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ORIGINAL ARTICLE

Decreased leptin concentration in neonates is associated with enhanced postnatal growth during the first year

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Abstract Leptin regulates maternal metabolism and fetal growth by reducing food intake and increasing energy expenditure, particularly during the third trimester. In this study, we investigated the relationships between leptin and growth, and explored the longitudinal change of leptin in early postnatal life. A total of 58 infants were categorized according to gestational length and birth weight. Arterial blood samples were taken within 24 hours (Day 1), and on Days 4 and 7 of life. Plasma leptin levels were measured by commercial human leptin enzyme immunometric assay. The average serum leptin level declined in the first week of life. There was a positive correlation between leptin level and body weight on Day 4. Neonates with leptin decrease between Day 1 and Day 4 had better weight gain at one year old, and the hospital stay day was shorter. Furthermore, the full feeding days and the duration of feeding priming and full feeding days in the leptin decrease group were less than in the leptin increase group. Serum leptin was significantly decreased and positively correlated with neonates' body weight gain in the first week of life. A rapid decline in serum leptin after birth is associated with greater future weight gain and physiological advantage for infants' life.

Introduction

Leptin is a 16 KDa hormone that is secreted from adipose tissue and influences metabolism by reducing nutrient intake and increasing energy expenditure [1,2]. Leptin also acts as a negative feedback adipostatic signal by promoting satiety, energy expenditure, fat oxidation, and by inhibiting lipogenesis [3]. Body weight is regulated by a feedback loop

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in which peripheral signals report nutritional information to an integration center in the hypothalamus [4]. In children, the leptin level closely correlate with body weight and body fat mass [5]. Several studies have demonstrated a positive correlation between leptin concentration of cord blood and birth weight of neonates [5–7]. The leptin could serve as a physiologic signal of nutritional status during the periods of food deprivation in childhood [8]. In addition, previous study showed that the leptin of neonates usually declined at six days of life [9]. However, the functional role of leptin during the neonatal period after birth is still unclear.

The specific aim of our study was to evaluate the dynamic changes of leptin concentration and analyze the correlation between weight gain and leptin level in the first year after birth.

Patients and methods

Patient population and demographic record

Fifty-eight newborn infants in Shin-Kong Memorial Hospital were enrolled in this study during a period of 6 months in 2004. The inclusion criteria were neonates with respiratory distress admitted in the neonatal intensive care unit. We excluded patients with chromosomal anomalies, congenital heart disease and major organ anomalies. Gestational age was determined by maternal menstrual history, antenatal ultrasound, and Ballard assessment [10]. Perinatal-neonatal characteristics and morbidities including number of hospital days and the use of ventilator were recorded. The chronologic ages were adjusted. Maternal charts were reviewed, including maternal weight, length, age, delivery mode, and placental weight. Antenatal steroids consisted of two doses of 12 mg of betamethasone 24 hours apart. We also prospectively recorded the weight of infants 1 year of age.

With regard to the difference of leptin level between Day 1 and Day 4 after birth, some neonates showed a decrease, while the others displayed an increase. We divided the patients into leptin increase and decrease groups and prospectively followed up their anthropometric parameters to the age of 1 year.

Sample collection and serum leptin analysis

Arterial blood was drawn within 24 hours after birth. Two additional blood samplings were performed, on Days 4 and 7 after birth. Sera were obtained by centrifugation, frozen immediately, and stored at −20 °C until additional analysis. The leptin levels were measured by commercial human leptin TiterZyme enzyme immunometric assay kit (Assay Designs, Inc., MI, USA). Samples were analyzed in one assay with duplication. The interassay and intraassay coefficients of variation were 10% and 5%, respectively.

