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Original Article

Insulin-like growth factor-1 and growth in infants 0-6 months of age

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Abstract

Background During infancy, growth is affected by many factors, including hormones. Insulin-like growth factor-1 (IGF-1) is a hormone with an important role in regulating somatic growth and organ development.

Objective To analyze for possible correlations between IGF-1 levels and infant growth from 0-6 months of age.

Methods A prospective study was conducted on 38 infants from birth to 6 months of age. Inclusion criteria were full-term newborns with normal birth weight and singleton birth. Serum IGF-1 was measured twice, from umbilical cord blood at birth and at 6 months of age. Anthropometric measurements were made every three months. Paired T-test was used to analyze mean IGF-1 among time points, and Pearson's correlation test was used to analyze IGF-1 levels and growth.

Results Mean IGF-1 level decreased from birth to 6 months of age (89.6 ng/mL vs. 48.3 ng/mL, respectively; $P<0.001$). Delta IGF-1 had positive significant correlations with delta weight at 3 months ($r=0.347$; $P=0.033$) and 6 months ($r=0.386$; $P=0.017$), as well as delta head circumference at 3 months ($r= 0.356$; $P=0.028$) and 6 months ($r=0.357$; $P=0.028$). However, there were significant negative correlations between umbilical cord IGF-1 with delta body weight ($r= -0.459$; $P=0.004$) and delta length at 6 months ($r= -0.414$; $P=0.010$).

Conclusions There is a decrease in IGF-1 levels at the first 6 months of life. Umbilical cord IGF-1 level has negative correlations with the weight and length increment at the age of 6 months. **[Paediatr Indones. 2021;61:89-93 ; DOI: 10.14238/pi61.2.2021.89-93]**.

Keywords: *umbilical cord IGF-1; IGF-1 at 6 months of age; growth*

Insulin-like growth factor-1 (IGF-1) is a hormone that mediates the effects of growth hormone (GH) and has a significant role in regulating somatic growth and organ development. This hormone is secreted by the anterior pituitary, and regulated by growth hormone releasing hormone (GNRH) and somatostatin. Growth hormone induces IGF-1 in the liver and regulates paracrine IGF-1 production in other tissues.[1] The IGF-1 system is very sensitive to metabolic changes and IGF-1 concentrations. The insulin-like growth factor binding protein (IGFBP) is suspected of having a role in growth and nutrition because postnatal growth is influenced by infants' nutritional intake, especially that of protein and energy.[2] A previous study in Denmark showed that IGF-1 and IGFBP-3 levels positively correlated with increased body weight and length, until the age of 3 months in full-term infants. The IGF-1 levels were lower in breast-fed infants than in those receiving formula at 3 months.[3] The IGF-1 in infants who breastfed for 6-12 months was assumed to affect GH

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production by suppressing the GH-IGF-1 axis.[4]

We aimed to analyze for possible correlations between IGF-1 levels and infant growth from 0-6 months of age, to be used as a management guideline to help children reach their optimal growth.

Methods

We conducted an observational, analytic study with prospective cohort design in May 2017-August 2018. This was the first report of an umbrella study entitled, "*Correlations of Mother's Protein Intake and Intrauterine Growth until 6 Months of Age: A Study of Breast Milk Composition, IGF-1 levels, and Leptin*". The inclusion criteria were healthy vigorous newborns, full-term, singleton, and delivered from healthy mothers with no pregnancy complications, maternal age <40 years, and consented to participate for six months. Subject selection started from the third trimester of pregnancy, to include mothers anticipating delivery in various Semarang health care facilities from 2017 until 2018. The minimum required sample size was calculated for bivariate correlation, with $\alpha=0.05$ ($Z\alpha=1.96$), power 90% ($Z\beta=1.282$), and $r=0.5$. Although we collected 50 umbilical cord blood specimens, three infants did not visit for follow up, eight infants did not provide blood specimens at 6 months, and one infant died during the study. Thus, 38 subjects were included; this number fulfilled the minimum required sample size calculation.

Anthropometry measurements were conducted in a longitudinal method, including body weight, length, and head circumference of the infants. Infant body length was measured in a supine position using a portable infantometer (*SECA 417*) with an error of 0.1 cm, then the mean value was calculated from three measurements. Infant body weight was measured by digital infant scale (*SECA 354*), without clothes; the mean value was calculated from three measurements. Head circumference was measured when the baby was quiet, using a ribbon (*SECA 212*); the mean value was calculated from three measurements. Measurements were made right after birth, and at 3 and 6 months of age.

