

Changes in the interrelationship between leptin, resistin and adiponectin in early neonatal life

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1. ABSTRACT

The aim of this study was to investigate the interrelationship between leptin, adiponectin and resistin in the fetal and early postnatal period and the association of these hormones with anthropometric and metabolic indexes. Serum concentrations of leptin, adiponectin and resistin were measured in maternal and neonatal circulation at delivery and on the 3rd day after birth in 40 healthy newborns and their mothers. Serum leptin levels were significantly higher in fetuses than in newborn infants on 3rd day after delivery, whereas concentration of adiponectin and resistin were maintained in either maternal and neonatal circulation after delivery. Leptin serum concentrations correlated with those of adiponectin in the fetal circulation, but not in neonatal life. On the other hand no correlation was found between leptin and resistin levels in cord blood, whereas a positive correlation between leptin and resistin concentrations was present in the neonatal circulation on 3rd day. Fetal leptin, adiponectin and resistin levels are largely independent of maternal influences and immediately after birth, important changes in the relation among adipokines occurred compared to intrauterine life.

2. INTRODUCTION

Adipose tissue is an endocrinologically active tissue that releases peptides known as adipokines in response to specific extracellular stimuli or changes in metabolic status. It is now clear that adipokines-hormones are critically important in endocrine and metabolic regulation. Leptin, adiponectin and resistin are adipokines derived from adipose tissue which play a role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues in both human and animals. Leptin acts to regulate food intake and energy expenditure via the hypothalamus (1). Serum leptin concentration was shown to be increased in humans with obesity, insulin resistance and dyslipidemia, suggesting the development of "leptin resistance" (2). In adult life, leptin is inversely related to adiponectin concentrations. Adiponectin is a adipocyte-derived protein with anti-inflammatory and anti-atherogenic activity. In adults it correlates with body weight and is inversely associated to obesity, type 2 diabetes, inflammation and endothelial dysfunction (3). Resistin is another protein secreted by adipocytes which is implicated in the impairment of glucose tolerance (4); it

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decreases insulin sensitivity (5). Resistin is increased with diet-induced obesity. Hyperleptinemia, hyperresistinemia and hypo adiponectinemia during adulthood play a major part in the development of metabolic syndrome, characterized by hypertension, obesity, and insulin resistance.

Leptin, adiponectin and resistin are known to be produced within the intrauterine environment and have been suggested to be implicated in the regulation of placental growth, development and function and in fetal growth. Maternal plasma leptin levels rise in the first trimester in human pregnancy and high levels are been found in the fetal circulation near term. Recent studies have demonstrated a strong correlation between leptin levels in fetal circulation and fetal body weight gain. The contribution of placental production to fetal leptin levels is controversial (6,7). Adiponectin is actively secreted by human placenta and fetal membranes (8), however maternal plasma adiponectin concentrations are not elevated in human pregnancy (9). Adiponectin is present in cord blood and in neonatal life its concentrations are significantly higher than in adult life (10-12). Moreover, in contrast to adults, adiponectin levels in the fetus are unrelated to the degree of adiposity (13).

Although many studies have investigated leptin, some have studied adiponectin and very few resistin concentrations in human pregnancy or in the early postnatal life, no information is available in respect to the dynamic changes of the relationship between these adipokines in maternal and fetal circulation during pregnancy and in the early post-natal period. The aim of the present study was to explore the interrelationship of leptin, adiponectin and resistin in the fetal and early postnatal period and the association of these hormones with anthropometric and metabolic indexes at birth and after birth in term healthy newborns.

3. MATERIALS AND METHODS

3.1. Patients

Forty fetuses delivered while two of the authors were the obstetrics on call by elective cesarean section between 37 and 41 weeks of gestation (39.5 ± 2.0 week) from uncomplicated pregnancy with an appropriate weight for gestational age (3361 ± 336 g) and with an uneventful postnatal course were included in the study (Table 1). All the mothers had singleton pregnancies; indication for elective cesarean section included maternal (previous uterine surgery, severe myopia) and obstetrical indications (breech or shoulder presentation, placenta praevia). None of the mothers was taking any medication except for iron supplement and all the mothers had a pregravidic BMI <25 and a body weight gain during pregnancy between 9 and 14 kg (mean 12.1 ± 2.4 kg), which did not exceed 20% of pregravidic weight. All the mothers had a 50-g oral glucose tolerance test performed at 26-28 weeks of gestation resulted within the range of normality (<140 mg/dl).

