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Investigating the Relationship between Insulin-like Growth Factor-1 (IGF-1) in diabetic mother's breast milk and the blood serum of their babies

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Abstract

Introduction: Since research investigating IGF-1 levels in breast milk are few, the goal of this study was to analyze the IGF-1 levels in the breast milk of diabetic mothers as well as in the serum of their newborn babies and to identify what relationship exists between blood serum and IGF-1 milk levels through patient measurement of mothers and their babies.

Methods: This case control study was undertaken under the auspices of the Clinic of Neonatology at Al Minia University Pediatric Hospital over May 2012 through May 2013. With a total of 30 diabetic mothers and their babies forming the experimental group and the control group consisting of 15 non-diabetic mothers and their babies. A detailed medical history, anthropometric assessments, as well as the measurement of the baby's serum IGF-1 and their mother's breast milk IGF-1 levels were taken from all participants using ELSIA. The resulting data were analyzed via Statistical Package for the Social Sciences (SPSS) version 16 and measurements of descriptive statistics, t-test, Chi-square test, as well as the Pearson Correlation Coefficient.

Results: The Infants born to Diabetic Mothers (IDMs) demonstrated significantly greater anthropometric measurement. Both the serum levels and the milk IGF-1 levels as well as all of the physical measurements taken were found to have a positive correlation between the level of IGF-1 in mother's milk and all of the anthropometric measurements studied with the exception of delivered baby's length.

Conclusion: Higher levels of IGF-1 are present in the milk of diabetic mothers and the blood serum of their babies and this characteristic could be used as a prenatal biomarker for macrosomia.

Keywords: IGF-1, IDM, Breast milk, Anthropometric measurements

1. Introduction

1.1. Background and study logic

Mother's breast milk is known to contain a variety of biologically active compounds, these include immunological growth factors, cytokines, hormones, oligosaccharides, antimicrobial peptides, enzymes, and immunoglobulins (1). Growth factors are such as epidermal growth factor (EGF), insulin-like growth factor-I (IGF-I), transforming growth factor (TGF), and hepatocyte growth factor (HGF) (2). The hormone IGF-1 is a mediator of human Growth Hormone (HGH) and serves to stimulate bodily growth, regulates growth hormone independent anabolic reactions in many types of cells and tissues.IGF-1 is an atypical peptide in that it is composed nearly 99% of bound proteins (3). IGF-1 uses specified cell receptors located on the cell membrane surface to accomplish many mitogenic cell functions that include the induction of cell growth, cell division, and differentiation (4). IGF-1 tends to initiate an anabolic effect, which increased the utilization of glucose and amino acids while inhibiting protein catabolysis (5). Since mothers with diabetes tend to suffer from perioidic hyperglycemia, this exposes their fetuses to high glucose

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levels causing fetal hyperglycemia that stimulates fetal growth and glycogen disposition encouraging macrosomia (6).

1.2. Objective

The goal of this research study seeks to determine the IGF-1 levels in breast milk of mothers with diabetes and the blood serum of their newborn babies and to establish if their exists any relationship between these measures and the anthropometric measurements of diabetic mother's babies.

2. Material and Methods

This prospective case-control study was conducted on 45 neonates and their mothers who were selected from among the neonates present at the NICU and outpatient clinic of Neonatology at Al Minia University Pediatric Hospital during the period from May 2012 to May 2013. Informed written consent was received from the mothers before the study was begun. The neonates and their mothers were divided into two groups: Group I (cases) included 30 diabetic mothers and their infants, with a gestational age from 37-40 weeks, Group II (control) included 15 non-diabetic healthy mothers and their infants with a gestational age from 37- 40 weeks. Newborns having congenital anomalies, chromosomal disorders, perinatal asphyxia, sepsis, and whose mothers had disease complications during pregnancy were excluded from the study. All the newborns included in the study were subjected to a comprehensive medical history as well as taking complete medical examination including anthropometric measurement (body weight, length, Rohrer's neonatal ponderal index (NPI), skin fold thickness at triceps and subscapular areas, abdominal circumference, and head circumference) were performed on the same day, using standardized equipment. Three consecutive measurements were taken and when the differences between the readings were acceptable, then the mean was recorded. Neonatal blood sample: under complete aseptic technique, 3 cc of venous blood withdrawn into plain tubes for clotting, centrifugation, and serum fractionation. These sera are collected in sterile tubes, then stored at -20 °C until used, breast milk samples (10 mL) were collected by a trained nurse from both breasts by manual expression before feeding and then frozen at -20 °C within 24 hours or until used. The assay of the IGF-1: This was accomplished by using the Enzyme-Linked Immuno-Sorbent Assay (IGF-1 600 ELISA) technique (RayBiotech Inc.) by Awareness Technology Inc. The data were analyzed by SPSS version 16 (SPSS Inc. Chicago, Illinois, USA) using descriptive statistics, t-test, Chi-square test, and the Pearson product-moment correlation coefficient.

