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Pediatric Non-High-Density Lipoprotein Cholesterol, the Metabolic syndrome, and Insulin Resistance

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The article by Li et al in this issue of *The Journal* presents interesting new data on the cross-sectional association of non-HDL-cholesterol (LDL- and VLDL-cholesterol) with the metabolic syndrome (MetS) in US youth (1). This finding that raises as many issues as it settles, but should guide future analyses into new directions. The data come from the 1999–2004 National Health and Nutrition Survey, with the cohort including a population-based sample of 2,734 adolescents ages 12–19 years. Because there is no single definition for MetS for this age group, the authors employed four different definitions: 1) the Third Report of the National Cholesterol Education program Expert Panel (NCEP III), 2) the NCEP II adapted for children and adolescents (NCEP III Peds), 3) the International Diabetes Federation (IDF) for adults, and 4) the IDF adapted for children and adolescents (IDF-Peds). These definitions were carefully laid out and different cutoffs of non-HDL-C used.

For each MetS definition, a ROC curve was generated from a logistic model, which used non-HDL-C to predict MetS. The optimum cutoff for non-HDL-C was determined using Youdan's index. Then, for the optimum cutoff as well as 70th and 90th percentiles of non-HDL-C, the sensitivities and specificities of MetS were calculated according to each MetS definition. Results differed across cutoffs and definitions, but consistently showed that non-HDL-C was a significant predictor of concurrent MetS.

A central link in the non-HDL-C—MetS chain is insulin resistance (IR). The spark that ignited interest in MetS was Reaven's Banting Lecture in 1988 (1), in which he argued forcefully for a central role of IR and resulting hyperinsulinemia in both type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Stating that IR is necessary but not sufficient for development of T2DM, Reaven (1) discussed the ways individuals respond to IR, concluding that the "fact that an insulin-resistant subject may not become diabetic does *not* mean that they suffer no untoward consequences (emphasis added)." Reaven then discussed some of the "untoward" sequelae of IR beyond the inability of the β -cell to compensate by producing more insulin (i.e., diabetes), weaving together several risk factors including hypertension, low HDL-C and high triglyceride (TG) that are associated with IR—hyperinsulinemia and hyperglycemic states (1). He concluded "...there is a series of related variables—syndrome X—that tends to occur in the same individual and may be of enormous

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importance in the genesis of CAD.” He brought his argument to a close by pointing out the association of IR with obesity and lack of physical activity (1). Thus, based on a foundation of IR-hyperinsulinemia (2), we have here all the essential elements of what became the MetS, an alternative physiological model for development of CVD without recourse to LDL-C, one that supplemented and extended the original model. From Reaven’s 1988 Banting Lecture (1) onwards, there has been a steady stream of articles focusing on the conjoint occurrence of the MetS factors in people with or at risk of T2DM and CVD, noting among other things that although the relative risk of CVD associated with high LDL-C is significant, most people with incident CVD do not have high LDL-C, defined by the upper 5 or 10 percentiles. The findings of Li et al suggest a kind of “unified field theory,” pulling together the standard lipid model (LDL-C—apoB 100) with an apoB48 model, with dense LDL and linking the two models together.

The strong association of fasting non-HDL-C concentration with MetS among U.S. youth described by Li et al (1) makes sense physiologically, given the underlying association of IR-hyperinsulinemia (IR) with MetS (2,3) and with overproduction of VLDL cholesterol, a major component of non-HDL-C (4). IR and resulting hyperinsulinemia are associated with all of the major components of the MetS, glucose, triglycerides, HDL-C, obesity and centripetal obesity, and hypertension (5). IR is also associated with an increased concentration of dense LDL particles, (rich in apoB 100 and relatively lipid poor), which is prospectively associated with both T2DM and CVD (6–8). IR also associates with increased apo B 48 (chylomicrons and VLDL-C), involving increased TG, and is inversely associated with HDL-C (2). The TG/HDL-C ratio appears to be a marker for hyperinsulinemia (3). Fasting serum insulin independently and uniformly improves the prediction of CVD status beyond traditional risk factors and lipid variables in patients referred for treatment of hyperlipidemia (9). IR is an independent risk factor for future CVD (10), thus explaining to some degree the occurrence of CVD in patients with “normal” LDL-C.

Childhood MetS and its separate components are associated with T2DM in young adulthood (11,12). Pre-teen IR and insulin level and rapidly increasing IR during adolescence identify girls who are at greater risk of future impaired fasting glucose and T2DM (13). In addition, pre-teen IR, interacting with high fat diets, identifies adolescent girls who are at greater risk of weight gain (14). Ten-year increases in BMI from ages 8–9 to 18–19 are significantly and independently associated with a 3-way interaction between age 9–10 insulin, adolescent caloric intake, and race (higher in black girls (14). Hyperinsulinemia and MetS at mean age 10 years in black and white schoolgirls predict development of impaired fasting glucose and T2DM by age 24 (15).

Childhood insulin Z scores and insulin Z scores 15 years later are correlated, $r = 0.30$, $p < .001$ (15). In a 15 year prospective study of schoolgirls, childhood insulin (partial $R^2 = 40\%$ was a major independent predictor for average insulin Z score during the 15-year follow-up (16). Childhood insulin tracks into young adulthood (15), and it would be expected that IR-hyperinsulinemia’s effect on the components of MetS would persist from childhood into young adulthood. Thus, MetS in childhood predicts adult MetS and T2DM 25–30 years later in adulthood (12).

The pediatric link between MetS and non-HDL-C cholesterol, as identified by Li et al in the current issue of *The Journal*, may be related both to the association of IR with TG, a major component of MetS, and the role of TG (VLDL-C) as a major component of non-HDL-C and an independent risk factor for CVD. We have recently assessed the relationship of childhood TG to adult cardiovascular events in the Princeton Follow-up Study, prospective 22- to 31-year follow-up studies (1998–2003) in former schoolchildren first studied in 1973–1976 (17). The major novel finding of this study was that childhood TG was

consistently and independently associated with young adult CVD. The distributions of both childhood and adult TG were shifted to higher levels in cases compared with controls (17). Childhood TG level was a significant, independent explanatory variable for young adult CVD hazard (hazard ratio, 5.35; 95% confidence interval, 1.69–20 (for each 1 unit increase in natural logarithm scale), along with adult T2DM (hazard ratio, 19.4; 95% confidence interval, 4.24–114.2). These findings are congruent with studies in adults where non-fasting TG (18–20) and fasting TG (18,21) are independent risk factors for CVD.

What is needed are prospective studies between pediatric non-HDL-C, TG, IR, MetS, and the development of CVD events and T2DM in adulthood. We have recently assessed relationships of childhood non-HDL-C to adult CVD events In the Princeton Follow-up Study, a prospective 22- to 31-year follow-up of former schoolchildren first studied in 1973–1976 (17). Unlike childhood TG, which was a significant independent correlate of CVD events in adulthood, non-HDL-C was not a significant risk factor for CVD in this cohort at mean age 38.5 years, possibly due to widespread reported use of statins by cohort members. Future research will help to refine our understanding of those relationships.

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