All the newborns were breastfed and serum

bilirubin and glucose levels were within the range of normality. The anthropometric variables of the newborn studied were: birth weight, birth length, abdominal and circumference at birth, ponderal index at birth, neonatal weight at the 3rd days of life. Glucose metabolism (fasting blood glucose) and lipid profile (by total cholesterol, HDL-C and LDL-C, and triglyceride concentrations) were assessed in cord blood. Blood pressure at upper and lower limbs were measured in all newborns at the 3rd days of life. Placental weight at delivery was also recorded.

This protocol was approved by the ethics committee of University 'La Sapienza', all the mothers have provided informed consent.

3.2. Sample collection

Maternal venous blood samples were obtained at elective caesarean section in absence of labor and at 72 hours from delivery. Samples were immediately centrifuged at 650 g for 15 min at 4°C. The serum was divided into aliquots and stored at -80°C until assayed. Samples of cord blood was obtained from umbilical vein at elective cesarean section delivery. Neonatal blood samples were collected at the 3rd day of life in conjunction with a routine morning blood draw. Umbilical and neonatal blood samples were processed and stored in the same manner as the maternal blood samples.

3.3. Biochemistry

Routine clinical methods were used to estimate values in blood for fasting blood glucose, total triglycerides, total cholesterol, HDL-C, LDL-C.

3.4. Adipokines assay

Leptin levels were measured by using the enzyme-linked immunosorbent assay (ELISA) kit from Diagnostic Biochem, Canada as reported (12). The sensitivity of the kit was 1 ng/ml and the intra- and inter-assay coefficients of variation obtained for leptin were 7.4% and 9.6% respectively.

Adiponectin levels were measured by using the human adiponectin ELISA kit (BioVendor Laboratory Medicine Inc., Biovendor GmbH, Germany) as reported (12). With this method, the intra- and inter-assay coefficients of variation obtained for adiponectin were 6.2% and 7.2% respectively. The analytical limit of detection of the kit was 7 microg/ml while the assay sensitivity was 210 microg/ml.

Resistin was measured by using the human resistin ELISA kit (BioVendor Laboratory Medicine, Inc., Biovendor GmbH, Germany). The sensitivity of the kit was 0.1 ng/ml with the analytic limit of detection of 0.033 ng/ml. The intra- and inter-assay coefficients of variation obtained for adiponectin were 5.8% and 8.1% respectively.

3.5. Data analysis

All demographic, biochemical, anthropometric and hemodynamic data are expressed as mean \pm SD. Hormonal data are expressed as mean \pm SEM. Statistical analysis was performed by using Sigmastat Software 3.1 (Systat Software

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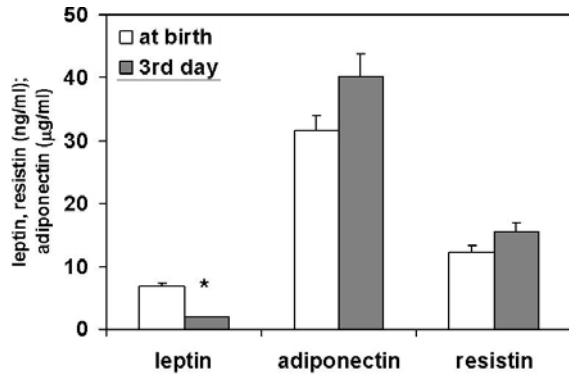


Figure 1. Histograms representing concentration of leptin, adiponectin and resistin in neonatal circulation at birth (cord blood) and on the 3rd day of life. Data are shown as mean \pm SEM. *, $P < 0.01$.

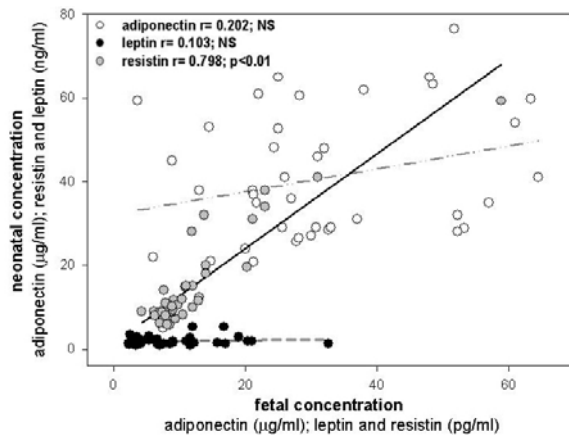


Figure 2. Correlation between concentration of leptin, adiponectin and resistin in fetal (cord blood) and neonatal (on 3rd day) circulation

Inc. Point Richmond, CA, USA) and all values were analyzed with analysis of variance (ANOVA) followed by Student t test whenever appropriate. Differences in adipokines concentrations in neonatal plasma at the different time-points were sought using analysis of variance for repeated measurements, followed by Duncan's test if a significant F ratio was obtained ($p < 0.05$). Spearman's correlation coefficient was used to evaluate the interrelationship between different metabolic hormones and between the adipokines and anthropometric, demographic, or clinical parameters. However, the P values of the correlation were not adjusted for multiple testing. The Mann-Whitney U test was also used to assess the difference in various adipokines between the sexes. Statistically significant anthropometric parameters associated with adipokines were also subjected to multivariate stepwise regression analysis. Statistical significance was set at $p < 0.05$.

