
COMBINED DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS

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ABSTRACT

Combined dyslipidemia (CD) is now the predominant hyperlipidemic pattern in childhood, characterized by moderate to severe elevation in triglycerides (TG) and non-high-density lipoprotein cholesterol (non-HDL-C) with reduced high-density lipoprotein cholesterol (HDL-C). In youth, CD occurs almost exclusively with obesity and is highly prevalent, seen in 30-60% of obese adolescents. With nuclear magnetic resonance spectroscopy, the CD pattern is represented as increased small, dense LDL and overall LDL particle number and decreased total HDL-C and large HDL particles, a highly atherogenic pattern. CD in childhood is associated with pathologic evidence of atherosclerosis and ultrasound findings of vascular dysfunction in children, adolescents, and young adults; it is also predictive of early clinical cardiovascular events in adult life. CD is strongly associated with visceral adiposity, insulin resistance, non-alcoholic fatty liver disease (NAFLD), and the metabolic syndrome, suggesting an underlying, integrated pathophysiologic response to excessive weight gain. In almost all cases, CD responds well to lifestyle intervention including weight loss, changes in dietary composition, and increased physical activity. Evidence-based recommendations for management of CD are provided. Rarely, drug therapy is needed and the evidence for drug treatment of CD in childhood is reviewed.

DEFINITION, ATHEROGENICITY, AND PREVALENCE

The pediatric obesity epidemic has resulted in a large population of children and adolescents with secondary combined dyslipidemia (CD). This is now the predominant hyperlipidemic pattern in childhood, characterized by moderate to severe elevation in triglycerides (TG) and non-high-density lipoprotein cholesterol (non-HDL-C) with reduced high-density lipoprotein cholesterol (HDL-C) (1).

Analysis by nuclear magnetic resonance spectroscopy (NMR) shows that the combined dyslipidemia pattern on standard lipid profile is represented at the lipid subpopulation level as increased small, dense LDL and LDL particle number with decreased total HDL-C and large HDL particles (2,3,4). High LDL particle number and elevated small, dense LDL particles have each been shown to predict clinical cardiovascular disease (5-11). The atherogenicity of this lipid subpopulation pattern is complex and includes 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). Consistent with these findings, genetic evidence from mutational analyses, genome-wide association studies, and Mendelian randomization studies indicates that triglycerides and

triglyceride-rich lipoproteins are an important source of increased small, dense LDL particle populations. The combined dyslipidemia pattern on traditional lipid profile analysis identifies the atherogenic pattern on lipid sub-population analysis.

Obesity is highly prevalent, affecting 18.5% of all-American youth and 20.6% in adolescents based on NHANES data from 2015-2016; up to 85% of overweight adolescents become obese adults (19,20). In the short term, 50% of obese adolescents have at least one, and 10% have 3 or more cardiovascular risk factors, including combined dyslipidemia, hypertension, and insulin resistance (21,22). In the long term, childhood obesity predicts type 2 diabetes mellitus, premature cardiovascular disease (CVD), and early mortality (23). NHANES data from 1999-2006 indicated CD was highly prevalent in obese youth, present in more than 40% of adolescents with body mass index (BMI) >95thile (24). A 2019 analysis of trends in fasting serum lipids using NHANES data from 1999-2000 to 2015-2016 in US adolescents aged 12 to 19 years showed significant favorable changes in mean levels of all lipid parameters for the sample population as a whole. By contrast, when analyzed by BMI category, obese adolescents showed no significant trend towards improvement in mean HDL-C or LDL-C levels. Although there was a trend towards improvement among obese subjects in total cholesterol, TGs, and

non-HDL-C, the prevalence of adverse levels in the last survey in 2015-2016 remained high: 22.3% for TGs, 29% for HDL-C and 10% for LDL-C (25). In cross-sectional data from multiple populations, 30 to 60% of obese youth have elevated TGs, usually associated with reduced HDL-C (26-28). The prevalence of CD increases as obesity severity increases (29-31).

In addition, selected second generation antipsychotic medications, increasingly prescribed in pediatric patients, are associated with severe weight gain and significant increases in triglycerides and reductions in HDL-C (32,33). Thus, CD is a prevalent and important problem.

LIPID PROFILE MEASURES

Normal lipid values in childhood are shown in Table 1 (1). In children younger than 10 years, the 95thile for TG is 100 mg/dL and at 10-18 years, the 95thile is 130 mg/dL. 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 a mean of 45 mg/dL in males. The diagnosis of CD requires that the average of a least 2 measurements of TG and/or non-HDL-C fall above the 95thile, plus HDL-C at or below the 5thile. TC and LDL-C levels may also be mildly elevated. In the typical lipid profile of a child or adolescent with CD, TG levels are between 150 and 400 mg/dL, HDL-C is ≤ 40mg/dL, non-HDL-C is ≥145 mg/dL and TG/HDL-C ratio exceeds 3 in whites and 2.5 in blacks.