Statistical analyses

Values are expressed as mean ± standard deviation (SD), median ± intraquarter range or frequency (percentage). An independent two-sample *t*-test was used for statistical analysis. The Pearson correlation method was used to evaluate the correlation between dynamic profile and body weight, and Mann-Whitney U test and median test were used to compare between leptin decrease and increase groups. A p value of less than 0.05 was considered significant. Analyses were performed using the SPSS statistical package (version 12.0, SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the demographic and clinical characteristics of the study population. The longitudinal profiles of the plasma leptin levels and the change in body weight during first week of postnatal life are summarized in Table 2. The average serum leptin levels were 602.4 960.9 pg/ml, 297.8 476.4 pg/ml, 237.9 415.1 pg/ml on Days 1, 4, and 7, respectively. The median and IQR values of male leptin levels were 84.1 433.5 pg/ml, 110.2 138.4 pg/ml, 67.5 133.0 pg/ml on Days 1, 4, and 7; female leptin levels were 322.1 973.1 pg/ml, 105.5 543.1 pg/ml, 100.7 399.3 pg/ml on Days 1, 4, and 7. There were no significant differences of leptin ($p = 0.062$, 1.000, 1.000) within sex. There was a positive relationship between serum leptin level and body weight between day 1 and Day 4 (Table 2). Moreover, there

Table 1 Clinical characteristics of the study population.

Parameters	Data	Parameters	Data
Gestational age (wk)	33.8 ± 3.1	Antenatal steroid	31 (62.0%)
Birth weight (g)	2127.9 ± 627.9	Infants whose mothers were treated (*n*)	1: 1.15
Birth length (cm)	43.7 ± 5.5	Male:Female ratio	23 (44.2%)
BMI at 1 yr (kg/m^2)	10.6 ± 1.4	Caesarean section (*n*)	20.1 ± 15.8
Placental weight (g)	658.8 ± 225.7	Patients on mechanical ventilation	31 (62.0%)
Apgar scores	**Data**	**Hospital days (d)**	**Data**
At 5 min	6.9 ± 1.7	Day 1	14 (26.9%)
At 1 min	8.1 ± 1.4	Day 5	4 (7.7%)
Arterial cord blood		Day 14	2 (3.8%)
pH	7.3 ± 0.10		
Base excess	−3.2 ± 4.2		

Results expressed as mean ± standard deviation or frequency (percentage).

Table 2 Dynamic change of leptin level and the body weight in the first week of postnatal life.

	Day 1	Day 4	Day 7
Birth weight (g)	2090.6 ± 597.8*	2014.7 ± 619.2*	1911.8 ± 519.1
Leptin (pg/ml)	602.4 ± 960.9	297.8 ± 476.4	237.9 ± 415.1
N	52	38	38

Results expressed as mean ± standard deviation.
* $p < 0.05$ by Pearson correlation method.

was no significant correlation between serum leptin level and body weight on Day 7.

We separated patients into leptin increase and leptin decrease groups according to changes of leptin between Days 1 and 4 after birth. Table 3 summarizes the clinical characteristics of these infants. There was no significant difference in gestational age and birth weight between these two groups. Serum leptin concentration on Day 1 in the leptin decrease group was higher than in the leptin increase group. The body weight gain at one year old in the leptin decrease group was higher than that in the leptin increase group. However, the maternal BMI and body length at one year old were not statistically different between the two groups. In addition, the change of serum leptin between Days 1 and 7 after birth was not significantly associated with body weight gain and body length at 1 year of age (Table 4).

Since patients in the serum leptin decrease group had good body weight gain at 1 year of age. The significant correlation between hospital days and the change of serum leptin concentration between Days 1 and 4 is shown in Fig. 1. The greater the decline of serum leptin level meant that there were fewer hospitalization days. Furthermore, there were significant differences in full feeding days and duration of feeding priming to full feeding between leptin increased and decreased groups (Table 5). In feeding priming, there was no difference between the two groups. The leptin-decreased group has fewer full feeding days and shorter feeding duration than the leptin increased group.

