There has been increasing realization that cardiovascular risk begins in childhood, coinciding with mounting evidence for pathological change and tracking of risk factors—including high-density lipoprotein cholesterol (HDL-C)\(^1\)—to adulthood. Consequently, American Academy of Pediatrics and American Heart Association guidelines based on the available evidence have largely targeted low-density lipoprotein cholesterol (LDL-C), with additional recommendations on managing HDL-C and triglyceride as secondary targets.\(^2,3\) However, low HDL-C consistently has had a high prevalence relative to the other metabolic syndrome criteria\(^4\) and, over the past two decades, the metabolic syndrome has unfortunately been increasingly recognized in adolescents. The following case illustrates a fairly common presentation and clinical course in which an adolescent presents with risk factors including low HDL-C.

**Case:** A 14-year-old Hispanic boy presented for evaluation of risk factors associated with obesity. His body mass index (BMI) was 40.2, blood pressure (BP) 132/84, P92. The family history was positive for type 2 diabetes in his father and paternal grandmother. His maternal grandfather had a heart attack at age 57. His father smokes one pack of cigarettes a day. The teen’s physical examination revealed mild acanthosis nigricans around the neck and on the elbows. Laboratory testing: glucose 96 mg/dL; lipid profile: triglyceride 156, cholesterol 148, HDL-C 23, calculated LDL-C 94 and non HDL-C 125 mg/dL. The initial assessment was that he is insulin-resistant with risk for type 2 diabetes and associated cardiovascular disease. He was referred to a dietitian for instruction to exercise for more than 30 minutes a day (walking with family and football with friends). At the six-month follow-up, his BMI had increased to 42.

A repeat lipid profile showed triglyceride 172, cholesterol 152, HDL-C 22, LDL-C 96, non HDL-C 130 mg/dL, fasting glucose 95 mg/dL and glycated hemoglobin (HbA1c) 5.9%. The lifestyle treatment plan was continued. Four months later, he presented with polyuria and polydipsia, and random glucose was 182 mg/dL with HbA1c 7.1%. He was treated with 500mg of metformin twice daily (bid) with intensive revision of lifestyle measures. After three months, the lipid profile showed triglyceride 148, cholesterol 154, HDL-C 24, LDL-C 100 and non HDL-C 130 mg/dL. His BMI has decreased to 36 and his HbA1c is 6.4 %.
Commentary
This boy’s clinical course characterizes an initial presentation with the metabolic syndrome and progression to type 2 diabetes. HDL-C was low at the onset and was only moderately responsive to lifestyle therapy. Unfortunately, the presentation is consistent with the worldwide trend for a classic sequence of events in adolescents, particularly in predisposed populations.

In the National Health and Nutrition Examination Survey (NHANES) conducted from 2001 to 2006, the metabolic syndrome prevalence was highest in Hispanic youths (11.2%) at ages 12 to 19, followed by non-Hispanic whites (8.9%) and lowest in African-Americans (4.0%), in part attributed to their higher HDL-C.4 Pooled data from the Australian Childhood Determinants of Adult Health Study, the Cardiovascular Risk in Young Finns Study and the United States Bogalusa Heart Study have provided combined longitudinal data on lipoprotein levels, including HDL-C, that tracks to levels in adulthood and predicts carotid intima-media thickness, particularly when they are obese5, and consequently have strengthened the case for early detection and lifestyle intervention with the goal of reversing the risk factors.

It can be assumed that the patient’s obesity contributed to the low HDL-C. Although his triglyceride of 156 mg/dL does not appear high, the Lipid Research Clinic’s 90th percentile for 14-year-old boys is 112 mg/dL. Triglyceride values often can be well above 150 mg/dL and, therefore, can play a significant role in HDL-C lowering via enhanced cholesteryl ester transfer protein (CETP)-mediated delivery of triglyceride to HDL. A significant number of cases with low HDL-C may be non-obese and without the metabolic syndrome, as seen in the NHANES study.4 Such cases may present with persistently low HDL-C and could be associated with a genetic disorder of HDL metabolism.

Monogenic or multi-genic causes can be operative6 and could be an explanation for persistently low levels despite treatment. The C230 allele for the ABCA1 transporter is selective for Native American and Hispanic populations and could accentuate the HDL-C-lowering effect of obesity by compromising cholesterol efflux and both cardiovascular and diabetes risk.7 The allele was found in 29 of 36 Native American groups, but not in European, Asian or African individuals. Human embryonic kidney cells expressing the C230 allele showed a 27% cholesterol efflux reduction (p< 0.001), confirming that this variant has a functional effect in vitro.