Table 1. Acceptable, Borderline, and High Plasma Lipid and Lipoprotein Concentrations (mg/dL) for Children and Adolescents* (1)			
Category	Acceptable	Borderline	High
TC	< 170	170-199	≥ 200
LDL-C	< 110	110-129	≥ 130
Non-HDL-C	< 120	120-144	≥ 145
Triglycerides			
0-9 years	< 75	75-99	≥ 100
10-19 years	< 90	90-129	≥ 130
Category	Acceptable	Borderline	Low
HDL-C	>45	40-45	<40

NOTE: Values given are in mg/dL; to convert to SI units, divide the results for TC, LDL-C, HDL-C and non-HDL-C by 38.6; for TG, divide by 88.6.

* Values for plasma lipid and lipoprotein levels are from the 2011 NHLBI Expert Panel Guidelines (1). The cut points for high and borderline high represent the 95th and 75th percentiles, respectively. The low-cut point for HDL-C represents the 10th percentile.

www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm.

In addition to the standard lipid profile measures, non-HDL-C and the TG/HDL-C ratio are useful measures in patients being evaluated for CD. 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 the non-fasting state 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, independent of baseline BMI and BMI change (34). In autopsy studies in children, adolescents and young adults, non-HDL-C and HDL-C levels were the best lipid predictors of pathologic atherosclerotic lesions, better than any other lipid measure (35). Non-HDL-C measured in childhood was a significant predictor of subclinical atherosclerosis in adulthood, assessed by higher carotid intima media thickness (cIMT) measurements (36). In adults, non-HDL-C has been shown to be the best independent lipid predictor of cardiovascular disease events (37,38). Normative values for non-HDL-C are included in the 2011 NHLBI pediatric guidelines which recommend this measure for population screening (1) (Table 1).

The TG/HDL-C ratio is 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 (39,40). In children, an elevated TG/HDL-C ratio correlates with insulin resistance and with non-alcoholic fatty liver disease (41-43). 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 (43). There are ethnic differences in lipid measures which manifest during adolescence: African-Americans have significantly lower triglycerides and higher HDL-C levels and this impacts non-HDL-C and the TG/HDL-C ratio (44-47). In a study of obese black and white adolescents, TG/HDL-C and non-HDL-C were surrogate markers for elevated small dense lipoprotein particles on NMR spectroscopic analysis (48). 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 were the best lipid predictors of LDL-C particle concentration (48). The HEALTHY study characterized lipids in a large, diverse population of sixth grade children and found that 33% of overweight/obese children had an elevated TG/HDL-C ratio and 11.2% had an elevated non-HDL-C (49). NMR spectroscopy confirmed that the CD findings on standard lipid profile identified the

lipid subpopulation pattern of increased total and small, dense LDL particles (50).

GENETIC ASPECTS OF COMBINED DYSLIPIDEMIA

In the literature, the terminology describing combined dyslipidemia also includes “mixed dyslipidemia” and “atherogenic dyslipidemia” (51,52). Combined dyslipidemia is the term used most commonly in pediatrics (53). There is overlap in the lipid phenotype between CD and familial combined hyperlipidemia (FCHL), which was originally considered to be a genetically discrete entity (54,55). However, current evidence suggests that FCHL is a multigenic dyslipidemia with variable expression in different pedigrees (56,57). There is well-established familial aggregation of the combined dyslipidemia phenotype in pediatric and adult studies, beyond the historic studies of FCHL (58,59). Emerging evidence from gene sequencing studies suggests that variants in the genes controlling TG metabolism, particularly those encoding lipoprotein lipase, may be important factors in the expression of hypertriglyceridemia and combined dyslipidemia (59,60). As with CD, the mechanism of increased CVD risk in FCHL is the presence of increased numbers of apolipoprotein B-containing particles, particularly small, dense LDL particles, so genetic analysis is not critical for patient management at this time (61,62).

EVIDENCE FOR ACCELERATED ATHEROSCLEROSIS WITH COMBINED DYSLIPIDEMIA

An important initiating step in atherosclerosis is subendothelial retention of LDL-containing lipoproteins (63). Combined dyslipidemia is highly atherogenic because its sub-population composition with increased LDL particles and small dense LDL is associated with facilitated sub-endothelial retention by multiple mechanisms (12-18). Consistent with these findings, recent genetic evidence from mutational analyses, genome-wide association studies, and Mendelian randomization studies indicates that

