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The effect of insulin, leptin, adiponectin, ghrelin levels in cord blood on growth in the first two years

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Abstract

Objective: The main hormones and adipokines that regulate growth, energy metabolism and adipogenesis in the intrauterine period are insulin, leptin, ghrelin, and adiponectin. Changes in these hormones and adipokines may affect weight gain, obesity and metabolic syndrome in advanced ages. In this study, it was aimed to investigate the relationship between insulin, leptin, ghrelin, adiponectin levels in the cord blood of term newborns and growth in the first two years of age.

Methods: Term newborns in our hospital between May 2019 and October 2019 were included in the study. Insulin, glucose, ghrelin, leptin and adiponectin levels were studied in the umbilical cord blood of 80 newborns. The growth of 44 of the 80 newborns included in the study was monitored until the age of two years.

Results: The relationship between insulin, ghrelin, leptin and adiponectin levels in the cord blood of 44 newborns included in the study with growth up to two years of age was investigated. A positive correlation was found between the insulin level in the cord blood and birth weight, birth head circumference, and the weights at the 12th and 24th months of life. A negative correlation was found between the level of ghrelin in the cord blood and the weights at the 6th and 24th months of life. A positive correlation was found between the level of adiponectin in the cord blood and the weight in the 6th month of life. There was no significant correlation between cord leptin level and anthropometric measurements in the first two years of age.

Conclusion: While the levels of insulin and adiponectin in the cord blood were positively correlated with the weight in the first two years of life, they were negatively correlated with the ghrelin level in the cord blood. The level of leptin in cord blood did not correlate significantly with the weight in the first two years of life.

Keywords: Cord blood, insulin, ghrelin, adiponectin, leptin, growth.

Introduction

Fetal growth is a complex process regulated by genetics, maternal factors, intrauterine environment, and maternal and fetal hormones.[1] During fetal life, the body goes through critical developmental stages with lasting and lifelong effects, and changes in the intrauterine environment can program future adipose tissue and metabolic disorders.[2] Identifying these high-risk infants may help develop preventive strategies to reduce childhood obesity and cardiometabolic disorders. Cord blood adipocytokines such as leptin and adiponectin are used as objective markers to predict future obesity.[3]

The main axis in the regulation of fetal growth is glucose-insulin-insulin-like growth factor-1.[4] During pregnancy, leptin levels also regulate fetal growth and development. It has been shown that leptin levels are regulated by insulin in the early stages of pregnancy and are in an adipoinsular axis balance throughout fetal life.[5] Ghrelin increases the secretion of growth hormone, maintains a positive energy balance, and increases body weight and lipid accumulation.[6] Adiponectin modulates

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the action of insulin and has antiatherogenic and anti-inflammatory effects. Adiponectin levels are inversely proportional to the amount of body fat and negatively correlate with insulin resistance.[7,8] Alteration of insulin and adiponectin secretion may contribute to the development of metabolic syndrome.[9]

Since these adipokines are associated with fetal growth and adipose tissue, they are considered to be determinants of long-term metabolic health after birth and as indicators of fetal metabolic health. These adipokines in cord blood may be useful in the early recognition of problems related to postnatal growth and metabolic health.[10] In this study, we aimed to investigate the relationship between the levels of insulin, leptin, ghrelin, and adiponectin in the cord blood of term newborns with growth in the first two years of age and to investigate their effects on the weight in early childhood.

Methods

Eighty term newborns (gestational age ≥38 weeks according to the last menstrual period) who were born alive in Manisa Celal Bayar University Faculty of Medicine Hafsa Sultan Hospital between May 2019 and October 2019 were included in the study. Multiple pregnancies, premature birth (gestational age <38 weeks), stillbirths, pre-pregnancy diabetes in the mother, gestational diabetes, hypertension and infants of mothers with premature rupture of membranes were excluded from the study. After birth, newborns were examined and weight, height and head circumference measurements were recorded. After the umbilical cord was clamped after delivery, blood sample was taken from the umbilical cord, and the serum sample was centrifuged at 5000 rpm for 10 minutes and the serum sample was stored at -80°C in MCBU Hafsa Sultan Hospital Biochemistry Laboratory until leptin, adiponectin, and ghrelin levels were studied. After all blood samples were collected, insulin, ghrelin, leptin and adiponectin levels in the separated serum samples were studied with ELISA kits.

Eighty infants included in the study were followed up in the neonatal outpatient clinic. However, the growth and development of 44 of the 80 newborns included in the study could be followed up to the age of two. The weight, height, and head circumference were measured at the 6th, 12th, and 24th months, and percentile values were calculated. Insulin, ghrelin, leptin and adiponectin levels in cord blood and anthropometric measurements during the first 2 years of life were compared.

