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# Serum insulin-like growth factor-I (IGF-I) IGF binding protein-3 (IGFBP-3) and leptin levels are related to abdominal aortic intima-media thickness in macrosomic newborns

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**Abstract**

*Objective:* Exposure to diabetes in utero has been established as a significant risk factor for some of the components of metabolic syndrome, and was associated with increased levels of maternal, placental, and fetal insulin-like growth factors and leptin. The atherogenic effects of leptin and insulin-like growth factor-I (IGF-I) have been extensively described. The present study was therefore designed to investigate relationships between abdominal aortic intima-media thickness (aIMT), serum IGF-I, IGF binding protein-3 (IGFBP-3) and leptin levels in macrosomic newborns.
*Design:* Neonates whose birth weights exceed 90th percentile for gestational age and gender are termed macrosomic. Abdominal aortic intima-media thickness was measured in 30 macrosomic neonates of diabetic mothers (group A), 30 macrosomic neonates of healthy mothers (group B) and 30 healthy neonates (group C). Serum IGF-I, IGFBP-3 and leptin levels were determined in all infants and their mothers. Stepwise logistic regression analysis was used to determine independent risk factors for aortic intima-media thickness.
*Results:* Mean aortic intima-media thickness was significantly higher in groups A and B ($0.489 \pm 0.015, 0.466 \pm 0.019$ mm, respectively) than in controls ($0.375 \pm 0.024$ mm, $p < 0.0001$). Weight-adjusted aortic intima-media thickness was significantly higher in-group A than in groups B ($p = 0.004$) and C ($p = 0.048$). Serum leptin concentration in-group B ($37.4 \pm 10.7$ ng/ml) was significantly greater than in-group C ($23.5 \pm 7.1$ ng/ml, $p < 0.0001$), but significantly lower than in-group A ($46.6 \pm 14.1$ ng/ml, $p < 0.0001$). Serum IGF-I levels of the infants were significantly lower in-group C ($113.2 \pm 33.1$ ng/ml) than in groups A and B ($205.2 \pm 60.1$ and $179.3 \pm 55.1$ ng/ml respectively, $p < 0.0001$). Serum IGF-I, IGFBP-3 and leptin levels of the infants were positively correlated with mean ($p < 0.0001$) and weight-adjusted aortic intima-media thickness measurements ($p = 0.003$, $p = 0.006$ and $p = 0.001$, respectively).
*Conclusions:* Macrosomic neonates of diabetic mothers have significantly increased aortic intima-media thickness with higher serum IGF-I, IGFBP-3 and leptin concentrations *than those of controls*. It might be speculated that these changes may exaggerate the atherosclerotic process later in life.
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*Keywords:* Macrosomia; IGF-I; IGFBP-3; Leptin; Abdominal aortic intima-media thickness

## 1. Introduction

Macrosomia is a hallmark of maternal diabetes on the fetus [1]. It is probably due to the result of

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biochemical events along the maternal-hyperglycemia–fetal hyperinsulinemia pathway [2]. The probable pathogenic sequence is, maternal hyperglycemia causes fetal hyperglycemia, and the fetal pancreatic response leads to fetal hyperinsulinemia; fetal hyperinsulinemia and hyperglycemia then cause increased hepatic glucose uptake and glycogen synthesis. Related pathologic findings are hypertrophy and hyperplasia of the pancreatic islets with a disproportionate increase in the number of β cells, increased weight of the placenta and infant organs except for brain, myocardial hypertrophy, increased amount of cytoplasma in liver cells [3]. Exposure to diabetes in utero has been established as a significant risk factor for some of the components of *the metabolic syndrome* [4]. An interaction of maternal, placental, and fetal endocrine factors is likely to govern partitioning of nutrients and rate of fetal cell proliferation and maturation. The main established endocrine regulators of fetal growth include insulin and the insulin-like growth factor system [5,6]. As recently reviewed by Randhawa and Cohen [6], over the last decade it has been recognized that the insulin-like growth factor axis has a critical role in mediating fetal and postnatal growth. The metabolic processes that are responsible for the fetus pathophysiology of the diabetic mother have been elucidated in recent years and include increased levels of maternal, placental, and fetal insulin-like growth factors and leptin [7]. Insulin-like growth factor-I is a ubiquitous peptide that has both growth hormone-like and insulin-like effects. Alterations in expression of IGF-I may result in developmental abnormalities, macrosomia, and intrauterine growth retardation, which occur with a higher incidence in diabetic pregnancies [8]. Alterations in growth hormone (GH)/IGF-I axis are also associated with cardiovascular disease (CVD). Growth hormone hypersecretion as well as GH deficiency are characterized by an increased prevalence of CVD [9].