4. RESULTS

Anthropometric characteristics of neonates and their mothers are shown in Table 1 and 2. Mean adipokines

concentrations in serum of newborns collected at birth and on the 3rd day after birth are shown in Figure 1. Maternal concentrations of adipokines are shown in Table 3.

4.1. Leptin

In neonatal circulation leptin serum concentration was significantly ($p < 0.01$) lower than in cord blood at birth, being 1.9 ± 0.3 ng/ml and 6.8 ± 1.6 ng/ml, respectively (Figure 1). Similarly a significant decrease ($p < 0.01$) was found in maternal leptin concentration between samples collected at delivery and 72 hours after delivery (Table 3). Non correlation was found between maternal and fetal leptin concentration at the time of delivery.

Multivariate regression analysis showed that fetal leptin levels were positively associated with female gender but not with anthropometric characteristics nor with fetal metabolic parameters. In female ($n = 21$) leptin concentration were significantly higher than in male newborns ($n = 19$) either at birth and at 72 hours from birth (Table 4; $p < 0.05$). No significant differences were found in birth weight, length, gestational age and serum biochemical values either at birth or after birth between male and female newborns (Table 1). No correlation was found between serum concentration of leptin in newborn circulation at birth and after birth (Figure 2)

4.2. Adiponectin

Serum concentrations of adiponectin were 31.5 ± 3.8 microg/ml in cord blood and 40.3 ± 4.9 microg/ml in the neonatal circulation at the 3rd day of life (Figure 1). No changes in adiponectin levels were found in maternal circulation after delivery (Table 3). No correlation was found between serum concentration of adiponectin in newborn circulation at birth and after birth (Figure 2). Multivariate regression analysis showed that either fetal and neonatal adiponectin levels were not associated with gender, gestational age or any newborn anthropometric or metabolic characteristics. However, mean adiponectin levels in female were slightly higher than in male newborns at the 3rd day of life (Table 4). In female neonates, indeed, serum adiponectin concentration was increased by about 40% compared to cord blood. Overall fetal adiponectin levels did not correlate with maternal adiponectin concentrations at the time of delivery.

4.3. Resistin

Mean serum resistin concentrations in newborns were 12.3 ± 2.5 ng/ml and 15.5 ± 3.5 ng/ml at birth and after birth, respectively (Figure 1). In newborns resistin levels at birth and at the 3rd day of life were significantly correlated ($r = 0.798$; $P < 0.01$; Figure 2). Concentrations of resistin in maternal circulation are shown in Table 3. At the time of delivery fetal and maternal resistin levels were not significantly correlated. Multivariate analysis showed that both fetal and maternal resistin concentration at delivery was positively associated with birth weight ($r = 0.566$; $p < 0.01$) but not with gender. Fetal resistin levels correlated negatively with newborn lipid profile ($r = -0.635$; $p < 0.05$), but not with glucose levels. Serum concentrations of resistin in maternal circulation at the time of delivery and at the 3rd day after delivery were significantly correlated ($r = 0.488$; $p < 0.05$).

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Table 1. Anthropometric, and clinical characteristics of newborns

	Total (n=40)	Male (n=19)	Female (n=21)
Gestational age (wk)	38.5 ± 2.0	39.2 ± 2.1	38.1 ± 2.4
birth weight (g)	3161 ± 336	3243 ± 303	3112 ± 357
weight (g) on 3 rd day	3092 ± 356	3159 ± 206	2923 ± 381
birth length (cm)	48.5 ± 1.5	49.1 ± 0.2	48.1 ± 1.6
CC (cm)	34 ± 1	34 ± 1	34 ± 1
AC (cm)	32 ± 1	32 ± 2	32 ± 1
placental weight (g)	498 ± 72	519 ± 79	485 ± 66
serum glucose at birth (mg/dl)	61 ± 11	73 ± 6	57 ± 10
pH	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1
Hb (g/dl)	15.2 ± 3.4	16.1 ± 3.1	14.9 ± 3.7
PO2 (mmHg)	28 ± 9	27 ± 11	28 ± 9
PCO2 (mmHg)	41 ± 6	41 ± 4	42 ± 6
Total cholesterol (mmol/L)	1.7 ± 0.5	1.6 ± 0.4	1.7 ± 0.5
HDL (mmol/L)	1.1 ± 0.3	1.1 ± 0.4	1.0 ± 0.2
LDL (mmol/L)	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2
Triglycerides (mmol/L)	0.33 ± 0.1	0.35 ± 0.1	0.31 ± 0.1
Systolic PA (mmHg)	71 ± 10	73 ± 9	69 ± 11
Diastolic PA (mmHg)	46 ± 12	45 ± 7	46 ± 14