triglycerides and triglyceride-rich lipoproteins are an important source of increased small, dense LDL particle populations. In childhood, the atherogenicity of combined dyslipidemia is seen in anatomic and histologic changes at autopsy and with structural and functional vascular changes in vivo. CD in childhood is also predictive of accelerated atherosclerosis and of early cardiovascular events in adult life. In both the Pathobiological Determinants of Atherosclerosis in Youth Study and the Bogalusa Heart Study, high non-HDL-C and low HDL-C were strongly associated with autopsy evidence of premature atherosclerosis (64-66). Obese youth with elevations in TG and low HDL-C had thicker CIMT, higher pulse wave velocity (PWV), and increased carotid artery stiffness (67-69). A strong association between higher TG/HDL-C ratio, higher non-HDL-C, and higher PWV in both lean and obese children has been demonstrated after adjustment for other CVD risk factors (70). CD identified in childhood is associated with atherosclerotic vascular change measured in adulthood by CIMT and PWV (71-73). Most importantly, in the long-term Princeton Follow-up Study, elevated TG and TG/HDL-C ratio at a mean age of 12 years predicted clinical cardiovascular events at late follow-up 3 to 4 decades later (74,75). This is the first childhood lipid parameter shown to be associated with premature clinical cardiovascular disease. Thus, the combined dyslipidemia pattern seen with obesity in childhood and adolescence identifies pathologic evidence of atherosclerosis and vascular dysfunction in adolescence and young adulthood, and predicts early clinical events in adult life.

While evidence like this in pediatrics strongly supported the importance of high triglycerides/combined dyslipidemia in the development of atherosclerotic vascular change and subsequent premature cardiovascular clinical cardiovascular disease, LDL-C has been the principal, long-time focus for investigation and management in adult atherosclerosis. Since the time this chapter was first developed in 2016, a flurry of studies in adults have addressed the importance of hypertriglyceridemia –

the “neglected major cardiovascular risk factor” – in atherogenesis (76). These include epidemiologic studies which identify high serum TGs as a marker for TG-rich lipoproteins, now recognized as strong, independent predictors of ASCVD and all-cause mortality; Mendelian randomization studies which identify TG-rich lipoproteins as causally associated with ASCVD and all-cause mortality; and intervention trials identifying high TGs and non-HDL-C as the mediators of residual atherosclerotic risk when LDL-C levels are below prescribed targets (77-80). Unfortunately, as discussed in other Endotext chapters, recent randomized trials using triglyceride lowering drugs have failed to demonstrate a decrease in atherosclerotic cardiovascular events in adults.

PATHOPHYSIOLOGIC ASSOCIATIONS

There is a tight connection between CD and obesity, visceral adiposity, insulin resistance, non-alcoholic fatty liver disease (NAFLD), and the metabolic syndrome.

Obesity

The association between CD and obesity is strong and consistent with CD seen in 20 to 60% of obese youth (25-27). The prevalence of CD increases as obesity severity increases (28-30). In multiple studies, excessive intake of sugars, particularly fructose, has been associated with obesity and with combined dyslipidemia in children and adults (81-87). By contrast, low sugar intake is associated with higher HDL in females during adolescence (88).

Visceral Adiposity

There is a close correlation between CD and abdominal obesity. In susceptible individuals with an underlying racial/ethnic/familial/genetic predisposition, excessive weight gain occurs disproportionately as visceral fat (VAT). This is thought to reflect the inability of the subcutaneous adipose tissue depot to expand, resulting in ectopic fat deposition, primarily in the viscera but also in the liver, heart, and skeletal muscle

(89,90). Based on correlation with dual-energy x-ray absorptiometry, waist circumference (WC) is an effective measure of abdominal obesity in youth, with WC above the 90th %ile for age and sex strongly predicting high TGs, reduced HDL-C, and hyperinsulinemia (91,92). Using NHANES norms for WC, the prevalence of abdominal obesity increased more than 65% in boys and girls aged 2 to 19 years between 1988-1994 and 1999-2004 (93,94). From NHANES survey results in 5- to 18-year-olds from 1999 to 2008, waist/height ratio (WHtR), another measure of central adiposity, was integrated with BMI percentiles and measures of cardiometabolic risk: obese subjects with normal WHtR < 0.5 had cardiometabolic risk similar to subjects with normal BMI percentiles, while increasing WHtR was significantly associated with dyslipidemia, insulin resistance and the metabolic syndrome (95).

There are known racial/ethnic differences in the tendency to develop visceral adiposity with Hispanic, Native-American, and Asian populations at elevated risk (96). Especially in Asians, increased VAT can develop in the absence of any other measure of adiposity and this is associated with hypertriglyceridemia, CD, insulin resistance, and type 2 diabetes (T2DM) (97). VAT contributes directly to high TGs because delivery of FFAs to the liver via the portal vein is proportionate to visceral fat mass. Progression of VAT correlates significantly with development of CD (98)

Insulin Resistance and Type 2 Diabetes

Insulin resistance is considered a primary abnormality in development of CD and associated cardiovascular disease. Obesity correlates with hyperinsulinemia in children, adolescents, and adults (99,100). In the Bogalusa Heart Study, serial cross-sectional surveys showed that higher BMI was associated with higher fasting insulin levels in childhood and adolescence and with higher fasting glucose levels in young adulthood (101). Insulin resistance (IR) correlates strongly with abdominal obesity, high TGs, and reduced HDL-C in children, adolescents, and adults.

