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Combined dyslipidemia in childhood

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Abstract: Combined dyslipidemia (CD) is now the predominant dyslipidemic pattern in childhood, characterized by moderate-to-severe elevation in triglycerides and non–high-density lipoprotein cholesterol (non-HDL-C), minimal elevation in low-density lipoprotein cholesterol (LDL-C), and reduced HDL-C. Nuclear magnetic resonance spectroscopy shows that the CD pattern is represented at the lipid subpopulation level as an increase in small, dense LDL and in overall LDL particle number plus a reduction in total HDL-C and large HDL particles, a highly atherogenic pattern. In youth, CD occurs almost exclusively with obesity and is highly prevalent, seen in more than 40% of obese adolescents. CD in childhood predicts pathologic evidence of atherosclerosis and vascular dysfunction in adolescence and young adulthood, and early clinical cardiovascular events in adult life. There is a tight connection between CD, visceral adiposity, insulin resistance, nonalcoholic fatty liver disease, and the metabolic syndrome, suggesting an integrated pathophysiological response to excessive weight gain. Weight loss, changes in dietary composition, and increases in physical activity have all been shown to improve CD significantly in children and adolescents in short-term studies. Most importantly, even small amounts of weight loss are associated with significant decreases in triglyceride levels and increases in HDL-C levels with improvement in lipid subpopulations. Diet change focused on limitation of simple carbohydrate intake with specific elimination of all sugar-sweetened beverages is very effective. Evidence-based recommendations for initiating diet and activity change are provided. Rarely, drug therapy is needed, and the evidence for drug treatment of CD in childhood is reviewed.

Definition and prevalence

The pediatric obesity epidemic has resulted in a large population of children and adolescents with secondary combined dyslipidemia (CD), the combined dyslipidemia of obesity (CDO). This is now the predominant dyslipidemic pattern in childhood, with moderate-to-severe elevation in triglycerides (TGs) and non–high-density lipoprotein cholesterol (non-HDL-C), no or mild elevation in low-density lipoprotein cholesterol (LDL-C), and reduced HDL-C.[1] Analysis by nuclear magnetic resonance (NMR) spectroscopy shows that the CD pattern on standard lipid profile is represented at the lipid subpopulation level as both an increase in small, dense LDL and in overall LDL particle number plus a reduction in total HDL-C and in large HDL particles.[2–4] High LDL particle number and elevated small, dense LDL particles have each been shown to predict clinical cardiovascular disease (CVD).[5–11] The atherogenicity of high LDL particle number and small, dense LDL is complex and is thought to include the high concentration of circulating LDL particles, decreased binding of small, dense LDL particles to the LDL receptor, prolonged residence time in plasma and therefore prolonged arterial wall exposure, greater binding of small, dense LDL particles to arterial wall proteoglycans and increased susceptibility to oxidation.[12–18] The association of the atherogenic lipoprotein subclass profile with obesity

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in childhood has been recognized for many years.[19] The CD pattern seen with traditional lipid profile analysis identifies the atherogenic pattern seen with lipid subpopulation analysis. National Health and Nutrition Examination Survey (NHANES) data indicate this pattern is highly prevalent, present in more than 40% of adolescents with body mass index (BMI) >95th percentile.[20] Obesity is also highly prevalent, affecting 16.9% of American children and adolescents, with up to 85% of overweight adolescents becoming obese adults.[21,22] In the short term, 50% of obese adolescents have at least one, and 10% have 3 or more cardiovascular risk factors, including CD, hypertension, and insulin resistance.[23,24] In the long term, childhood obesity predicts type II diabetes mellitus, premature CVD, and early mortality.[25] From NHANES data, the mean and median values of total cholesterol (TC), LDL-C, and glucose have remained unchanged over multiple successive cohorts of US children and adolescents, but there has been a significant increase in mean and median values of TG and a decrease in HDL-C.[26] A subgroup of patients often seen with CDO are children and adolescents who are being treated with second-generation antipsychotic medications. These medications are being commonly and increasingly prescribed in the pediatric age group.[27] Among these drugs, several are known to be associated with sudden and severe weight gain and with significant increases in TGs and TC and reductions in HDL-C.[28] Taken together, these findings suggest that CD may become even more prevalent in the future.