Statistical analysis

Statistical evaluation of the data was carried out using the "SPSS (Statistical Package for Social Sciences) 25.0 for Windows" (IBM Corp., Armonk, NY, USA) program. Data were presented as minimum, maximum, and mean ± standard deviation. Spearman's correlation test was used to determine the relationship between insulin, ghrelin, leptin and adiponectin levels in cord blood and anthropometric measurements at 6th, 12th and 24th months of life. $p<0.05$ was considered statistically significant.

Results

Forty-four infants were included in the study. When the demographic characteristics of the infants were examined, the mean gestational age was 38.23±1.03 weeks. Twenty-four of the infants included in the study were girls and 20 were boys. The mode of delivery was cesarean section in 42 (95.4%) cases and vaginal in 2 (4.6%) cases. The demographic characteristics of the infants are shown in **Table 1**.

Table 1. Demographic characteristics of infants.

	Infants included in the study (n=44)
Birth weight (g)	3204.65±435.74
Birth length (cm)	49.27±1.98
Head circumference at birth (cm)	35.54±1.98
Birth weight by week of gestation	
- SGA	0 (0%)
- AGA	40 (90.9%)
- LGA	4 (9.1%)
Gender	
- Female	24 (54.5%)
- Male	20 (45.5%)
Mode of delivery	
- Vaginal	2 (4.5%)
- Cesarian section	42 (95.5%)
Gestational age (weeks)	38.23±1.03
Apgar score, mean (1-minute)	8
Apgar score, mean (5-minute)	9
Duration of exclusive breastfeeding (month)	4.54±2.16
Total breastfeeding time (month)	12.58±8.01
Transition time to additional food (month)	5.83±0.47

Table 2. Antenatal characteristics of infants.

	Infants included in the study (n=44)
Maternal age	32.56±5.90
Number of pregnancies of the mother, n	3
Number of births of the mother, n	3
Body weight before pregnancy (kg)	71.25±12.59
Body weight at the end of pregnancy (kg)	83.33±12.25
Weight gained during pregnancy (kg)	5.37±12.08
Mother's height (cm)	161.37±6.22
Maternal body mass index (kg/cm^2)	27.30±4.58
According to body mass index	
- Normal (18.5–24.9)	20 (45.4%)
- Overweight (25–29.9)	14 (31.8%)
- Obese (>30)	14 (31.8%)

The mean maternal age of the infants included in the study was 32.56±5.90. The mean value of the number of maternal pregnancies and deliveries was 3. In the anthropometric measurements of the mothers according to body mass index, 20 were normal, 14 were overweight, and 14 were obese (**Table 2**).

Insulin value in the cord blood of the newborns included in the study was 4.99±3.17 mIU/ml, leptin value was 4.28±3.12 ng/ml, ghrelin value was 0.51±0.99 ng/ml, and adiponectin value was 3.65±0.47 ng/ml (**Table 3**).

The mean birth weight of the infants was 3204.65±435.74 g, the mean birth length was 49.27±1.98 cm, and the mean head circumference was 35.54±1.98 cm. The growth and normal growth percentile of the infants in the first two years of life are shown in **Tables 4** and **5**.

Considering the relationship between insulin, leptin, ghrelin and adiponectin levels in the cord blood and anthropometric measurements in the first two years of age, there is a positive correlation between the insulin level in the cord blood and the weights at the 12th and 24th months (p=0.013 and p=0.023). There was a negative correlation between the weights at 6th and 24th months (p=0.022 and p=0.011), and a positive correlation between adiponectin in cord blood and the weight at 6th month (p=0.037). There was no significant positive or negative correlation between leptin in cord blood and anthropometric measurements in the first two years of age (**Table 6**).

Table 3. Insulin, glucose, leptin, ghrelin and adiponectin values in the cord blood of newborns.

	Infants included in the study (n=44)
Insulin (mIU/ml)	4.99±3.17
Leptin (ng/ml)	4.28±3.12
Ghrelin (ng/ml)	0.51±0.99
Adiponectin (ng/ml)	3.65±0.47

Table 4. Anthropometric measurements of infants in the first two years.

	Infants included in the study (n=44)
Birth	
- Weight (g)	3204.65±435.74
- Height (cm)	49.27±1.98
- Head circumference (cm)	35.54±1.98
6th month	
- Weight (kg)	7.02±1.06
- Height (cm)	65.53±2.85
- Head circumference (cm)	42.36±1.79
12th month	
- Weight (kg)	9.92±1.18
- Height (cm)	76.36±3.11
- Head circumference (cm)	45.92±1.71
24th month	
- Weight (kg)	12.30±1.66
- Height (cm)	84.11±3.24
- Head circumference (cm)	48.60±1.81

Table 5. Growth percentiles of infants in the first two years of age.