During puberty, insulin resistance is physiologic with an average 50% decrease in insulin sensitivity, associated with compensatory doubling of insulin secretion to maintain glucose homeostasis. The pattern of insulin resistance is exaggerated in obese adolescents and persists after puberty is complete (102).

Hyperinsulinemia enhances hepatic VLDL synthesis, manifest as high TGs (103). At the tissue level, IR promotes lipoprotein lipase dysfunction, further elevating TGs (104). In normoglycemic adolescents, IR and CD were seen only in obese subjects and the dyslipidemia correlated with the degree of IR (105). In a hyperinsulinemic–euglycemic clamp study, elevated TGs with reduced HDL-C identified *in vivo* IR (41).

Progression from IR to impaired fasting glucose to type 2 diabetes (T2DM) has been documented in youth, especially with a family history of diabetes (101). T2DM is increasingly common in adolescents with a prevalence of 0.46 per 1000 individuals in 2009, a 31% increase from 2001 (106). In children and adults, the interplay between insulin resistance and dyslipidemia in normoglycemic and hyperglycemic individuals is complex and at this time, incompletely elucidated (107).

Non-Alcoholic Fatty Liver Disease

CD is also strongly linked with non-alcoholic fatty liver disease (NAFLD), defined as hepatic fat infiltration in >5% of hepatocytes with no evidence of hepatocellular injury on liver biopsy and no history of alcohol intake (109). NAFLD is highly correlated with obesity, affecting at least 38% of obese adolescents in autopsy series and ~50% in epidemiologic surveys (109,110). On evaluation, the most common findings are hepatomegaly and mild-to-moderate elevation in serum alanine aminotransferase (ALT) (108). Hepatic fat deposition usually occurs in the context of generalized obesity but reflects much more strongly, the presence of increased visceral adiposity. In obese children and adolescents, sequential increase in waist circumference, a proxy measure of visceral fat, is

associated with progressive increase in odds ratio for prediction of ultrasound-detected hepatic steatosis (112). NAFLD is strongly associated with insulin resistance and all of the components of the metabolic syndrome (112-114). In a study of adolescents with biopsy-proven NAFLD, 80% had biochemical evidence of insulin resistance (114). In more than half of subjects with NAFLD, the atherogenic CD pattern is seen on a standard lipid profile and with NMR analysis (115). As with CD, dietary sugar is considered to play a significant role in the development and progression of NAFLD – in a recent randomized controlled trial, provision of a diet low in free sugar content for 8 weeks led to significant improvements in hepatic steatosis (116). In children and adolescents, NAFLD is associated with atherosclerosis at autopsy and with ultrasound vascular markers associated with atherosclerosis (117). In adults, NAFLD has been shown to be a strong, independent predictor of CVD (118).

Metabolic Syndrome

CD, insulin resistance, and visceral adiposity are each components of the metabolic syndrome (MS), first described by Reaven in 1988 and identified as a high-risk constellation for atherosclerotic disease (119). Non-alcoholic fatty liver disease (NAFLD) has been added as a sixth component of the metabolic syndrome (120). In the U.S., the metabolic syndrome is reported in 23% of adults, including 7% of men and 6% of women in the 20- to 30-year-old age group (121,122). There is as yet no agreed-upon definition for the metabolic syndrome in childhood, but analysis of cross-sectional data from NHANES (1988-1994) revealed the MS cluster in 28.7% of obese adolescents compared with 0.1% of those with a BMI below the 85th percentile. As age and the degree of obesity increased, the prevalence of the MS cluster increased, reported in 38.7% of moderately obese (mean body mass index [BMI] 33.4 kg/m²) and 49.7% of severely obese (mean BMI 40.6 kg/m²) adolescents (123,124). Presence of the metabolic syndrome cluster at a mean of 12 years of age was an

independent predictor of adult cardiovascular disease 25 years later (125).

Summary

CD is strongly associated with a complex of related cardiometabolic factors. From existing studies, it appears that visceral adiposity develops in children and adolescents with underlying racial/ethnic/familial/genetic susceptibility in response to excessive weight gain. This initiates a cascade of pathophysiologic reactions which result in CD, insulin resistance/ T2DM, and NAFLD and combined, the metabolic syndrome. These prevalent combinations are powerful predictors of cardiometabolic risk (1,115,116).

