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Apelin, vaspin, visfatin and adiponectin in large for gestational age infants with insulin resistance

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ABSTRACT

Objective: To investigate the relation of circulating four adipokines (apelin, vaspin, visfatin, adiponectin) with markers of insulin sensitivity in large for gestational age (LGA) infants.
Patients and methods: Forty LGA infants (20 LGA born from diabetic mothers and 20 LGA born from non-diabetic mothers) and 34 appropriate for gestational age (AGA) infants were recruited. Hyperinsulinism and insulin resistance was evaluated using the homeostasis model assessment (HOMA-IR), fasting glucose-to-insulin ratio (FGIR), quantitative insulin-sensitivity check index (QUICK-I) from fasting samples. Plasma adiponectin and vaspin levels were determined by radioimmunoassay. Determination of visfatin and apelin levels was performed by enzyme immunoassay.
Results: HOMA-IR, apelin and visfatin levels ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively) were significantly elevated and adiponectin levels, FGIR and QUICK-I values. ($p < 0.001$, $p < 0.001$, $p < 0.05$, respectively) were significantly lower in the LGA group. Vaspin levels were higher in the LGA group than AGA neonates without a significance. The LGA infants with diabetic mother had significantly higher visfatin, apelin, HOMA-IR values, fasting insulin levels and significantly lower adiponectin, FGIR, QUICK-I values. Apelin and visfatin were correlated positively, and adiponectin was correlated negatively with birthweight, HOMA-IR values and fasting insulin levels.
Conclusion: Based on the findings of this study, it is too difficult to explain relation between birthweight and these adipocytokines, but findings of high insulin, HOMA-IR, visfatin, apelin and low adiponectin levels in the LGA neonates showed that these adipocytokines can be used as a good predictor for metabolic syndrome.

1. Introduction

Large for gestational age (LGA) infants are at increased risk of developing disturbances in glucose metabolism [1]. Maternal hyperglycemia leads to fetal hyperglycemia, which in turn stimulates the fetal pancreatic islet cells and causes hyperinsulinaemia [2,3]. In LGA neonates, hyperinsulinaemia in utero leads to fetal macrosomia and may also cause alterations in metabolic programming, which can have long-term effects, such as impaired glucose homeostasis during childhood [1].

Hyperinsulinaemia in large birth weight neonates is usually present before these abnormalities (hypertension, dyslipidaemia, obesity and insulin resistance) become detectable and has been proposed as the common trigger of the constellation [4]. However, more recent studies indicate an important role of adipose tissue hormones or "adipokines" in obesity-associated complications. Adiponectin is exclusively expressed and secreted by the adipose tissue and is involved in glucose and lipid metabolism [5]. Hypoadiponectinaemia has been shown to be associated with insulin resistance in animal and human studies [5]. Plasma adiponectin levels are decreased in subjects with obesity and insulin resistance or type 2 diabetes mellitus, and are inversely correlated with visfatin and fasting insulin levels [6,7]. Both tissue expression and plasma levels of visfatin increase in parallel with obesity. It has insulin-mimetic effects and lowers plasma glucose levels [8].

Abbreviations: LGA, large for gestational age; AGA, appropriate for gestational age; HOMA-IR, homeostasis model assessment for insulin resistance; QUICK-I, quantitative insulin-sensitivity check index; FGIR, fasting glucose-to-insulin ratio; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, Low density lipoprotein cholesterol.

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Apelin synthesis in adipocytes is stimulated by insulin, and plasma apelin level markedly increases in obesity associated with insulin resistance and hyperinsulinemia [9]. Vaspin was identified as an adipokine with insulin-sensitizing effects, which is predominantly secreted from visceral adipose tissue in a rat model of type 2 diabetes [10]. Studies have recently showed that mRNA of vaspin expression in adipose tissue is related to parameters of obesity and glucose metabolism [11].

We hypothesized that circulating visfatin, adiponectin, apelin and vaspin concentrations are linked to markers of insulin sensitivity and metabolic disturbances in the LGA infants.

2. Material and methods

2.1. Subjects

Newborn infants born in GATA Medical Faculty between July, 2007 and March, 2008 by normal spontaneous vaginal delivery were enrolled in the present study. Gestational age was assessed by maternal menstrual dating, obstetrical ultrasonography and confirmed by Dubowitz scoring. We excluded infants whose mothers had any clinical conditions such as parathyroid, bone, renal, and gastrointestinal disorders. None of the participating mothers smoked during pregnancy. Women with singleton term pregnancies were recruited consecutively from the delivery suite. The mothers recruited were in good health with no known underlying medical disorder.

A total of 74 babies were included in the study. Subjects were divided into two groups using the Fenton's intrauterine growth curves [12] as LGA and Appropriate for gestational age (AGA). The LGA group was divided into two groups according to having diabetic mother or non-diabetic mother.

AGA Group: Normal birth weight, included 34 babies between 10th and 90th percentiles of Fenton intrauterine growth curve or birthweight between 2500 and 4000 g.
LGA Group: Large birth weight infant, included 40 babies of birthweight higher than 90th percentile or 4000 g.