Normal growth percentile	Infants included in the study (n=44)
Birth weight	40 (90.9%)
Birth height	44 (100%)
Birth head circumference	39 (88.6%)
6th month weight	34 (77.2%)
6th month height	35 (79.5%)
6th month head circumference	40 (90.9%)
12th month weight	38 (86.3%)
12th month height	42 (95.4%)
12th month head circumference	42 (95.4%)
24th month weight	42 (95.4%)
24th month height	40 (90.9%)
24th month head circumference	42 (95.4%)

Table 6. The relationship between insulin, leptin, ghrelin and adiponectin values in cord blood and anthropometric measurements in the first two years of age.

Anthropometric measurements		Insulin		Leptin		Ghrelin		Adiponectinr	
		p	r	p	r	p	r	p	r
Weight	Birth	0.492	**<0.001**	0.155	0.292	-0.161	0.276	-0.184	0.211
	6th month	0.090	0.390	0.099	0.502	-0.329	**0.022**	0.303	**0.037**
	12th month	0.357	**0.013**	0.000	0.999	-0.193	0.188	0.201	0.171
	24th month	0.335	**0.023**	0.077	0.613	-0.369	**0.011**	0.154	0.306
Height	Birth	0.092	0.533	0.214	0.144	-0.140	0.342	0.129	0.382
	6th month	0.093	0.444	0.232	0.161	-0.044	0.794	0.300	0.068
	12th month	-0.198	0.314	0.0087	0.959	0.197	0.314	-0.173	0.378
	24th month	0.244	0.152	0.267	0.116	-0.214	0.210	-0.143	0.405
Head circumference	Birth	0.424	**0.003**	0.127	0.391	-0.178	0.225	0.062	0.674
	6th month	0.203	0.106	0.107	0.534	-0.149	0.240	0.151	0.379
	12th month	0.143	0.355	-0.131	0.524	-0.123	0.549	-0.002	0.992
	24th month	0.308	0.098	-0.193	0.307	-0.097	0.608	0.015	0.938

Discussion

Many animal and human studies have confirmed that fetal and early postnatal growth is a critical developmental period associated with long-term health outcomes. Calculation of fetal and early postnatal growth based on birth weight alone can be misleading. Trigger markers are needed in this particular epigenetic development process.[11] Several hormones are believed to play a regulating role in this complex process, which hormonal influence also has an impact on later health outcomes. Adiponectin, ghrelin, leptin and insulin, which are generally accepted as regulators of energy homeostasis and appetite, are adipokines associated with fetal and early postnatal growth.[12] Their role in this complex process is still a matter of debate. Adipokines, mainly peptides produced by adipose tissue, play critical roles in energy homeostasis and metabolic regulation in addition to peptides produced from the digestive tract.[13,14] Insulin plays an important role in fetal growth. Insulin stimulates leptin synthesis by creating a regulatory feedback loop. Leptin is an appetite suppressant and a regulator of both the amount of energy stored as fat and blood glucose levels.[15] Leptin level reflects the nutritional status of the newborn, and insulin is a potent physiological regulator of leptin expression in adipose tissue. Leptin and insulin are key factors in regulating fetal and neonatal energy balance, growth and development. Leptin regulates fetal growth and development during pregnancy, and umbilical cord leptin has a positive correlation with newborn body weight and fat mass.[16] Another peptide hormone that is important in fetal growth and reduces body weight and food intake as it acts as a leptin antagonist is ghrelin. Ghrelin increases body weight, the secretion of growth hormone produces a positive energy balance, reduces energy consumption and increases lipid accumulation.[6] Total ghrelin levels were higher in SGA and had weak but significant negative partial correlation with IGF1 levels. In the light of these data, we show that ghrelin has a role in supporting a positive energy balance in fetal growth in late pregnancy and that total ghrelin levels, fetal weight, and IGF1 are regulated by a negative feedback system.[17] Another adipocytokine involved in intrauterine growth is adiponectin. Adiponectin is lower in infants with SGA. Adiponectin is an indicator of insulin sensitivity and fatty acid oxidation.[15,18]

In our study, we investigated the effects of insulin, leptin, ghrelin and adiponectin hormones and adipokines, which have important effects on growth in the intrauterine and extrauterine periods, on birth weight and the weight in the first two years of age. Insulin value in cord blood was positively correlated with birth weight at birth and the weights at 12th and 24th months after birth. We found a negative correlation between ghrelin level in cord blood and the weights at postnatal 6th and 24th months. Adiponectin value in cord blood showed a positive correlation at the postnatal 6th month. However, there was no correlation between leptin value in cord blood and the weight at birth and in the first two years after birth.

