 to 400 g. During the whole duration of pregnancy, 5 mothers reported smoking 10 cigarettes per day. Doppler studies of the uterine and umbilical arteries performed serially in the IUGR group every 10–15 days, starting from the 32nd gestational week, were at the upper physiological limits for gestational age in 13 cases, while in the remaining 7 cases they showed increased impedance to flow. Doppler studies of middle cerebral arteries revealed resistance at the lower physiological limits for gestational age in all IUGR cases, indicating initiation of the blood flow redistribution process. Amniotic fluid as assessed by the largest fluid column on the vertical plane was decreased (<2 cm) in all IUGR cases.

In the AGA group, mothers were healthy and were either non-smokers or abstained from smoking during pregnancy. Moreover, placentas in the AGA group were normal in appearance and weight. Tests for congenital infections were negative in all women of both groups and neonates showed no symptoms of intrauterine infections or signs of genetic syndromes. In all neonates, 1- and 5-min Apgar scores were ≥ 8 . Clinical

characteristics of participating infants and their mothers are presented in Table 1.

Protocol

Blood was collected in sterile, pyrogen-free tubes from: i) mothers during the first stage of labor or before receiving anesthesia in cases of elective cesarean section, ii) the doubly clamped umbilical cords (UC) reflecting fetal state, and iii) neonates on *post partum* day 1 (d1) and day 4 (d4), characterizing transition and stabilization to extrauterine life respectively. Blood was immediately centrifuged after clotting and the supernatant serum was kept frozen at -80°C until assay. Ponderal index ($\text{PI} = \text{weight}(\text{kg})/\text{height}(\text{m})^3$), an anthropometric marker employed to define fetal growth, was calculated (27).

Hormone measurements

Serum leptin levels were measured by employing an RIA kit (Linco Research Inc., St Charles, MO, USA). The minimum detectable concentration, intra- and inter-assay coefficients of variation were $0.001\text{ }\mu\text{g/l}$, 3.6%, and 8.2% respectively. Serum adiponectin levels were measured by employing an RIA kit (Linco Research Inc.). The minimum detectable concentration, intra-, and interassay coefficients of variation were 0.1 mg/l , 3.9%, and 8.5% respectively. Serum cortisol levels were measured by employing an electrochemiluminescence immunoassay (Roche Co). The intra- and interassay coefficients of variation were 1.1–1.3 and $<8\%$ respectively.

Statistical analysis

Leptin, adiponectin, and cortisol values were normally distributed in the studied groups. Wherever needed, unpaired samples *t*-test and ANOVA for repeated measures followed by Fisher's *post hoc* test were employed. Results were expressed as mean $\pm$ S.E.M. Regression analysis was applied to detect positive

Table 1 Demographic data of appropriate for gestational age (AGA) and intrauterine growth restricted (IUGR) mother/infant pairs expressed as mean $\pm$ S.E.M.

	IUGR	AGA	P values
Maternal age (years)	30.8 ± 6.9	31.2 ± 4.3	NS
Maternal height (cm)	161 ± 6	167 ± 6	<0.05
Maternal weight (kg)	59.4 ± 8.5	60.3 ± 8.9	NS
Maternal BMI (cm/kg)	22.9 ± 3.1	21.4 ± 2.5	NS
Gestational age (days)	265.6 ± 9.7	272.3 ± 7.1	<0.05
Parity (first/other)	17/3	9/11	<0.05
Neonatal weight (kg)	2.37 ± 0.26	3.16 ± 0.26	<0.05
Male/female fetuses	7/13	8/12	NS
Mode of delivery (VD/ECS)	8/12	14/6	<0.05

VD, vaginal delivery; ECS, elective cesarean section; NS, non-significant.

or negative correlations. The level of statistical significance was set at $P < 0.05$. Statistical assessment was conducted using STATISTICA 6.0 software package (Tulsa, OK, USA) (28).

