Developmental Origins of Cardiovascular Disease
– Cholesterol Metabolism and Higher Carotid Artery Intima-Media Thickness in Young Adults Born Small for Gestational Age –
Tomoo Okada, MD, PhD

Cardiovascular risk factors are identifiable in childhood and are predictive of adulthood risk for coronary artery disease.\(^1\) Autopsy studies of youths have established a strong association between cardiovascular risk factors and early stages of coronary atherosclerosis.\(^2\) Longitudinal observation studies have shown that coronary heart disease (CHD) risk factors measured in adolescence predict markers of atherosclerosis measured by noninvasive methods. The Muscatine Study,\(^3\) the Bogalusa Heart Study\(^4\) and the Cardiovascular Risk in Young Finns Study\(^5\) showed that the CHD risk factors, including elevated low-density lipoprotein (LDL)-cholesterol concentration, predicted carotid artery intima-media thickness (CA-IMT) measured 15–20 years later.

On the other hand, it became apparent that birth weight was inversely correlated with increased early death secondary to CHD. Barker et al proposed a hypothesis that undernutrition in utero permanently changes the body’s structure, function and metabolism in ways that lead to CHD in later life.\(^6\) Their epidemiological findings have been confirmed around the world. In a meta-analysis, the relative risk of adult CHD was 0.84 for each 1 kg increase in birth weight.\(^7\) In addition, profound effects are demonstrated if there is a “mismatch” between the pre- and postnatal environments. The degree of mismatch can be increased by poorer intrauterine conditions or richer conditions after birth.\(^8\) An animal study confirmed that mismatched pre- and postnatal nutrition leads to cardiovascular dysfunction.\(^9\) However, the precise mechanisms underlying the association between birth weight and atherosclerosis remain poorly understood.

In this issue of the Journal, Salonen et al investigated cardiovascular risks in 20-year-old adults born small-for-gestational age (SGA).\(^10\) At first, they demonstrated that at 12 and 20 years of age the SGA subjects had higher serum LDL-cholesterol concentrations, lower high-density lipoprotein (HDL)-cholesterol concentrations and higher LDL/HDL-cholesterol ratios than the subjects that were born appropriate-for-gestational age (AGA). In a meta-analysis of 28 studies with 32 observations (6 in infants, 14 in adolescents, 12 in adults),\(^11\) an inverse association between birth weight and total cholesterol (TC) in the cross-sectional studies was observed (\(-0.048\) mmol/L per kg) that was similar in strength at all ages. Thus, the relationship of birth weight to TC appears to be weak and is probably of limited public health importance. However, in order to evaluate intrauterine undernutrition, birth weight should be analyzed for gestational age. Furthermore, the degree of mismatch should also be considered. It has been reported that SGA infants with postnatal rapid weight gain exhibit a higher percentage of body fat, more central adiposity, higher triglyceride and lower HDL-cholesterol levels, and reduced insulin sensitivity, which predisposes them to cardiovascular disease and type 2 diabetes when they become young adults.\(^12\) Rapid postnatal weight gain during the first few months may be a good clinical marker of nutritional mismatch.\(^13\)

Second, Salonen et al investigated CA-IMT and brachial artery flow-mediated dilatation, which can detect precursors of atherosclerotic changes. However, no significant difference between SGA and AGA subjects at 20 years of age was demonstrated. In a study of young adults aged 27–30 years, low birth weight was only associated with increased CA-IMT in those who experienced severe intrauterine growth retardation and in those who showed rapid postnatal growth.\(^13\) Recently, it was also found that low birth weight has been associated with impaired endothelial function in children, such as increased pulse wave velocity, abnormal various arterial stiffness, distensibility and compliance measured by various techniques, which impair the aortic elastin synthesis in fetuses with growth restriction.\(^14\) A study tested endothelial function for vasodilator response to acetylcholine in neonates, and infants born with a low birth weight or SGA showed decreased vasodilation.\(^14\) Thus, nutritional mismatch may be a key factor for increased CA-IMT or decreased vasodilatation in arteries.

Other cardiovascular risk factors that have been detected in adults born SGA include reduced adiponectin concentration, hypertension and increased inflammatory markers. Perinatal nutritional status is critical for various risk factors. In previous studies, undernutrition in utero has been evaluated simply by birth weight itself or birth weight for gestational age. In addition, the degree of mismatch was estimated

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received August 22, 2010; accepted August 23, 2010; released online October 16, 2010
Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan
Mailing address: Tomoo Okada, MD, PhD, Department of Pediatrics and Child Health, Nihon University School of Medicine, 30-1 Oyaguchi Kamicho, Itabashi-ku, Tokyo 173-8610, Japan. E-mail: tomokada@med.nihon-u.ac.jp
All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
by postnatal rapid weight gain. However, adiponectin, insulin-like growth factor-I and lipoprotein lipase mass concentrations, which are closely linked with the development of atherosclerosis, also demonstrate a rapid increase in neonatal period with fat accumulation.15

The mechanism of developmental origins of health and disease (DOHaD), including mediating metabolic and hormonal factors, should be precisely investigated in further studies. The concept of DOHaD has provided us with a new approach to preventing cardiovascular disease. Better management of undernutrition during gestation and neonatal growth during the early postnatal period is an important theme for future health.

References