MAKING THE DIAGNOSIS OF COMBINED DYSLIPIDEMIA

The 2011 NHLBI pediatric guidelines were the first to recognize the importance of high TGs and CD in childhood (1). The guidelines recommend selective lipid screening when overweight or obesity is first identified ($\text{BMI} \geq 85^{\text{th}}$ ile for age/sex); when any other major cardiovascular risk is present; and when there is a family history of early cardiovascular disease or of treated dyslipidemia (1). While non-fasting measures of total cholesterol and HDL-C are accurate and non-HDL-C can be used for general screening, hypertriglyceridemia can only be identified on a fasting lipid profile (FLP) so a FLP is recommended for selective screening in these settings.

- Normative values for the lipid components are shown in table 1 with values above the 95thile considered elevated for TC, TG, non-HDL-C, and LDL-C; and below the 5thile considered as reduced for HDL-C.
- If the first FLP results are abnormal, testing should be repeated after 2 weeks but before 3 months and results averaged to determine baseline lipid values.

- Measurement of TGs is subject to considerable biologic variability with median variation between measurements of 23.5% compared with ~ 5-6% for cholesterol and HDL-C so if the first 2 test results are highly disparate, a third fasting measurement is recommended (127,128).
- For the rare child with CD in whom TGs consistently exceed 500 mg/dL and who is at risk for pancreatitis, treatment is described in detail in the NHLBI guidelines and in other Endotext chapters (1).
- When high TGs or CD are confirmed, specific evaluation for co-morbidities is recommended:
 - ➔ Waist circumference and WHtR as measures of visceral adiposity (91-93)
 - ➔ Assessment of fasting glucose to evaluate glucose intolerance per the recommendations of the American Diabetic Association (129)
 - ➔ ALT measurement to check for NAFLD (108)
 - ➔ Evaluation for the MS cluster

As noted, there are racial, ethnic and gender differences in TG levels in childhood and adolescence. African-Americans have significantly lower triglycerides and higher HDL-C levels compared with Hispanics and non-Hispanic whites (45-47). With puberty, HDL-C levels drop a mean of 10 mg/dL in males with no change in females, regardless of race/ethnicity (1). These differences suggest that race-, gender- and developmental stage-specific cut points may be needed to optimally identify high TGs and CD but normative tables for American youth based on these factors are not currently available.

LIFESTYLE MANAGEMENT OF COMBINED DYSLIPIDEMIA

Evidence for Response to Lifestyle Changes

Multiple studies have shown significant improvements in CD in response to weight loss, change in diet composition, and increased activity (130). In all age groups, even small amounts of weight loss are associated with significant decreases in TGs, often

with increases in HDL-C (1,131-137). In adults, weight loss of as little as 5% results in a 20% decrease in TGs and an 8 to 10 % increase in HDL-C (133). In youth, a decrease in BMI z-score of at least 0.15 kg/m² is associated with significant improvement in triglycerides and HDL-C (134). The magnitude of TG decreases correlates directly with the amount of weight loss. Acute weight loss in children and adolescents has been shown to significantly decrease TGs and LDL particles and small dense LDL on NMR analysis (137).

Changes in diet composition have also been shown to be an effective treatment for high TGs and CD. In light of the strong evidence in children and adults associating excessive sugar intake with obesity and with combined dyslipidemia, decreasing simple carbohydrate intake especially in the form of added sugars is a common and important focus (73-80). In adults, a low-carbohydrate diet with monounsaturated fat enrichment significantly decreased TGs by a mean of 63%, with associated increases in HDL-C (138). One-year follow-up of young children (mean age 21 months) with elevated TGs treated with a diet restricted in sugar and carbohydrates was associated with a significant TG decrease from a mean of 274.1 +/- 13.1 mg/dL before treatment to 88.8 +/- 13.3 mg/dL (139). In adolescents and young adults, low glycemic-load diets are as effective as low-fat diets in achieving weight loss and are associated with decreased TGs and increased HDL-C (140-143). In obese children and adolescents, a low-carbohydrate diet with or without weight loss significantly reduces TGs (144,145). These diet composition changes have also been shown to significantly improve the LDL subpopulation pattern (138,148). Combined, diet composition changes lower TGs by at least 20% (135).

Exercise has also been effective in treating CD in youth, alone and in the context of a weight loss plan. Aerobic activity facilitates the hydrolysis and utilization of triglycerides in skeletal muscle, reducing deposition as adipose tissue. In adults, moderately intense activity vs no activity was associated with 20% lower TGs, with lowest levels in the highest activity subjects

(147). In cross-sectional studies in youth, low cardiorespiratory fitness is a strong predictor of high triglycerides as part of the MS cluster, and high fitness is associated with a low metabolic risk score (149-151). In randomized controlled trials, aerobic exercise interventions are associated with significant decreases in TG levels and increases in HDL-C, proportionate to training intensity (152-155).