Results

Maternal, fetal, and neonatal hormones levels

Leptin, adiponectin, and cortisol levels of the mothers of the IUGR and AGA fetuses are reported on Table 2. Leptin (Fig. 1) and adiponectin (Fig. 2) levels were higher and lower respectively in IUGR when compared with AGA mothers ($P < 0.05$). There was no statistically significant difference in leptin and adiponectin levels between smoker and non-smoker IUGR mothers. The ratio of leptin to BMI and that of adiponectin to BMI was higher and lower respectively in IUGR when compared with AGA mothers (leptin to BMI: 1.41 ± 0.17 and 0.96 ± 0.1 respectively, $P < 0.05$; adiponectin to BMI: 0.24 ± 0.04 and 0.56 ± 0.06 respectively, $P < 0.05$), although maternal BMI did not differ between IUGR and AGA mothers.

Leptin, adiponectin, and cortisol levels in UC, d1, and d4 are reported on Table 3. UC, d1, and d4 leptin and adiponectin levels did not differ between IUGR and AGA groups. UC leptin levels were significantly higher than d1 leptin levels ($P < 0.05$) in the IUGR but not in the AGA group, while in both groups they were higher than d4 leptin levels ($P < 0.05$). No difference was observed between leptin levels of male and female fetuses and neonates. The UC cortisol levels were significantly higher than d4 cortisol levels ($P < 0.05$) in the IUGR but not in the AGA group. The ratio of cortisol to neonatal body weight was significantly higher in IUGR when compared with AGA in fetuses (UC) only (mean $\pm$ S.E.M., 4.45 ± 0.93 vs 2.87 ± 0.53 , $P < 0.05$) but not in neonates (d1 and d4).

Correlations among maternal, fetal, and neonatal hormone levels and anthropometric measurements

In the IUGR group, maternal adiponectin positively correlated with d1 adiponectin levels ($r = 0.504$, $P < 0.05$). In the AGA, but not in the IUGR group, maternal leptin positively correlated with maternal

Table 2 Leptin, adiponectin, and cortisol levels in intrauterine growth restricted (IUGR) and appropriate for gestational age (AGA) mothers expressed as mean $\pm$ S.E.M.

	Leptin ($\mu\text{g/l}$)	Adiponectin (mg/l)	Cortisol ($\mu\text{g/dl}$)
IUGR	32.5 ± 3.8	5.4 ± 0.9	33.3 ± 3.8
AGA	20.4 ± 2.1	11.8 ± 1.3	33.8 ± 2.7
<i>P</i> values	< 0.05	< 0.05	NS

NS, non-significant.

Figure 1 Box and whiskers plot presentation of maternal leptin levels. Each box represents the median concentration with the 5th and 95th percentile ranges. The upper and lower whiskers represent the range.

adiponectin levels ($r = 0.547$, $P < 0.05$). No correlation was found between maternal and UC leptin and adiponectin levels in any group.

In the IUGR group, UC adiponectin positively correlated with d1 adiponectin levels ($r = 0.863$, $P < 0.05$). In the same group, d1 leptin levels positively correlated with PI ($r = 0.5$, $P < 0.05$), whereas d4 leptin levels positively correlated with gestational age ($r = 0.597$, $P < 0.05$), neonatal weight ($r = 0.662$, $P < 0.05$), and length ($r = 0.577$, $P < 0.05$).

In the AGA group, UC leptin positively correlated with d1 ($r = 0.749$, $P < 0.05$) and d4 leptin ($r = 0.784$, $P < 0.05$) levels. In the same group, UC leptin levels

Figure 2 Box and whiskers plots presentation of maternal adiponectin levels. Each box represents the median concentration with the 5th and 95th percentile ranges. The upper and lower whiskers represent the range.

Table 3 Leptin, adiponectin, and cortisol levels in intrauterine growth restricted (IUGR) and appropriate for gestational age (AGA) umbilical cord (UC), d1, and d4 expressed as mean $\pm$ S.E.M.