Umbilical cord blood specimens were collected after the baby was delivered and before placental delivery. The second clamp was clipped ± 10-15 cm on the umbilical cord, then 3 mL of umbilical venous blood was collected using a 5-mL syringe, placed into a non-EDTA tube, and sent to *Dr. Kariadi Hospital Laboratory*, Semarang, Central Java, within 4 hours. At the laboratory, the specimen was centrifuged at 3000 rpm for 10 minutes to separate the serum. This serum was divided into two specimen containers, and stored at -20^{o}C. Frozen specimens were sent to *GAKI Laboratory* of Diponegoro National Hospital by a packed cold-chain method. The IGF-1 concentration was measured by the *Quantikine Human IGF-I Immunoassay RD Systems®*. Inter-assay and intra-assay variations were 8.1% and 3.5%, respectively. The detection limit was 20 ng/mL.

Body weight, length, and head circumference were converted into Z-scores of WAZ, HAZ, WHZ, and HC, according to the 2005 WHO growth chart.5 The delta *z* score at 3 months or 6 months was obtained by subtracting the *z*-score at 3 months or 6 months with the *z*-score at birth. Data were analyzed using *SPSS 25* software. Normality test was done to determine data distribution for numeric scales. Numerical data with normal distribution were presented in mean (standard deviation), meanwhile the categorical data are presented as frequency distribution. Bivariate analysis of umbilical cord blood IGF-1 and IGF-1 level at 6 months was done using paired T-test. Pearson's correlation test was used to analyze umbilical cord blood IGF-I levels and infant delta growth until the age of 6 months.

The study protocol was authorized by the Ethics Committee of Universitas Diponegoro Medical School/Dr. Kariadi Hospital, Semarang, and similar authorizations were acquired from other facilities involved in the study. Parents/guardians provided written informed consent after understanding the objective, procedures, and side effects of the study.

Results

The characteristics of subjects and mean IGF-1 levels in umbilical cord blood and at 6 months are shown in **Table 1**. Mean serum IGF-1 level significantly decreased from birth (umbilical cord blood) to 6 months of age (89.6 ng/mL *vs.* 48.3 ng/mL, respectively; $P<0.001$). Of all infants, 44.7% received exclusive breast milk, however there was no relationship between exclusive breastfeeding with the growth of the infants (P>0.05).

Table 1. Characteristics of subjects

Characteristics	n	Mean (SD)
Sex		
Male	21	
Female	17	
Gestational age, weeks		38.8 (2.21)
Exclusively breastfed 6 months	18	
Umbilical cord IGF-1, ng/mL		89.6 (30.99)
IGF-1 at 6 months, ng/mL		48.3 (27.86)
Birth weight, grams		3120.3 (349.9)
Birth length, cm		49.2 (1.24)
Birth head circumference, cm		34.1 (1.56)
Weight at 3 months, grams		5893.8 (756.7)
Length at 3 months, cm		59.4 (1.71)
HC at 3 months, cm		39.5 (1.56)
Weight at 6 months, grams		7183.5 (872.2)
Length at 6 months, cm		65.2 (2.18)
HC at 6 months, cm		42.5 (1.36)

Analysis of umbilical IGF-1 levels and infant growth at 3 and 6 months are shown in **Table 2**. Umbilical cord IGF-1 level had significant negative correlations with the weight increment at the age of 3 months (r=-0.366; P=0.024) and 6 months (r=-0.459, P=0.004). Umbilical cord IGF-1 level also had a significant negative correlation with length increment at 6 months (r=-0.414; P=0.010).

Table 2. Analysis of umbilical IGF-1 level and infant growth parameters at 3 and 6 months

Variables	Group	Umbilical cord IGF-1	
		r	P value
Delta WAZ	0-3 months	-0.366	0.024§
Delta HAZ	0-3 months	-0.111	0.508§
Delta WHZ	0-3 months	-0.104	0.534§
Delta HC	0-3 months	-0.247	0.134§
Delta WAZ	0-6 months	-0.459	0.004§
Delta HAZ	0-6 months	-0.414	0.010§
Delta WHZ	0-6 months	-0.182	0.273§
Delta HC	0-6 months	-0.317	0.052§

§Pearson's correlation

Analyis of delta IGF-1 levels and change in growth parameters between 0 and 3 months as well as between 0 and 6 months (delta WAZ, HAZ, WHZ, and HC) are shown in **Table 3**. Delta IGF-1 levels had significant positive correlations with the following growth parameters: delta WAZ between 0 and 3 months (P=0.033), delta WAZ between 0 and 6 months (P=0.017), delta HC between 0 and 3 months (P=0.028), and delta HC between 0 and 6 months (P=0.028). Delta IGF-1 was obtained from the changes of IGF-1 cord with the blood IGF-1 at 6 months of age. Our study found that the IGF-1 level decreased from birth (umbilical cord blood) to 6 months of age. It meant that the greater of decreasing IGF-1 levels at birth compared to IGF-1 at 6 months of age, the better growth of infants were found.