Several studies have attempted to define the optimal type, volume, and intensity of activity required for cardiovascular risk reduction. A systematic review of activity-related benefits concluded that youth aged 5 to 17 years required at least 60 minutes of at least moderate intensity activity every day (156). Aerobic activities should make up the majority, at vigorous intensity whenever possible. These recommendations are very similar to the Physical Activity Guidelines from the U.S. Department of Health and Human Services (157). A randomized, controlled trial in obese children showed that 20 or 40 minutes of supervised aerobic exercise 5 days per week demonstrated dose-response benefits for insulin resistance and visceral adiposity, both strongly associated with CD (158). Pooled data from the International Children's Accelerometry Database shows that replacement of 10 mins of sedentary time/day with 10 minutes of moderate-to-vigorous activity was associated with significantly lower fasting insulin and TG levels (159).

No studies of youth with high TGs or CD have evaluated clinical cardiovascular events in response to lifestyle changes initiated in childhood. However, in longitudinal cohort studies, low cardiovascular risk in childhood is significantly predictive of better vascular health in adulthood and lifestyle interventions have been shown to improve vascular measures (160-162). In obese youth with high TGs and CD, diet and exercise intervention studies show that subjects who were successful in weight loss showed improvements in vascular measures (163-165).

Lifestyle Intervention: Diet and Exercise Recommendations

With this evidence, primary recommended treatment for CD and for related visceral adiposity, IR, and NAFLD is weight loss with optimized diet composition. A comprehensive, straightforward weight management approach can be initiated in any practice

setting, beginning with calculation of appropriate energy intake for age, gender, and activity using table 2 from the 2011 NHLBI pediatric guidelines (1). Estimation of current caloric intake allows development of a plan to gradually decrease calories towards the appropriate level over several weeks with the guidance of a registered dietitian.

Table 2. Estimated Calorie Requirements (in Kilocalories [kcal]) for Gender and Age Group at Three Levels of Physical Activity^a

		Calorie Requirements (kcal) by Activity Level ^{b,c,d}		
Gender	Age (Years)	Sedentary ^b	Moderately Active ^c	Active ^d
Child	2–3	1,000	1,000–1,400 ^e	1,000–1,400 ^e
Female	4–8	1,200	1,400–1,600	1,400–1,800
	9–13	1,600	1,600–2,000	1,800–2,200
	14–18	1,800	2,000	2,400
	19–30	2,000	2,000–2,200	2,400
Male	4–8	1,400	1,400–1,600	1,600–2,000
	9–13	1,800	1,800–2,200	2,000–2,600
	14–18	2,200	2,400–2,800	2,800–3,200
	19–30	2,400	2,600–2,800	3,000

(Estimates determined using the Institute of Medicine equation & rounded to nearest 200 kcals.)

^a These levels are based on Estimated Energy Requirements from the IOM *Dietary Reference Intakes* macronutrients report (2002), calculated by gender, age, and activity level for reference-size individuals. “Reference size,” as determined by the IOM, is based on median height and weight for ages up to age 18 years and median height and weight for that height to give a body mass index of 21.5 for adult females and 22.5 for adult males.

^b A sedentary activity level in childhood, as in adults, means a lifestyle that includes only the light physical activity associated with typical day-to-day life.

^c Moderately active in childhood means a lifestyle that includes some physical activity, equivalent to an adult walking about 1.5 to 3 miles per day at 3 to 4 miles per hour, in addition to the light physical activity associated with typical day-to-day life.

^d Active means a lifestyle that includes more physical activity, equivalent to an adult walking more than 3 miles per day at 3 to 4 miles per hour, in addition to the light physical activity associated with typical day-to-day life.

Diet composition is focused on limitation of simple carbohydrates especially sweets and added sugars with complete elimination of all sugar-sweetened

beverages. The diet recommendations from the NHLBI guidelines are shown in table 3.

Table 3. DIET COMPOSITION: Healthy Lifestyle/ Combined Dyslipidemia/ High TGs
1) Teach portions based on estimated energy requirements for age/gender/activity level. (Table 2)
2) Primary beverage: Fat-free unflavored milk.
3) No sugar-sweetened beverages; encourage water intake.
4) Limit refined carbohydrates (sugars, baked goods, white rice, white bread, plain pasta), replacing with complex carbohydrates (brown rice, whole grain bread, whole grain pasta).
5) Encourage dietary fish content* * The Food and Drug Administration (FDA) and the Environmental Protection Agency are advising women of childbearing age who may become pregnant, pregnant women, nursing mothers, and young children to avoid some types of fish and shellfish and eat fish and shellfish that are lower in mercury. For more information, call the FDA's food information line toll free at 1-888-SAFEFOOD or visit: http://www.cfsan.fda.gov/~dms/admehg3.html
6) Fat content: Total fat 25–30% of daily kcal/EER Saturated fat \leq 8% of daily kcal/EER Cholesterol <300 mg/d Avoid <i>trans</i> fats as much as possible Mono- and polyunsaturated fat up to 20% of daily kcal/ EER
7) Encourage high dietary fiber intake from naturally fiber-rich foods (fruits, vegetables, whole grains) with a goal of “age plus 5 g/d.