The recently discovered hormone leptin, a 16 kDa adipocyte derived protein encoded by the *ob* gene, is important for neuroendocrine regulation of body fat, feeding behaviour, energy homeostasis, reproduction, puberty and pregnancy. Dysregulation of autocrine/paracrine function of leptin at feto–placento–maternal interface may be implicated in the pathogenesis of recurrent miscarriage, gestational diabetes, pre-eclampsia and intra-uterine growth retardation [10]. Leptin is an adipose tissue hormone that has recently been proposed as a cardiovascular risk factor in obese patients [11]. Although the clinical complications of atherosclerosis occur in adult life, the process of atherogenesis begins in childhood [12]. We presented the ultrasound-based measurement of distal segment of the dorsolateral aIMT in the newborns as a feasible, accurate, and sensitive marker of atherosclerosis risk [13]. Additionally, we aimed to investigate the relationship among aIMT, serum IGF-I, IGFBP-3 and leptin levels in macrosomic newborns.

## 2. Materials and methods

### 2.1. Patients

The subjects were neonates delivered at Gevher Nesibe Hospital between January and June 2006. Informed consent was obtained from the parents before enrolment, and the project was approved by Erciyes University hospital Committee for Research on Human Subjects. Volunteer mothers and their term neonates ($\geqslant 37$ weeks) were included in the study. Gestational ages were determined from one or a combination of maternal menstrual dating, obstetrical ultrasound before 20 weeks of gestation, and Ballard score obtained at birth. Infants of mothers with known CVD, hypercholesterolemia, hypertension, smoking or pre-eclampsia were excluded. The exclusion criterions were: asphyxiated at birth, major congenital anomalies and blood pressures alterations on the 5th day of birth. An oscillometric monitor that has been demonstrated to be reliable was used to determine mean blood pressure in the newborn infants [14]. Mean blood pressure measurements were obtained and an average of three measurements was calculated. The mean blood pressures of all infants were normal on the 5th day of birth. Data concerning the mothers, their pregnancies and deliveries were obtained from the records made by obstetricians and pediatricians. Eighty-seven macrosomic infants in the gestational age of interest were admitted. Of these, 16 infants were ineligible for the following reasons; asphyxiated at birth (5 infants), associated with major congenital anomalies and blood pressures alterations (4 infants), with maternal history of CVD (2 infants), whose mothers smoked (6 infants), and mothers whose pregnancies were complicated by hypertension (4 infants). Five infants had more than one reason. Of 71 eligible macrosomic infants, in 11 infants the parents declined consent. So, 60 macrosomic infants with their mothers were included in the study. Thirty control mothers and their infants after normal pregnancies served as control. Neonates whose birth weights exceed 90th percentile for gestational age and gender are termed macrosomic. Neonates were divided into three groups by birth-weight as group A: 30 LGA (large for gestational age) neonates of mothers with diabetes mellitus; group B: 30 LGA neonates of healthy mothers; group C: 30 AGA (appropriate for gestational age) neonates.

There were 22 neonates of mothers with gestational diabetes mellitus (GDM) and 8 neonates of mothers with pre-gestational type I diabetes mellitus (followed up for mean $7.9 \pm 1.3$ years) in group A. Gestational age at diagnosis of GDM was $27.4 \pm 2.4$ weeks, and

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