It has been suggested that insulin concentration throughout fetal life may affect not only prenatal growth but also postnatal growth. Insulin level in cord blood shows a positive correlation with birth weight. It has been found that the insulin value in the cord blood has a negative correlation with growth in the early period after birth, especially in the first year.[19] In another study, while insulin in the cord blood was positively associated with birth weight, it was found to be negatively associated with the weight up to two years of age.[20] In another study, it was found that insulin in the cord blood was positively associated with the skinfold thickness at 1 year old, and they stated that the insulin value in the cord blood may be associated with body fat accumulation in early childhood.[10]

Contrary to studies that argue that insulin and leptin in the cord blood can be considered predictive factors for weight gain later in life, there are studies that do not support this argument. In our study, we showed that insulin level continued to be positively correlated with the weight at birth and in the postpartum period. Changes in leptin levels cause an increase in leptin bioavailability in line with IGF1 and IGFBP-3 levels in the final stages of pregnancy. It has been suggested that this is a signal of adequate weight gain.[21] Leptin is a self-control mechanism to avoid excessive fetal growth at the end of pregnancy and the low free leptin index found in neonates with SGA constitutes an adaptive mechanism to fetal growth restriction. Leptin regulates fetal growth and development during pregnancy, and leptin in the umbilical cord has a positive correlation with newborn's body weight and fat mass.[16] In the meta-analysis of Karakosta et al.,[22] it was reported that there is a correlation between cord leptin levels and body weight.

Adiponectin is an adipokine secreted by adipose tissue and is inversely related to obesity in adults.[23] It is also abundant in the cord blood of term newborns, at concentrations two to three times higher than those reported in adults.[24] However, studies to date have yielded conflicting results regarding the relationship between cord blood adiponectin concentration and infant birth weight, ranging from an inverse relationship to no correlation or even a positive relationship.[25–27] There are few studies evaluating the long-term relationship between cord adiponectin level and growth.[26–28] Studies have shown that leptin and adiponectin levels in cord blood are positively associated with birth weight at birth, but negatively until the first 3 years of life. Low leptin value in cord blood correlated with low birth weight; however, it was observed that low leptin value accelerated weight gain in the later period. Adiponectin level in cord blood was found to be negatively associated with weight gain in the first 6 months of life, and positively associated with weight gain and central adiposity in the 3rd year of life.[29] In a systematic review and meta-analysis conducted in 2021, cord leptin and adiponectin levels were positively correlated with adipose tissue at birth, while the relationship between leptin and adipocyte was negative in early childhood, and the relationship between adiponectin and adipocyte was positive.[3] Another study states that the cord blood adiponectin concentration is a determinant of the baby's birth weight and weight gain in the first year of life.[30] In our study, on the contrary, we found no correlation between leptin value in cord blood and both birth weight at birth and the weight in the first two years of life. Adiponectin value in cord blood showed a positive correlation with the weight only at the 6th month of life.

The ghrelin in the cord blood is higher in newborns with a small birth weight for the week of birth than in newborns with a normal birth weight. Cord blood ghrelin is negatively correlated with birth weight. In addition, the low level of ghrelin in the cord blood in newborns with a small birth weight for the week of birth predicts that weight gain is slow after birth. The level of ghrelin in the cord blood is considered a predictive factor for weight gain in the first year of life. Ghrelin is mainly produced in the stomach, but also in the placenta, suggesting that it plays an important role in intrauterine energy balance. Studies have shown that total cord ghrelin levels increase with increasing gestational age, but remain constant throughout the late pregnancy.[31,32] Cord ghrelin value was not found to be associated with birth weight, height and head circumference in infants with a birth weight suitable for gestational age.[33] On the other hand, ghrelin in cord blood is negatively correlated with birth weight. Cord ghrelin value was found to be significantly higher in newborns with low birth weight for gestational age.[34,35] In addition, the low level of ghrelin in the cord blood in newborns with a small birth weight for the week of birth predicts that weight gain is slow after birth.[36,37] In our study, ghrelin level in cord blood did not show a significant correlation with birth weight. We found a negative correlation between the level of ghrelin in the cord blood and weight gain in the first two years of life. In another study, each increase in ghrelin level in cord blood was associated with a decrease in body mass index and skinfold thickness at the age of 1 year.[10]

Conclusion

In conclusion, the effect of adipokines in cord blood on growth in newborn and early childhood is very important. In our study, the correlation of insulin, ghrelin and adiponectin values in the cord blood with the weight in the first two years of age was significant, while the relationship between leptin value and the weight in the first two years of age was insignificant. As a result, insulin, ghrelin and adiponectin in the cord blood may guide the early diagnosis of feeding and growth problems in early childhood. There is a need for long-term and larger-scale studies on nutrition and growth problems in childhood.

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