Discussion

Energy homeostasis is accomplished through a highly integrated and redundant neurohormonal system that minimizes the impact of short-term fluctuations in energy balance of fat mass [11]. Assessing the dynamics of the leptin system rather than relying on a steady-state plasma leptin measurement can reveal the regulatory or dynamic effects that leptin might have in the early development of changes in body weight [12]. In our study, the leptin concentration in some neonates (23/34, 70.6%) decreased dramatically within the first 4 days after birth. The leptin levels could reflect the nutritional status of the neonates. Infants experience the physiologic decrease of body weight during the first week of life due to fluid loss and reduced nutritional intake. For neonates to make up their weight loss, increasing food intake is necessary. Low leptin levels in the brain during weight loss increase activity of anabolic neural pathways that stimulate eating and suppress energy expenditure [3]. Thus, rapid decrease in leptin levels after birth could be mediated by the period of starvation after birth and weight reduction. In our study, the postnatal change in leptin level was related to neonatal weight change in first 4 days after birth. Leptin level decline rapidly and dramatically after birth, and this transformation might be an important stimulus for the onset of feeding or energy uptake [13]. Leptin can inhibit food intake and induce thermogenesis. These leptin-mediated responses may have evolved as a protection against the threat of starvation by limiting energy utilization and increasing energy efficiency [14]. Leptin acting as an appetite-regulating protein could explain the leptin decrease group having fewer full feeding days and shorter duration from priming to full feeding compared with the increase group. Those infants with more declined leptin level had shorter hospital stay. Our results reveal better weight gain in the first year of life in the leptin decrease group.

Multiple studies report the involvement of leptin in various peripheral tissues, exerting its effects ranging from association with the autonomic nervous system to metabolism, linear growth, and involvement in transplantation and oncologic disease [15]. This abnormality suggests that the threshold for the various responses to leptin is set at different levels. It may indicate that neurons expressing

Table 3 Demographic data of leptin increase and leptin decrease groups between days 1 and 4 after birth.

	Leptin increase (*n*)	Leptin decrease (*n*)	*p* value
BW at 1 yr (kg)	8.0 ± 0.8 (7)	9.3 ± 1.0 (9)	0.012*
BL at 1 yr (cm)	40.6 ± 3.2 (7)	41.2 ± 4.2 (9)	0.749
GA (wk)	32.2 ± 2.8 (11)	33.9 ± 3.3 (23)	0.153
Birth weight (g)	1855.9 ± 452.1 (11)	2188.9 ± 624.6 (23)	0.222
Maternal BMI (kg/m^2)	24.4 ± 2.9 (10)	27.3 ± 4.3 (23)	0.062
Leptin-D (pg/ml)[a]	76.0 ± 112.79 (11)	−280.2 ± 652.3(23)	<0.001*

BL = birth length; BMI = body mass index; BW = body weight; GA = gestational age.
Results expressed as mean ± standard deviation.
* $p < 0.05$ by Mann-Whitney U test.
[a] Leptin-D indicates the difference of leptin between Days 1 and 4. The data of Leptin-D was shown by median ± intraquarter range and tested by median test.

Table 4 Demographic data of leptin increase and leptin decrease groups between days 1 and 7 after birth.

	Leptin increase (*n*)	Leptin decrease (*n*)	*p* value
BW at 1 yr (kg)	8.8 ± 0.8 (5)	8.5 ± 0.8 (10)	0.440
BL at 1 yr (cm)	41.2 ± 3.1 (5)	43.5 ± 4.6 (10)	0.371
GA (wk)	33.1 ± 2.2 (12)	33.2 ± 3.3 (23)	0.824
Birth weight (g)	1925.4 ± 231.9 (12)	2080.2 ± 607.2 (23)	0.694
Maternal BMI (kg/m^2)	25.3 ± 2.7 (11)	26.0 ± 4.0 (22)	0.603
Leptin-D (pg/ml)[a]	40.4 ± 118.2 (12)	−187.9 ± 652.0 (23)	<0.001*

BL = birth length; BMI = body mass index; BW = body weight; GA = gestational age.
Results expressed as mean ± standard deviation.
*$p < 0.05$ by Mann-Whitney U test.
[a] Leptin-D indicates the difference of leptin between Days 1 and 7. The data of Leptin-D was shown by median ± intraquarter range and tested by median test.