3. Results and discussion

A total of 45 mother-infant pairs were enrolled in this study. The study group consisted of 30 infants and their diabetic mothers and the control group consisted of 15 healthy infants and their mothers. In this study, the Infants of Diabetic Mothers (IDM's) showed a highly significant increase in the mean of weight, neonatal ponderal index, abdominal circumference, head circumference , triceps skin fold thickness, and sub-scapular skin fold thickness ($p < 0.001$) when compared to control group. Alao, regarding the mode of delivery of the IDMs born by Cesarean Section (CS) significantly increased over the control group ($p < 0.001$) (Table 1). In addition, IDMs showed highly significant increases in the level of IGF-1 in the blood serum as well as their mother's breast milk when compared to the control group ($p < 0.001$) (Table 2). There was a highly significant positive correlation between serum IGF-1 and all anthropometric measures (weight, head circumference, abdominal circumference, triceps skin fold thickness, sub-scapular skin fold thickness, NPI ($p < 0.001$), and length ($p < 0.01$) (Table 3). Also, there was a highly significant positive correlation between the milk IGF-1 and all of the anthropometric measures (weight, head circumference, abdominal circumference, triceps skin fold thickness, sub-scapular skin fold thickness, and NPI ($p < 0.001$) with the exception of length (Table 3). Insulin-like growth factor-1 (IGF-1) is a pleiotropic factor with a wide spectrum of actions in the central and peripheral nervous system (7, 8). It belongs to a superfamily of structurally related proteins that include insulin, IGF-1, and IGF-2. The biological functions of IGF-1 are mediated by specific membrane receptors designated as IGF-1 receptors. There are six IGF-binding proteins (IGFBPs), which modulate the bioavailability and receptor targeting of the IGFs (9). Higgins et al. (10) demonstrated that IGF-1 was present in mature and premature human milk samples, its levels were several-fold higher in colostrum than in mature milk and it tends to decrease over the first few days of lactation, they believed that IGF-1 could be either synthesized by the mammary gland or transferred from the maternal circulation. Additionally, Sevigny et al., (11) identified IGF-binding proteins (IGFBPs) in the human milk of term and preterm infants and found that infants fed with artificial formula during the first months of life showed higher IGF-1 levels than breast feeding ones. In the present study, diabetic mothers showed higher rates of performing CS when compared to the control group ($p < 0.0001$) and this is in agreement with Oussama et al., (12) their findings suggested that high birth body mass or fetal macrosomia could be considered to be a typical complication of GDM and may be linked to negative maternal and newborn health factors that could include a tendency for maternal postpartum hemorrhaging, perineal tearing, and a greater chance

for the need for CS. In the current study, IDMs showed a significantly higher mean weight, higher NPI, greater Abdominal Circumference (AC), greater triceps skin fold thickness (TSFT), greater sub-scapular skin fold thickness (SSFT), and head circumference (HC) when compared to the control group ($p < 0.001$), but there was no significant difference between the case and control groups with regards to neonatal length ($p > 0.05$); this is in agreement with Lauszus et al. (13). They studied diabetic pregnancy and noted increases in all of the anthropometric measures in IDM as compared to infants of non-diabetic mothers.

Table 1. Comparison between cases & control as regards clinical characteristics:

Variables		Cases	Control	p-value
Age of mother (year); Mean ± SD		30.7 ± 6.5	28.3 ± 5.7	0.2
Maternal weight (kg); Mean ± SD		85.3 ± 13.5	79.1 ± 11.1	0.1
Gestational age (week); Mean ± SD		38.1 ± 1.1	38.7 ± 1.3	0.1
Neonatal age (day); Mean ± SD		6.2 ± 1.2	6.7 ± 1.5	0.2
Sex	Male	16	7	0.7
	Female	14	8	
Mode of delivery; n (%)	NVD	0 (0)	11 (73.3)	<0.001
	CS	30 (100)	4 (26.7)	
Neonatal Weight (Kg); Mean ± SD		3.45 ± 0.5	3.1 ± 0.3	0.03
Neonatal Length (cm); Mean ± SD		50.2 ± 1.3	49.7 ± 1.4	0.2
Neonatal Head circumference (cm); Mean ± SD		34.9 ± 0.8	33.7 ± 0.7	<0.001
Neonatal Abdominal circumference (cm); Mean ± SD		32.1 ± 1.9	29.2 ± 1.4	<0.001
NPI; Mean ± SD		2.7 ± 0.4	2.55 ± 0.26	0.2
Neonatal Triceps fold thickness; Mean ± SD		3.7 ± 0.5	2.2 ± 0.4	<0.001
Neonatal Subscapular fold thickness; Mean ± SD		3.7 ± 0.5	2.9 ± 0.5	<0.001

NVD: normal vaginal delivery; CS: cesarean section; NPI: neonatal ponderal index

Table 2. Comparison between cases & control as regards IGF-I state:

Variables	Cases (Mean ± SD)	Control (Mean ± SD)	p-value
Serum IGF-1 (ng/ml)	47.6 ± 10.7	16.3 ± 5.8	<0.001
Milk IGF-1 (ng/ml)	44.97 ± 7.35	2.7 ± 0.8	<0.001

Table 3. Correlation between IGF-I levels and anthropometric measures among group1.