Data are expressed as mean ± SD

Table 2. Anthropometric and clinical characteristics of pregnant women

maternal BMI	26.2 ± 2.9
mother's BMI before pregnancy	21.4 ± 2.2
mother's BMI on 3 rd day	24.5 ± 3.0
weight gain (%) in pregnancy	15.7 ± 4.3
weight loss (%) on 3 rd day	6.4 ± 1.9
serum glucose (mg/dl)	80.7 ± 11.8
Systolic BP at delivery (mmHg)	119 ± 13
Diastolic BP at delivery (mmHg)	72 ± 8
Systolic BP on 3 rd day (mmHg)	115 ± 10
Diastolic BP on 3 rd day (mmHg)	69 ± 8

Data are expressed as mean ± SD

Table 3. Adipokines concentration in maternal circulation at delivery and 72h after delivery.

	At delivery	72 h after delivery	p
leptin (ng/ml)	15.7 ± 2.2	6.1 ± 1.4	0.01
adiponectin (microg/ml)	15.0 ± 2.1	11.2 ± 1.2	ns
resistin (ng/ml)	6.7 ± 0.8	7.1 ± 1.4	ns

Table 4. Adipokines concentration in serum circulation of male and female newborns at birth (cord blood) and 72 hours after birth (newborn).

	MALE		FEMALE	
	Cord blood	newborn	Cord blood	newborn
leptin (ng/ml)	4.3 ± 0.9	1.4 ± 0.2 ¹	11.1 ± 2.4 ²	3.3 ± 0.4 ^{1,2}
adiponectin (microg/ml)	29.4 ± 5.7	32.6 ± 7.0	32.7 ± 5.2	46.3 ± 6.4
resistin (ng/ml)	9.4 ± 0.8	13.6 ± 4.2	14.1 ± 3.9	17.2 ± 5.5

Data are expressed as mean ± SE. ¹ p < 0.01 vs cord blood; ^{1,2} p < 0.05 vs male

4.4. Interrelationship between adipokines

In newborns, at the 3rd day after birth, changes in the interrelationship between adipokines compared with fetal life were found. Leptin serum concentrations correlated with those of adiponectin in the fetal circulation ($r = 0.602$; $p < 0.01$), but not in the early neonatal period (Figure 3). On the other hand no correlation was found between leptin and resistin levels in cord blood, whereas a positive correlation between leptin and resistin concentrations was present in the neonatal circulation at 72h from birth ($r = 0.506$; $p < 0.01$; Figure 4). Adiponectin concentration did not correlate with resistin levels in either fetal or neonatal circulation.

5. DISCUSSION

This study confirms that resistin, adiponectin and leptin are detectable in all term infants and did not correlate

with maternal metabolic hormones. Moreover it provides evidence of the occurrence of important changes in the interrelationship between adipokines in the early neonatal period compared to fetal life. In our study, the levels of serum leptin were significantly higher in cord blood than in newborn infants at the 3rd day of life, whereas concentration of adiponectin and resistin did not change after birth. In accordance with previous studies we found that, despite the dramatic decrease of circulating leptin that occurred after birth, leptin and adiponectin concentrations in newborn were still higher than those reported in adults (14,15).

We compared the levels of adiponectin, leptin and resistin between male and female infants at birth and after birth, but, in contrast to adult life (14) only leptin levels were found to be gender dependent in either fetal and neonatal period, with female having higher concentrations of

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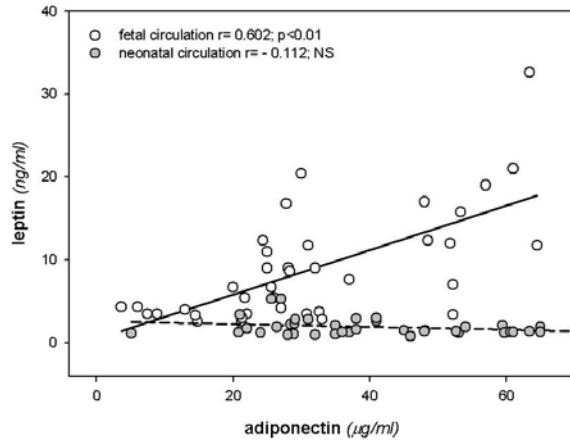


Figure 3. Correlation between leptin and adiponectin levels in fetal (cord blood) and neonatal (on 3rd day) circulation.