	IUGR	AGA
Leptin-UC (μ g/l)	12.5 $\pm$ 5.3* [†]	9.6 $\pm$ 1.9 [†]
Leptin-d1 (μ g/l)	1.7 $\pm$ 0.2	3.6 $\pm$ 0.9
Leptin-d4 (μ g/l)	2.0 $\pm$ 0.2	2.7 $\pm$ 0.3
Adiponectin-UC (mg/l)	19.9 $\pm$ 3.1	27.3 $\pm$ 2.1
Adiponectin-d1 (mg/l)	17.0 $\pm$ 3.4	26.0 $\pm$ 2.2
Adiponectin-d4 (mg/l)	20.4 $\pm$ 2.6	22.8 $\pm$ 2.2
Cortisol-UC (μ g/dl)	10.6 $\pm$ 2.2 [†]	9.1 $\pm$ 1.6
Cortisol-d1 (μ g/dl)	8.6 $\pm$ 1.6	7.0 $\pm$ 1.4
Cortisol-d4 (μ g/dl)	7.1 $\pm$ 1.0	5.5 $\pm$ 0.9

*Indicates statistically significant difference within the same group (either IUGR or AGA) between UC and d1 values at the level of $P < 0.05$. [†]Indicates statistically significant difference within the same group (either IUGR or AGA) between UC and d4 values at the level of $P < 0.05$.

positively correlated with gestational age ($r = 0.619$, $P < 0.05$), d1 leptin levels positively correlated with neonatal weight ($r = 0.447$, $P < 0.05$), and PI ($r = 0.552$, $P < 0.05$) and d4 leptin levels positively correlated with gestational age ($r = 0.729$, $P < 0.05$).

Discussion

We found that neonatal (d4) leptin levels were lower than fetal (UC) ones in both IUGR and AGA groups. It has been reported that in AGA and small for gestational age (SGA) infants, fetal leptin levels decreased within the first *post partum* days, regardless of birth body weight (29, 30). Leptin levels reflect the amount of adipose tissue (29) and during pregnancy, fetal leptin levels increase in parallel with its development (32, 33). The decrease of leptin levels during the first days of life might reflect the transitory loss of weight during that period of life (31). Leptin is involved in the regulation of body weight through a feedback loop between adipose tissue and the satiety center, resulting in decreased food intake and increased energy expenditure (31). Thus, the *post partum* leptin decrease limits neonatal body energy expenditure by conserving the nutritional reserves for growth and development (34), while it stimulates feeding behavior (35). Although leptin has been shown to have proinflammatory properties (36), the increased levels of this adipocytokine in the UC compared with d1 and d4 levels cannot be attributed to inflammation because the studied neonates, and presumably the fetuses, presented no sign of inflammation. No difference was observed between leptin levels of male and female fetuses and neonates of either studied group. In the past, certain studies have suggested that leptin levels are higher in female fetuses, while others did not confirm this finding (29, 32, 37, 38). Further studies with increased number of cases might be useful to clarify whether the known gender dimorphism in leptin levels found later in life might exist during intrauterine and neonatal life (39, 40).