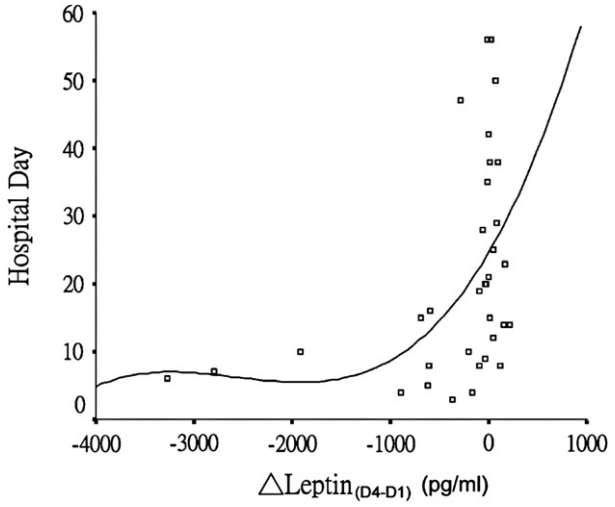

Figure 1. Scatter plot of hospitalization days versus the difference between leptin levels from day 4 to day 1 after birth (leptin levels $_{D4\text{-}D1}$) after excluding one extreme data set. ($n = 34$, $r = 0.198$, $p = 0.027$).

leptin receptor activate different pathways in response to different concentrations of leptin [16]. The discrepancy of Day 1 leptin between the leptin increase group and the leptin decrease group may reflect the different antepartum or intrapartum stress perception by both the mothers and infants and have initiated the different responses.

Table 5 Difference of feeding profile in leptin increase and decrease groups on days 1 to 4 interval.

	Leptin increase ($n = 12$)	Leptin decrease ($n = 24$)	*p* value
Feeding priming (d)	2.5 ± 1.1	2. 2 ± 0.8	0.361
Full feeding (d)	11.0 ± 1.8	7.3 ± 3.5	0.016*
Duration of feeding profile	8.5 ± 4.8	5.1 ± 3.2	0.021*

Duration of F-P means the days from feeding priming to full feeding. Results expressed as mean ± standard deviation.
* $p < 0.05$ by Mann-Whitney U test.

Leptin may interact with appetite-regulating system in the ventromedial hypothalamic arcuate nucleus by decreasing biosynthesis and secretion of neuropeptide Y, which is a potent stimulator of appetite [2]. These results demonstrated shorter hospital days and the better weight gain at the age of one year as serum leptin declined in the first 4 days after birth. The low leptin levels in cord blood strongly predicated high rates of weight gain in infancy and catch-up growth [9]. The leptin level could reflect the mechanisms that influence postnatal levels of satiety, peripheral metabolism, and weight gain. We speculate that a rapid fall of leptin levels in the first 4 days after birth might be an important stimulation for feeding behavior and energy uptake and be necessary for rapid neonatal growth.

In our study, there was positive correlation between serum leptin and body weight on day 4 and no significant correlation on Day 1. Due to transplacental effect of leptin, leptin level on Day 1 was influenced by neonates' mothers. The half-life of recombinant human leptin in lean adults is about 3 hours and longer in obese adults [17,18]. It is reasonable to assume that the maternal leptin was cleared out by neonates on Day 4.

In conclusion, the rapid decline of leptin levels in the first 4 days after birth might be strongly associated with weight gain by increasing the appetite to accelerate the early postnatal growth in the first year.

Ethics approval

This work was supervised by Ethics Committee and Institutional Review Board of Shin-Kong Medical Center. The parents of all subjects were informed of the purpose of the study and gave consent as required by the investigator.

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