These diet recommendations are those recommended for all healthy children over age 2 from the NHLBI Guidelines with intensification of limitation of simple carbohydrates.

Simple carbohydrates like white rice, white bread, and plain pasta are replaced with complex carbohydrates like brown rice and whole grain bread and pasta. Foods high in natural fiber are encouraged with a goal of age plus 5 grams per day. For all dietary change in youth, initial family-based training with a registered dietitian is the most effective way to begin and sustain

change (1). The DASH eating plan adapted for children and adolescents as part of the 2011 NHLBI guidelines reflects the recommended TG/CD diet composition and is easy to use, organized for selected energy(kcal) intake from table 2 and by servings per day per food group (Table 4) (1).

Table 4. DASH-Style Eating Plan: Servings per Day by Food Group & Total Energy Intake.

Food Group	1,200 Calories	1,400 Calories	1,600 Calories	1,800 Calories	2,000 Calories	2,600 Calories	Serving Sizes	Examples and Notes	Significance of Food Group to DASH Eating Plan
Grains*	4-5	5-6	6	6	6-8	10-11	1 slice bread 1 oz dry cereal ½ cup cooked rice, pasta, or cereal†	Whole-wheat bread and rolls, whole-wheat pasta, English muffin, pita bread, bagel, cereals, grits, oatmeal, brown rice, unsalted pretzels and popcorn	Major sources of energy and fiber
Vegetables	3-4	3-4	3-4	4-5	4-5	5-6	1 cup raw leafy vegetable ½ cup cut-up raw or cooked vegetable ½ cup vegetable juice	Broccoli, carrots, collards, green beans, green peas, kale, lima beans, potatoes, spinach, squash, sweet potatoes, tomatoes	Rich sources of potassium, magnesium, and fiber
Fruits	3-4	4	4	4-5	4-5	5-6	1 medium fruit ¼ cup dried fruit ½ cup fresh, frozen, or canned fruit ½ cup fruit juice	Apples, apricots, bananas, dates, grapes, oranges, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, raisins, strawberries, tangerines	Important sources of potassium, magnesium, and fiber
Fat-free or low-fat milk	2-3	2-3	2-3	2-3	2-3	3	1 cup milk or yogurt	Fat-free milk or buttermilk;	Major sources of

and milk products							1½ oz cheese	fat-free, low-fat, or reduced-fat cheese; fat-free/low-fat regular or frozen yogurt	calcium and protein
Lean meats, poultry, and fish	3 or less	3-4 or less	3-4 or less	6 or less	6 or less	6 or less	1 oz cooked meats, poultry, or fish 1 egg [†]	Select only lean; trim away visible fats; broil, roast, or poach; remove skin from poultry	Rich sources of protein and magnesium
Nuts, seeds, and legumes	3 per week	3 per week	3-4 per week	4 per week	4-5 per week	1	1/3 cup or 1½ oz nuts 2 Tbsp peanut butter 2 Tbsp or ½ oz seeds ½ cup cooked legumes (dried beans, peas)	Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, peanut butter, kidney beans, lentils, split peas	Rich sources of energy, magnesium, protein, and fiber
Fats and oils [^]	1	1	2	2-3	2-3	3	1 tsp soft margarine 1 tsp vegetable oil 1 Tbsp mayonnaise 2 Tbsp salad dressing	Soft margarine, vegetable oil (canola, corn, olive, safflower), low-fat mayonnaise light salad dressing	DASH study had 27% of calories as fat, including fat in or added to foods.
Sweets and added sugars	3 or less per week	3 or less per week	3 or less per week	5 or less per week	5 or less per week	≤ 2	1 Tbsp sugar 1 Tbsp jelly or jam ½ cup sorbet, gelatin dessert 1 cup lemonade	Fruit-flavored gelatin, fruit punch, hard candy, jelly, maple syrup, sorbet and ices, sugar	Sweets should be low in fat.

* Whole grains are recommended for most grain servings as a good source of fiber and nutrients.

† Serving sizes vary between ½ cup and 1 1/4 cups, depending on cereal type. Check product's Nutrition Facts label.

‡ Two egg whites have the same protein content as 1 oz meat.

^ Fat content changes serving amount for fats and oils. For example, 1 Tbsp regular salad dressing = one serving; 1 Tbsp low-fat dressing = one-half serving; 1 Tbsp fat-free dressing = zero servings.