All of the neonates were healthy, and their mothers had no remarkable complications during pregnancy. None of the infants had congenital malformations, chromosomal abnormalities, or intrauterine infections. Apgar scores in the 5th minute were $\geqslant 8$ and physical examinations were normal. Those with chronic conditions, systemic infections and nutrition defects were excluded from the study. Anthropometric measurements (height and weight) were recorded and blood samples were taken. Those without evidence of systemic disease, requiring no therapeutic intervention, and growing normally were enrolled. Birth weight and length were obtained from each neonate immediately after birth. Weight measurements were made with naked babies by an electronic weighing machine. Height measurements were accomplished with a height measuring board (head portion stable; feet portion mobile). GATA Medical Faculty Ethic Committee Approval (June 2007 and 95 session number) has been received and informed consents have been obtained before the blood samples were taken.

2.2. Blood samples

Blood was collected from cord blood. After clotting, the serum was separated and immediately explored for analyses. Plasma glucose was determined by the glucose oxidase method. Plasma insulin was measured using IMMULITE immunoassay (IMMULITE Diagnostic Products Corporation, Los Angeles, CA). Plasma concentrations of total cholesterol, triglycerides and high-density lipoprotein-cholesterol (HDL-cholesterol) were measured using routine enzymatic methods with Olympus 2700 Analyzer. Low density lipoprotein cholesterol (LDL-cholesterol) was calculated using Friedewald formula. Plasma adiponectin and vaspin levels were determined by radioimmunoassay (Linco Research, St. Charles, MO). Determination of visfatin, apelin levels was performed by enzyme immunoassay (visfatin C-terminal [human] EIA; Phoenix Pharmaceuticals, Belmont, CA).

2.3. Insulin sensitivity indices

Insulin resistance was estimated using the homeostasis model assessment for insulin resistance (HOMA-IR; fasting insulin X fasting glucose/22.5) [13]. Insulin resistance in children is defined as the levels of the homeostasis model assessment for insulin resistance (HOMA-IR) greater than 3.16 [14]. FGIR was calculated as fasting insulin concentration (μU/mL)/fasting glucose concentration (mg/dL). QUICK-I was calculated as 1/[(log fasting insulin concentration (μU/mL) + log fasting glucose concentration (mg/dL)] [15].

2.4. Statistical analysis

Data were expressed as mean ± SD. Differences in the means of variables were tested using both parametric and non-parametric tests depending on the distribution of the variables. Correlation analyses were conducted using Spearman or Pearson correlation coefficients depending once again on the distribution of the variables. A probability value of less than 0.05 was considered significant. SPSS version 17 (SPSS, Chicago, IL) was used for analysis.

3. Results

The characteristics of the 40 LGA and 34 AGA infants were summarized in Table 1. Both the LGA and AGA groups showed no significant differences in terms of total cholesterol and LDL-cholesterol. Triglyceride levels (129 ± 70 vs. 82 ± 41 mg/dL, p: 0.001) were significantly elevated and HDL-cholesterol levels (45 ± 9 vs. 55 ± 13) were significantly lower in LGA group.

Insulin sensitivity indices, FGIR and QUICK-I for the LGA and AGA infants were 4.8 ± 2.0 vs. 12 ± 3.7, $p < 0.001$; 0.29 ± 0.02 vs. 0.35 ± 0.01, $p < 0.001$, respectively. HOMA-IR, apelin and visfatin

Table 1
Clinical and laboratory characteristics of the study population.

	LGA infants	AGA infants	p
N(F/M)	22/18	20/14	
Birthweight (gr)	4320 ± 140	3200 ± 240	<0.001
Total cholesterol (mg/dL)	175 ± 36	166 ± 25	0.17
Triglycerides (mg/dL)	129 ± 70	82 ± 41	0.001
HDL-cholesterol (mg/dL)	45 ± 9	55 ± 13	<0.001
LDL-cholesterol (mg/dL)	105 ± 32	93 ± 24	0.059
Fasting glucose (mg/dL)	59.4 ± 9.5	65.8 ± 12.9	0.19
Fasting insulin (μU/mL)	12.3 ± 7.0	5.4 ± 1.4	<0.001
FGIR	4.8 ± 2.0	12 ± 3.7	<0.001
QUICK-I	0.29 ± 0.02	0.35 ± 0.01	<0.05
HOMA-IR	6.9 ± 2.8	1.5 ± 0.7	<0.001
Vaspin (μg/l)	0.75 ± 1.04	0.56 ± 0.33	0.25
Apelin (ng/mL)	2.22 ± 1.15	0.58 ± 0.16	<0.001
Adiponectin (μg/ml)	2.01 ± 1.02	12.5 ± 6.2	<0.001
Visfatin (ng/ml)	31.3 ± 11.1	18.5 ± 10.7	<0.001

Data are given as means ± SD. Difference at $p < 0.05$ level.
HOMA-IR, homeostasis model assessment for insulin resistance (fasting insulin (μU/mL) × fasting glucose (mg/dL)/22.5.
FGIR, Fasting glucose to insulin ratio.
QUICK-I, quantitative insulin-sensitivity check index.