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The relationship between the oxidative stress and the cardiac hypertrophy in infants of diabetic mothers☆

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ABSTRACT

Recently, oxidative stress was suggested to play a role in maternal and fetal complications of diabetic pregnancies. The aim of this study is to evaluate the global oxidant and antioxidant status in infants of diabetic mothers (IDM) via measurement of total antioxidant capacity (TAC) and total oxidant status (TOS) and to determine their association with the clinical and cardiac manifestations of gestational diabetes on infants. Forty five infants constituted the IDM group, 51 infants born to non diabetic mothers served as the control group. Umbilical cord blood was drawn from IDM and controls for TAC and TOS measurement. Echocardiographic measurements were performed in the first three days of life. Infants of diabetic mother had significantly higher TAC ($p = 0.024$), TOS ($p = 0.03$) and oxidative stress index (OSI, $p = 0.04$) levels compared to controls. Hemoglobin values were correlated to TOS ($r = 0.310$, $p = 0.03$) and OSI ($r = 0.310$, $p = 0.03$). Maternal HbA1c values were also correlated to TOS ($r = 0.576$, $p = 0.001$) and OSI ($r = 0.606$, $p < 0.001$). Systolic and diastolic interventicular septum measurements, and left ventricular mass were also correlated with TOS ($r = 0.330$, $p = 0.02$; $r = 0.453$, $p = 0.002$; $r = 0.404$, $p = 0.006$, respectively) and OSI ($r = 0.330$, $p = 0.02$; $r = 0.300$, $p = 0.04$, $r = 0.300$; $p = 0.04$, respectively). Oxidant–antioxidant balance is disturbed in favor of oxidants in IDM despite compensatory increase in TAC. The degree of oxidative stress is related to the severity of myocardial and hematological involvement in IDM in the first days of life and maternal glycemic control.

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1. Introduction

Gestational diabetes mellitus (GDM) is a common condition detected in 1–14% of all pregnancies [1]. It is associated with an increased risk of short and long-term adverse outcome for infant and mother [2]. Although hyperglycemia and fetal hyperinsulinemia are accused for the clinical manifestations of GDM, it was shown that even strict glycemic control could be associated with the development of diabetic complications [3,4]. Recently, oxidative stress was suggested to play a role in maternal and fetal complications of diabetic pregnancies [5–7]. In diabetic condition, end products of abnormal glucose metabolism lead to an increased synthesis of reactive oxygen species (ROS). Formation of advanced glycation end products, activation of hexosamine biosynthetic pathway, increased lipid peroxidation and the impaired antioxidant defense system result in accumulation of free radicals, eventually [8]. Both experimental and clinical studies have shown that in the presence of gestational diabetes, there is enhanced oxidative stress detectable in maternal and neonatal blood samples, placental tissue and amniotic fluid [8].

The degree of oxidative stress might change the course and the severity of the complications of the disease. There is no study assessing the effects of gestational diabetes associated oxidative stress on neonatal complications in the literature. In this study, we aimed to evaluate the global oxidant and antioxidant status in infants of diabetic mothers (IDM) via measurement of total antioxidant capacity (TAC) and total oxidant status (TOS) and to determine their association with the clinical and cardiac manifestations of gestational diabetes on infants.

2. Materials and methods

2.1. Patients

This prospective, observational study was conducted at Zeynep Kamil Maternity and Children's Education and Training Hospital. The NICU is a 60 bed unit with approximately 1500 annual admissions. Fifty infants born to mothers with GDM were enrolled between August 2011 and May 2012 in the study and constituted the study group. The control group consisted of 53 gestational age and weight matched infants whose mothers did not have GDM. Five patients in GDM group, two patients in control group were excluded because of ventricular septal defect and/or PDA detected with echocardiography. Gestational age was determined by the first day of the last menstrual period, prenatal ultrasound performed at 17–18 weeks or The New Ballard Score. Gestational diabetes mellitus was diagnosed according to American College of Obstetricians and Gynecologyst criteria [9]. A 50 g glucose challenge test was carried out independent of the time of day at 24–28 weeks of gestation to all pregnant women in the study and control groups. Patients with abnormal test result (plasma glucose at 1 h $\geq$ 140 mg/dL) underwent 100 g 3-h oral glucose tolerance test. If two of four diagnostic criteria were met (fasting plasma glucose, 1st, 2nd and 3rd hour plasma glucose levels of $\geq$95, $\geq$180, $\geq$155, and $\geq$140 mg/dL, respectively), GDM was diagnosed. All pregnant women with risk factors like obesity, GDM in previous pregnancy, family history of diabetes mellitus, and glucosuria are searched for diabetes mellitus in first visit in our hospital. None of the mothers in this study had previously established diabetes mellitus.

Exclusion criteria were maternal smoking habit, preeclampsia, chorioamnionitis, chromosomal or congenital malformation, asphyxia, early-onset sepsis, hemodynamically significant patent ductus arteriosus, tricuspid, mitral or aortic regurgitation, any congenital heart disease, hypotension requiring positive inotrope.

The study was approved by the local Ethics Committee. Written informed consent was obtained from the parents of each patient before recruiting into the study.

2.2. Biochemical methods

Blood samples were obtained from the umbilical cord at birth. After centrifugation at 5000 rpm, serum samples were stored at −80 °C before analysis. Serum TAC and TOS levels were measured as described by Erel [10,11]. Erel's method for serum TAC level measurement is based on the bleaching of the characteristic color of a more stable 2,2,2-azino-bis(3-ethylbenz-thiazoline-6-sulfonic acid) radical cation by antioxidants. The results were expressed in mmol trolox equivalent per liter. Erel's TOS measurement is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidative species and the measurement of the ferric ion by xylenol orange. The results were expressed in μmol H_2O_2 equivalents per liter. To evaluate the degree of oxidative stress, the oxidative stress index (OSI) was calculated with the TOS to TAC ratio [12]. For OSI calculation, the unit for TAC (mmol of trolox equivalent per liter) was converted to μmol of trolox equivalent per liter, and the OSI value was calculated as OSI = (TOS, μmol/L)/(TAC, μmol trolox equivalent/L/100).

Hemoglobin A1c levels of diabetic mothers at the last week of pregnancy were measured by a high perfusion liquid chromatography method (Roche, Mannheim, Germany).

2.3. Echocardiography

Echocardiographic and Doppler ultrasound scannings were performed with Philips EnVisor C HD (Royal Philips Electronics, Amsterdam, Netherlands) with a multifrequency 12 MHz sector probe in the first three days of life. All echocardiographic measurements were carried out by the same pediatric cardiologist (TY) in the standard precordial positions according to the recommendations of American Society of Echocardiography [13]. During the examination, patients were lying quietly in a supine position. The end-diastolic and end-systolic left ventricular dimensions, interventricular septal thickness (IVSs, IVSd), posterior wall thickness (PWs, PWd) were measured by two dimensionally guided M-mode echocardiography, using the leading-edge-to-leading-edge method and indexed by body surface area [13]. The left ventricular mass (LVM) was calculated with the formula derived by Devereux et al. and indexed by body surface area [14]. The fractional shortening (FS) was calculated from the standard formula to evaluate the systolic function. To estimate the whole left ventricular wall motion, fractional shortening area (FSA) was