In this study, leptin levels did not differ between IUGR and AGA fetuses or neonates. In the past, Harigaya *et al.* reported no significant differences in leptin levels among AGA, SGA, and large for gestational age infants after 48 h of life (29), while certain studies reported lower leptin levels in SGA than in AGA infants (38, 41, 42). In these studies, the authors examined SGA rather than IUGR infants, while in our study IUGR infants had a birth weight below the 3rd customized centile as calculated by the GROW computer-generated program (25). This selection bias might result in the discrepancies observed in leptin levels. Percent body fat is reduced in IUGR when compared with AGA neonates, while intra-abdominal adipose tissue is not reduced in the former when compared with the latter (43). It is possible that the lack of difference in leptin levels between IUGR and AGA in this study might reflect a more active leptin production from intra-abdominal adipose tissue in IUGR than in AGA fetuses. Intra-abdominal adipose tissue, as well as leptin, is implicated in the development of insulin resistance. The latter has been linked to IUGR pathophysiology (44, 45). In a recent study of 6- to 8-year-old SGA and AGA children, the former were more insulin resistant than the latter (46). In another study, metabolic syndrome was observed in 2.3% of adults born SGA versus 4% of adults born AGA (47). In the AGA group, fetal leptin levels correlate with neonatal d1 and d4 leptin levels. This does not happen in the IUGR group, probably because the fall of leptin levels between UC and d4 is more pronounced than that in the AGA group. Eventually, this is due to the *post partum* disappearance of the intrauterine stress factor that is presumably responsible for the IUGR state. Indeed, the ratio of UC cortisol to birth weight is higher in IUGR than AGA neonates, while in extrauterine life (d1 and d4) this ratio does not differ between them. Cortisol levels should be considered as a reliable stress index.

In the present study, in the IUGR group, neonatal d4 leptin levels correlated with gestational age, while in the AGA group both fetal and neonatal d4 leptin levels correlated with gestational age. These correlations reflect the increase of adipose tissue along with the gestational progress, particularly during late gestation in AGA (48), and possibly a *post partum* catch-up in IUGR group. In the past, in AGA, a positive correlation has been shown between fetal leptin levels and gestational age (49, 50). Thus, it seems that maturity, as indicated by gestational age, is a significant determinant of leptin levels in fetuses and neonates, also according to previous studies performed in preterm and term infants (29, 32, 51).

Adiponectin levels did not differ from fetal to neonatal d1 and d4 in IUGR and AGA groups, as well as between these two groups in all time points studied. Similarly, Martinez *et al.* did not find any difference in adiponectin levels between SGA and AGA infants (38) and Kotani *et al.* did not find different adiponectin levels

in neonates (postnatal day 3–7) compared with those in cord blood (52).

In our study, maternal adiponectin and leptin levels were lower and higher respectively in IUGR compared with AGA mothers. This finding might reflect the state of inflammation and chronic stress in IUGR mothers, eventually predisposing them to the development of insulin resistance. Mise *et al.* postulate that elevated maternal plasma leptin concentration in preeclampsia is caused mostly by the augmentation of placental production of leptin in response to hypoxia (53). Reduced uteroplacental blood flow, leading to fetoplacental hypoxia, is important in the pathogenesis of IUGR (54). On the other hand, maternal leptin levels positively correlated with maternal adiponectin levels in the AGA but not in the IUGR group, possibly indicating the crucial role of leptin for the development of insulin resistance in the mothers of IUGR. Thus, it seems that these two adipocytokines are interrelated in AGA but not in IUGR mothers. Given the anti-inflammatory role of adiponectin (55), in contrast to the pro-inflammatory role of leptin (36), this correlation may reflect a compensatory mechanism to counteract directly and/or indirectly the inflammatory state of parturition, which is functional in AGA but not in IUGR cases. The higher leptin-to-BMI and the lower adiponectin-to-BMI ratios in IUGR when compared with AGA mothers, although their BMI did not differ, might imply that there is a predisposition of the IUGR mothers' adipocytes to produce more leptin and less adiponectin. Therefore, it is possible that IUGR fetuses bear a genetic predisposition to increased leptin and decreased adiponectin production.

We conclude that the relatively increased leptin levels in IUGR fetuses compared with d1 IUGR neonates might be directly and/or indirectly related to later development of insulin resistance. This pathologic situation seems to be related to a specific maternal profile of increased leptin and decreased adiponectin levels in IUGR mothers indicating a genetic predisposition for the development of insulin resistance. Because increased percent adipose tissue correlates well with insulin resistance and preeclampsia, it would be useful to propose to pregnant IUGR mothers to pay attention to their weight because this could be detrimental for them and their offspring.

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