Effective lifestyle education requires an individualized approach.

HDL-C is low in adolescents when they become obese and insulin resistant, as observed in the nationally representative NHANES population4, and the declines with increasing BMI tend to be worse in adolescent boys than in girls, most likely because of the action of testosterone on hepatic triglyceride lipase.8 Low HDL-C levels in youths with type 2 diabetes are attributable to persistent insulin resistance9 which, in our case, began before diabetes onset and continued during the transition from obesity to diabetes, as suggested by the presence of acanthosis nigricans. The onset of diabetes is likely to have worsened the HDL status, because glycosylation and oxidation of apolipoprotein A-1 (apo A-1), and formation of advanced glycosylation end-products impair HDL’s cardio-protective and anti-atherogenic properties, including the ability to promote cholesterol efflux, stabilize ABCA1 and inhibit the expression of adhesion molecules.10

Low and dysfunctional HDL has additional implications for populations at risk for type 2 diabetes, because there is mounting epidemiological11 and in vitro experimental data12 to support a role for HDL as the limiting factor in promoting cholesterol efflux from the β-cell and reducing the intracellular cholesterol load. The resulting intracellular cholesterol accumulation is found to compromise insulin secretion.12 Interestingly, other cell systems—such as fat and muscle cells—are under investigation for a similar interaction with HDL. This actively investigated area is supported by the finding that first-phase insulin secretion is decreased in Tangier heterozygotes because of their one defective ABCA1 allele, compromising cholesterol efflux from their β-cells.13 If the hypothesis is true, then it supports aggressive targeting of low or dysfunctional HDL for the primary prevention of type 2 diabetes. There also is support for preserving HDL’s important anti-inflammatory and anti-oxidative functions in the long term, beginning in childhood. The latter consideration becomes even more important in cases with elevated LDL-C or non-HDL-C.

Using lifestyle as the cornerstone of treatment can result in effective weight management and, generally, as triglycerides fall, HDL-C increases. A meta-analysis of randomized controlled trials showed that aerobic exercise decreases triglycerides in obese and overweight children and adolescents, but there was only a trend for increases in HDL-C.14 This is consistent with the moderate HDL-C elevation achieved in our case. Nevertheless, the cornerstone of management for low HDL-C in youths is lifestyle.15 This requires a comprehensive dietary and exercise prescription, preferably with sensitivity to motivational and behavioral needs,
including smoking-cessation counseling. Smoking strongly affects HDL-C and related outcomes in longitudinal studies such as the Young Finns study, in which smoking was identified as an unhealthy lifestyle occurring between youth and adulthood and affecting high-risk blood lipid and lipoprotein levels, including a low HDL-C in adulthood. Effective lifestyle education requires an individualized approach with sensitivity to age, gender, ethnic background, family support and participation, and close attention to all three pillars—diet, exercise and behavior—of successful intervention, ideally with support personnel for each modality delivered as a team approach in a multidisciplinary clinic setting.

We have observed obesity-related HDL lowering to occur at ages 5 to 9 years, suggesting that the onset of obesity and associated risk factors may occur even earlier, particularly in Native American and Hispanic populations. This includes babies exposed to the effects of diabetes during pregnancy. Thus, there is an increasingly good rationale for early and universal childhood screening for risk factors, including a lipid profile followed by early intervention, but this presents as a significant educational challenge for pediatricians and their support personnel.

HDL largely remains a residual risk factor in adults and is not yet regarded as a target for primary intervention. Thus, as in adults, there is no indication to target HDL-C with pharmaceutical agents as a primary target. Since “state of the art” approaches for increasing HDL-C in adults have largely been in the context of lowering residual risk after statin treatment, primary prevention by raising HDL-C with pharmaceutical agents has not yet had strong indication. However, when cases present with low HDL-C, it should be a signal to monitor LDL-C more closely and treat LDL-C to target, if indicated. Those of us who encounter cases with low HDL-C that is associated with apparent strong gene-environment interaction are watching with interest the developments of novel and potentially benign HDL-raising therapies. Treatment of lipid targets with a statin, fibrate or extended release (ER) niacin in childhood should be guideline-based and primarily directed at recommended dyslipidemic targets such as LDL-C and non-HDL-C, and preferably according to an ethics-approved protocol. New guidelines predicted to be announced this year may increase emphasis on HDL-C as a secondary target. In the case described, the LDL-C goal of 100mg/dL was achieved and good diabetes control was attained. Although the HDL-C remains low, lifestyle remains the main therapy, with no indication for further pharmaceutical intervention.

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