Variables	Serum IGF-I		Milk IGF-I	
	r	P-value	r	P-value
Weight (Kg)	0.83	<0.001	0.62	<0.001
Length (cm)	0.37	0.01	0.19	0.1
Head circumference (cm)	0.68	<0.001	0.64	<0.001
Abdominal circumference (cm)	0.71	<0.001	0.64	<0.001
NPI	0.71	<0.001	0.57	<0.001
Triceps skin fold thickness (mm)	0.88	<0.001	0.84	<0.001
Sub-scapular skin fold thickness (mm)	0.53	<0.001	0.60	<0.001

In our study, IDMs showed a significantly higher mean serum IGF-1 when compared to the control group ($p < 0.001$). This may be related to the pronounced metabolic disturbances characterized by hyperinsulinemia in these neonates, which was resulting from maternal hyperglycaemia, with this remaining in a negative correlation with IGFBP-1, intensifies IGF-1 secretion, which results in higher concentrations of IGF-I in infant serum. Additionally, this high level of serum IGF-1 may be due to the increased level of placental Growth Hormone (GH) found in serum of IDMs. This placental GH has a positive effect on IGF-1 level. This result is in agreement with Lindsay et al. (14) who found that mean levels of IGF-1 were significantly higher in the cord blood of the offspring of mothers with gestational diabetes. Studies done to investigate IGF-1 in the breast milk of diabetic mothers were very scarce. In this study, we found that there was a highly significant increase in the mean maternal milk IGF-1 when compared to the control group ($p < 0.001$). The breast milk of diabetic mothers has been shown to have a different composition from that of non-diabetic mothers, it may contain elevated levels of glucose and insulin as well as decreased polyunsaturated fatty acids and it is possible that this high level of insulin may elevate the level of IGF-1. Also,

maternal serum seems to be the primary source of milk IGF-1, so this leads to a high level of IGF-1 in the breast milk of diabetic mothers. This finding was in agreement with Ringholm et al. (15) who found that the IGF-1 concentration in serum of the pregnant diabetic women was significantly higher in comparison with healthy pregnant women. It can be suspected that the observed increased concentrations of IGF-1 in DM is a type of compensatory reaction to the increased insulin resistance and hyperinsulinemia, which increases the IGF-1 secretion, resulting in a higher concentration of IGF-1 in blood serum or manifesting a high level of IGF-1 in maternal serum that may be due to a higher level of placental GH found in the serum of pregnant diabetic women, which is the main driver of IGF-1 production.

The present study found that serum IGF-1 levels in IDMs was positively related to neonatal weight, length, NPI, HC, AC, TSFT and SSFT ($p < 0.05$). It has been reported that IGF-1 is an important modulator of growth hormone activity in linear growth. Also, IGF-1 plays a central role in the regulation of prenatal and postnatal growth and also exerts a growth modulating effect by decreasing apoptosis and increasing cell proliferation and angiogenesis so it may be said that IGF-1 is positively related to macrosomia and increasing anthropometric measures in IDM. This is in agreement with previous research studies (5, 16-19) that found that IGF-1 in cord blood of IDM was positively correlated to weight, length, HC, TSFT, and SSFT. All these findings were corroborated by the data, pointing to the fact that IGF-1 plays an active role in the regulation of fetal growth. Also, Lindsay et al. (14) emphasized that IGF-1 and IGFBP-1 showed significant positive and negative correlations, respectively, with birth weight in all of the offspring of diabetic mothers. This study found that maternal milk IGF-1 level in diabetic mothers was positively related to neonatal weight, NPI, HC, AC, TSFT, and SSFT ($p < 0.001$), but had no significant relationship to neonatal length.

4. Conclusions

IGF-1 increased in the milk of diabetic mothers and the serum of their infants there is an association between intrauterine fetal growth and IGF-1 in IDMs, as reflected by anthropometric measurements. There is evidence that the increased action of IGF-1 is likely in the offspring of diabetic mothers and represents part of the mechanism of fetal overgrowth. Further studies on larger scale are recommended to specify the exact effects of IGF-1 on IDMs and further studies are recommended to clarify the exact level and role of IGF-1 in the milk of diabetic mothers.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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