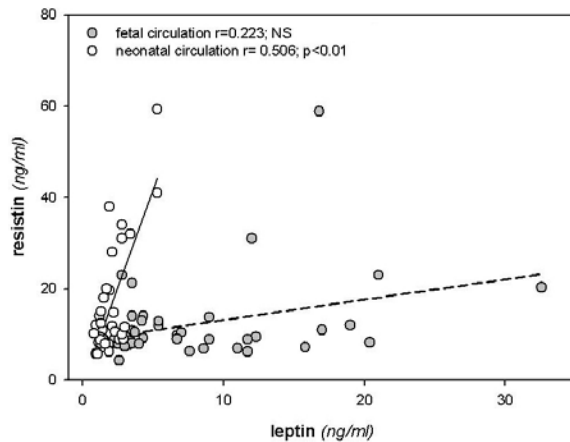


Figure 4. Correlation between leptin and resistin concentrations in fetal (cord blood) and neonatal (on 3rd day) circulation.

circulating leptin than male. despite the fact that infants in both sexes have similar birth weights and length weights. The levels of adiponectin in the fetus were not affected by gender, accordingly to previous reports (13). Interestingly, however, we observed that adiponectin concentration in the early postnatal period was higher in female than in male infants, with a significant increase of circulating adiponectin of about 40% after birth in female, not found in male infants. Our results did not correspond with previous studies on adiponectin serum levels in infants, where other investigators failed to demonstrate such a difference (16,17). The discrepancy might have been related to the lower serum glucose levels found in our series in female than in male newborns at birth. Since it has been reported that adiponectin levels are inversely correlated to insulin levels in early postnatal period (18), increased concentration of adiponectin in female infants may be related to decreased insulin concentration after birth. However, other mechanisms may be involved. Placental factors, such as cortisol, may inhibit adiponectin secretion by fetal tissues during intrauterine life.

After birth the removal of the placenta might allow a higher secretion of adiponectin in female than in male infants due to a different body composition; boys have relatively higher lean mass than girls at birth, or androgen concentrations. Adiponectin secretion is downregulated by androgens (19) and androgen concentrations are higher in male than in female newborns (20). As far as resistin levels are concerned, a correlation between fetal and neonatal levels was observed, confirming that biological mechanisms involved in the regulation of resistin secretion during intrauterine life can persist in the early postnatal period. Negative correlation between resistin concentration and lipid profile in neonates suggests that resistin might affect energy homeostasis through regulation of fatty acid metabolism (21). In the fetal circulation, leptin, adiponectin and resistin did not correlate significantly with birth weight, placental weight, anthropometric measures or metabolic parameters, consistently with some reports (13,22,23) but in contrast with others (17, 24,25). What is of interest is that, after birth, in neonatal circulation the relationship among adipokines changes. During fetal life, as already reported (12), a positive correlation was observed between leptin and adiponectin, in contrast to adults, when an inverse correlation is present (26). After birth, when leptin concentration in neonatal circulation decreased dramatically, the correlation between leptin and adiponectin levels was lost. No other correlations were observed among adipokines in the fetal circulation nor with maternal concentrations of resistin, adiponectin and leptin. Our results suggested that plasma leptin correlated significantly with serum resistin in the early postnatal period, in contrast with fetal period. This correlation was also observed by Ng *et al* (16) suggesting that the regulation of metabolic pathways is operational before birth but changes in the metabolic hormones occurs after birth. The contribution of intrauterine environment to the fetal concentration of adipokines has to be established. The relations with adiposity observed in adults do not appear to be present during fetal life. Although this and other studies (16,27) have provided evidence that adipokines may interact *in utero* and in the early postnatal period, the results of our study suggest that leptin, resistin and adiponectin do not seem to regulate fetal growth, at least not in a direct way. This may suggest that different biological mechanisms are involved in production or regulation of these adipokines in fetal and adult individuals. Recently we reported that glucocorticoids affect significantly leptin and adiponectin levels in fetal circulation and the relationship between these adipokines (12). Additional studies are required to delineate the mechanisms and the interrelationship between these hormones to fully understand their roles in regulating growth and development during intrauterine and early postnatal life.

6. ACKNOWLEDGEMENTS

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