In addition to standard lipid profile measures, elevated non–HDL-C and the TG/HDL-C ratio have emerged as useful additional lipid measures in patients being evaluated for CDO. Non–HDL-C is a measure of the cholesterol content of all the plasma atherogenic lipoproteins. TC and HDL-C can be measured accurately in plasma from nonfasting patients with non–HDL-C calculated by subtracting HDL-C from TC.[1] Epidemiologic studies show that childhood non–HDL-C correlates well with adult levels. In a longitudinal cohort of more than a 1000 subjects from the Bogalusa study, evaluated both as children ages 5 to 14 years and as adults 27 years later, non–HDL-C was a strong predictor of adult lipid levels independent of baseline BMI and BMI change.[29] In pathology studies in children, adolescents and young adults, non–HDL-C and HDL-C levels were the best lipid predictors of pathologic atherosclerotic lesions, each significantly associated with fatty streaks in the thoracic aorta and abdominal aorta and in the right coronary artery and with raised lesions in all 3 sites; non–HDL-C and HDL-C levels were more strongly associated with pathologic lesions than any other lipid measure.[30] Non–HDL-C and LDL-C measured in childhood were also significant predictors of subclinical atherosclerosis assessed by higher carotid intima media thickness (cIMT) measurements in adulthood.[31] Overall, childhood non–HDL-C was as good, or better, than other lipoprotein measures in predicting subclinical atherosclerosis assessed subsequently by cIMT in adulthood. Non–HDL-C concentrations were also associated with the metabolic syndrome in 12- to 19-year olds assessed as part of NHANES.[32] In adults, non–HDL-C has been shown to be a better independent predictor of CVD events than LDL-C.[33,34] The recent National Heart, Lung and Blood Institute (NHLBI) guidelines include normative values for non–HDL-C and recommend screening with non–HDL-C in childhood.[1]

The TG/HDL-C ratio has been shown to be a strong predictor of coronary disease extent in adults and is considered to be a surrogate index of the atherogenicity of the plasma lipid profile.[35,36] In children, an elevated TG/HDL-C ratio correlates with insulin resistance and with nonalcoholic fatty liver disease (NAFLD).[37–39] In a study of normal weight, overweight, and obese white children and adolescents, top tertile TG/HDL-C correlated significantly with increased cIMT in multivariate analysis.[39] There are ethnic differences in lipids and insulin resistance, which manifest during adolescence: African-Americans have significantly lower TGs and higher HDL-C levels, and this impacts non–HDL-C levels and the TG/HDL-C ratio.[40–43] In a study of obese black and white adolescents, TG/HDL-C has been shown to be a surrogate marker for elevated small dense lipoprotein particles on NMR spectroscopic analysis.[44] A TG/HDL-C ratio above 3 and non–HDL-C above 120 mg/dL in white subjects and TG/HDL-C ratio above 2.5 and non–HDL-C levels above 145 mg/dL in black subjects proved to be the best predictors of LDL-C particle concentration. In this study, the combination of waist circumference with TG/HDL-C ratio explained 79% of the variance in small LDL particle and total LDL particle burden.[44] The HEALTHY study characterized lipids in a diverse population of 2384 sixth grade children and found that 33% of overweight/obese children had a TG/HDL-C ratio >3.0 and 11.2% had non–HDL-C >145 mg/dL.[45] NMR spectroscopy confirmed that these values on standard lipid profile identified the lipid subpopulation pattern of increased total and small, dense LDL particles.[46] CDO expressed as TG/HDL ratio correlated significantly with greater BMI, waist circumference, and insulin resistance.

Normal lipid values in childhood are shown in Table 1.[1] Based on 95th percentile values, normal TG levels are <100 mg/dL in children younger than age 10 years and <130 mg/dL at ages 10 to 18 years. Normal non–HDL-C levels are <145 mg/dL. HDL-C averages 55 mg/dL in males and females before puberty, after which mean HDL-C drops to 45 mg/dL in males. The diagnosis of CD requires that among TC, LDL-C, TG, and non–HDL-C, the average of a least 2 measurements is above the 95th percentile, plus or minus HDL-C below the 5th percentile. In children or adolescents with CD, TG levels are usually between 150 and 400 mg/dL, HDL-C is ~40 mg/dL, non–HDL-C is ≥145 mg/dL, and TG/HDL-C ratio exceeds 3 in whites and 2.5 in blacks.

In the literature, the terminology describing CD also includes “mixed dyslipidemia” and “atherogenic