Table 3. Analysis of delta IGF-1 level with changes in growth parameters at 3 and 6 months

Variables	Mean (SD)	Delta IGF-1	
		r	P value
Delta WAZ			
0-3 months	-0.38 (1.15)	0.347	0.033§
0-6 months	-0.10 (1.07)	0.386	0.017§
Delta HAZ			
0-3 months	1.04 (1.01)	0.141	0.400§
0-6 months	-0.46 (1.12)	0.265	0.108§
Delta WHZ			
0-3 months	0.28 (1.76)	0.067	0.691§
0-6 months	0.26 (1.44)	0.237	0.152§
Delta HC			
0-3 months	-0.67 (1.43)	0.356	0.028§
0-6 months	-0.003 (1.30)	0.357	0.028§

§Pearson's correlation

Discussion

Mean IGF-1 level at the age of 6 months was significantly lower than at birth (48.3 ng/mL *vs.* 89.5 ng/mL, respectively (P<0.001). Previous studies that established IGF-1 reference values in children aged 0 to 5 years, showed that IGF-1 levels gradually decrease from birth until 24 months, then gradually increase and reach a peak at puberty.[6,7] Low serum IGF-1 level at 6 to 12 months may be affected by breast milk consumption, as IGF-1 in breast milk suppresses infants' GH-IGF-1 axis.[4] Several studies have reported a negative correlation between breastfeeding duration and growth hormone during the first year of life.[8,9] Likewise the European multicenter randomized clinical trial on 1090 term babies who found that breastfeeding will reduce IGF-1 levels compared to formula milk, and covariate adjustment such as infant weight at 6 months and maternal smoking during pregnancy.[10] Although 47.4% of infants received exclusive breastfeeding for 6 months in our study, but there was no significant relationship between infant growth and breastfeeding.

The IGF-1 is a hormone that plays a role in embryonic and post-natal growth. Growth hormone (GH) stimulates skeletal growth by stimulating IG-1 production in the liver and furthermore, IGF-1 will stimulate bone plate growth.[11-13] Besides IGF functions as a mediator of GH to target organs and tissues, as well as on brain development.[14] The objective of our study was to analyze for possible correlations between IGF-I levels and infant growth from 0-6 months of age. We found a negative correlation between umbilical cord IGF-1 and increased body weight at 0-3 months ($r=-0.366$; $P=0.024$) and 0-6 months ($r=-0.459$; $P=0.004$), as well as with delta body length at 0-6 months ($r=-0.414$; $P=0.010$). A study similarly reported a negative correlation between umbilical cord IGF-1 level and infant increasing body weight at 3 months of age.[3,15] This result supports the hypothesis that intrauterine undernutrition leads to changes in the IGF-1 axis. Elevated plasma IGF-1 in low birth weight infants can increase growth after birth. A high level of IGF-1 at birth may lead to decreased fetal growth.[15,16]

We analyzed for a possible correlation between delta IGF-1 and delta growth parameter z-scores until 6 months of age. Delta IGF-1 had negative correlated with delta WAZ at 3 months ($P=0.033$) and 6 months ($P=0.017$), as well as delta HC at 3 months ($P=0.028$) and 6 months ($P=0.028$). These results were similar to previous studies that showed negative correlations between IGF-1 with several growth parameters, such as increased body weight and length.[3,4] A recent study from the Netherlands also showed a significant correlation between IGF-1 with body weight and head circumference in full-term infants.[17]

A significant correlation between growth factors and other growth parameters, such as the rate of increasing sex-specific body weight and length, leads to the interaction of the IGF-I axis. The increasing growth rate positively correlates with IGF-1 from birth until the age of 3 months, then a negative correlation from 3 to 18 months of age.[3,18] Other study indicate that IGF-1 levels in term infants decreased slowly between 0 and 24 months but tend to increase slowly with age.[4] However, IGF-1 is only a small part of many other factors related to infant growth. Other factors such as protein consumption during pregnancy and nutritional content of breast milk, nutritional status, kidney, and liver function also contribute to the regulation of growth after birth.[10,12,19-20]

In conclusion, this longitudinal study shows a significant decrease in mean IGF-1 levels at 6 months compared to birth levels. Umbilical cord IGF-1 level has negative correlations with the weight and length increment at the age of 6 months, and the greater decreasing of IGF-1 levels at birth compared to IGF-1 at 6 months of age, resulting in a better growth at 6 months of age. Nevertheless, IGF-1 is only one of many factors influencing infant growth, and these factors may contribute to growth regulation after birth.

Conflicts of Interest

None declared.

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