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Original Article

Cord and maternal sera from small neonates share dysfunctional lipoproteins with proatherogenic properties: Evidence for Barker's hypothesis

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Embryo

BACKGROUND: Fetal growth restriction (GR) is associated with perinatal mortality and subsequent metabolic disorders in adulthood. Until now, there is little information regarding changes in the properties of lipoproteins from growth-restricted fetuses and their maternal sera.

OBJECTIVE: To identify unique lipoprotein biomarkers for fetal GR in maternal and cord sera from small neonates, we analyzed lipoprotein compositions and functions.

METHODS: Lipoprotein compositions and functions were compared between cord blood and maternal blood among small for gestational age neonates (SGA; n = 15, 2589 ± 50 g) and appropriate for gestational age neonates (AGA; n = 15) in Korea.

RESULTS: Cord blood from the SGA group showed 2-fold higher triglyceride (TG) and TG/high-density lipoprotein cholesterol levels than the AGA group as well as significantly lower (up to 20%) paraoxonase activity and apolipoprotein (apo) A-I content. The SGA group showed the highest cholesteryl ester transfer protein activities in both cord and maternal sera. SGA neonates showed elevated apo-B content in very low-density lipoprotein, 52% reduction of apo A-I content in high-density lipoprotein, and 30% increased glycation ($P < .001$) compared with AGA neonates. Especially, low-density lipoprotein from the SGA group showed 1.9-fold higher sensitivity to oxidation as well as 3-fold greater uptake into macrophages, suggesting stronger proatherosclerotic properties.

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Lipoproteins from maternal serum of SGA neonates showed greater oxidation along with TG enrichment and loss of antioxidant ability. On microinjection of cord serum (50 nL) into zebrafish embryos, the SGA group showed the most severe embryonic damage.

CONCLUSIONS: Lipoproteins from cord and maternal sera of SGA neonates resulted in severe impairment of functional and structural correlations accompanied by greater pro-oxidant and proatherosclerotic properties.

Introduction

Fetal growth restriction (GR) is known to be associated not only with perinatal mortality or morbidity but also with subsequent adult hypertension, atherosclerosis, diabetes, and metabolic disorders.[1,2] Previous studies have indicated that fetal GR may also affect development of fetal organs such as the heart or kidneys.[3]

It is well known that fetal GR is closely associated with increased rates of cardiovascular disease (CVD) and diabetes in adulthood (Barker's hypothesis).[4] Namely, fetal programming, which is the phenomenon of environmentally induced intrauterine adaptation to certain risk factors that impair fetal growth because of lifestyle and pollution exposure (diet, hormone exposure, and hypoxia), increases risk of various metabolic diseases later in life. Until now, there is a paucity of information on the possible mechanism that links intrauterine fetal GR with subsequent progression of metabolic diseases in adult life.

In terms of genetic factors, it is well known that small maternal height is associated with risk of preterm birth and low birthweight.[5] However, there has been no report investigating correlations among lipid and lipoprotein biomarkers between maternal and cord sera from low birthweight fetuses. Because incidence of CVD and diabetes is closely related with impaired lipid metabolism, it is possible that small for gestational age (SGA) neonates might have different characteristics in terms of lipid and lipoprotein metabolism.

High-density lipoprotein cholesterol (HDL-C) is inversely correlated with incidence of CVD and has potent antioxidant and anti-inflammatory activities.[6] However, HDL can be transformed into dysfunctional HDL, which is more atherogenic, via induction of aging stress such as oxidation and glycation.[7,8] In addition to the quantity of HDL-C, HDL quality has recently been demonstrated to prevent CVD and diabetes. However, there has been no report elucidating lipoprotein properties in cord and maternal sera with relation to fetal growth and cardiovascular risk.

To identify unique lipoprotein biomarkers for fetal GR in cord and maternal sera, we analyzed lipoprotein compositions and functions. This study was designed to compare lipid and lipoprotein properties in cord blood among SGA and AGA neonates as well as their mothers. We compared 4 classes of lipoproteins: very low-density lipoprotein (VLDL), LDL, HDL_2, and HDL_3, which were individually separated from subjects based on their structural and functional modifications. Finally, we analyzed cord sera between SGA and appropriate for gestational age (AGA) neonates as well as their mothers to compare biomarkers of lipoprotein parameters.

Materials and methods

Collection of umbilical cord blood and maternal blood

The study population consisted of SGA and AGA neonates who were delivered, and cord blood was collected between February 2014 and August 2014 at Seoul Metropolitan Government Seoul National University Boramae Medical Center.

During the study period, 15 SGA neonates (2589 ± 50 g) met the inclusion criteria: (1) term delivery; (2) singleton pregnancy; (3) without identifiable maternal disease or major fetal anomalies. SGA were defined as birthweight <10th percentile. AGA (n = 15, 3213 ± 63 g) neonates were defined as within the 10th to 90th percentile for gestational age and were selected after matching for gestational age upon delivery of SGA neonates. The 10th percentile values for each gestational age were derived from Korean reference data.[9] The Institutional Review Board of Seoul Metropolitan Government Seoul National University Boramae Medical Center approved this study, and patients provided written informed consent for the collection and use of cord blood samples for research purposes (IRB No. SNUH 16-2014-66).

Cord plasma analysis

Umbilical cord blood was taken at the time of delivery. Blood was collected using a vacutainer (BD sciences, Franklin Lakes, NJ) containing ethylenediaminetetraacetic acid (final 1 mM). Plasma was isolated by low-speed centrifugation and stored at −70°C until analysis. Blood parameters such as lipid and glucose concentrations were determined using an automatic blood analyzer (Chemistry analyzer AU4500; Olympus, Tokyo, Japan) and by manual determination using a commercially available assay kit. Plasma total cholesterol (TC), HDL-C, triglyceride (TG), and glucose levels were determined using commercial assay kits (Wako Pure Chemical, Osaka, Japan). LDL cholesterol (LDL-C) was calculated using the Friedewald formula: LDL-C = TC − (HDL-C − [TG/5]).