Abbreviations: oz = ounce; Tbsp = tablespoon; tsp = teaspoon.

Successful weight loss programs in children and adolescents include frequent contact for support and monitoring by the physician and/or dietitian, as often as weekly for the first 6 months and this should be considered when initiating diet changes for children with CD (166). While not necessary for lipid management, a repeat fasting lipid panel after 1 to 3 months of diet change can be an effective motivator for children and families since TG levels decrease rapidly in response to changes in diet composition and even minimal weight loss (167).

A regular exercise schedule derived from the evidence is prescribed, simultaneous with the diet recommendations. All children and adolescents should be involved in 60 minutes or more of moderate to vigorous aerobic activity daily, with vigorous intensity activity at least 3 days/week (1,168,169). Any kind of aerobic activity is useful but weight bearing activity is most effective. To promote compliance, a discussion about the kind of exercise that will be easiest for each child and family to sustain should be undertaken and specific follow-up of activity at subsequent evaluations is recommended. A combined diet and activity approach to weight loss like this has been shown to be effective in management of high TGs and CD (167-174).

For obese children and their families, weight loss can be an emotional issue so an alternative approach aimed at changing diet composition and activity without a direct approach to weight can be used. The same diet change and activity recommendations described above are prescribed but there is no

calculation of caloric needs and no specific focus on weight loss. This approach has been shown to be successful in addressing high TGs and CD, particularly when combined with cognitive behavioral therapy (167,174-180).

Follow-Up

After 6 months of the selected diet and activity plan, the fasting lipid profile (FLP) should be repeated:

- If TGs are normal (<100 mg/dL, <10 years; <130 mg/dL, 10–19 years), continue the diet and activity recommendations and reassess the FLP every 12 months
- If TGs are > 100 mg/dL but < 200 mg/dL in children < 10 years of age, > 130 mg/dL but < 200 mg/dL in 10-19 years old:
 - Intensify counselling for the high TG/CD diet and increased activity.
 - Recommend increased dietary fish content.
 - Increase frequency of contact with MD and/or RD.
 - Repeat FLP in 6 months
- If TG are > 200 mg/dL but less than 500 mg/dL and lifestyle recommendations have been attempted with no weight loss, consider referral to an intensive weight loss program (1).
- If TG are > 200 mg/dL but less than 500 mg/dL despite weight loss in an adolescent who has at least 2 additional high-level cardiovascular risk factors (table 5), medication can be considered (1).

Table 5. High Level Cardiovascular Risk Factors for Management of Combined Dyslipidemia in Childhood

(+) Family history: Myocardial infarction, angina, coronary artery bypass graft/ stent/ angioplasty, sudden cardiac death in parent, grandparent, aunt, or uncle; Male < 55 y, female < 65 y.
Diabetes mellitus, type 1 or type 2
Hypertension requiring drug treatment
Current cigarette smoking
BMI>97th%ile

Application of these recommendations is usually associated with significant improvements in hypertriglyceridemia and CD on intermediate-term follow-up, with increasing evidence of lipid subpopulation and vascular response to lifestyle change. There are no published long-term studies of lifestyle change.

MEDICATION THERAPY FOR HYPERTRIGLYCERIDEMIA AND COMBINED DYSLIPIDEMIA

Information on drug therapy for treatment of hypertriglyceridemia and CD in childhood is limited. Drugs which could potentially be used are described below.

HMG-CoA Reductase Inhibitors (Statins)

In adults with high cholesterol and CD, statin therapy beneficially alters the standard lipid and LDL particle profiles and improves vascular function and clinical cardiovascular outcomes (181-183). In childhood, statin treatment has focused on children with monogenic hypercholesterolemia (FH) in whom statins effectively lower LDL-C levels and improve LDL-C subpopulation characteristics (184,185). Two pediatric trials of children with FH showed improved vascular measures in response to statin therapy (185,186). There are as yet no published studies examining statin effects on clinical outcomes in youth with CD. A systematic review of statin therapy in

children with FH analyzed studies that included more than 1000 children (188). Treatment with statins significantly decreased LDL-C but change in TGs was much less consistent. No statistically significant differences were found between statin-treated and placebo-treated children for the occurrence of any adverse events, including problems with sexual development, muscle toxicity, or liver toxicity. An important study reported late follow-up of 184 patients with genetically confirmed familial hypercholesterolemia (FH) who were started on pravastatin therapy at a mean age of 12 years as part of a placebo-controlled trial. After 20 years, FH participants had mean LDL cholesterol levels 32% below baseline levels in the original trial. Mean progression of carotid intima-media thickness in FH subjects was similar to that of unaffected siblings. The cumulative incidence of cardiovascular events and death from cardiovascular causes was lower among the FH participants than among their affected parents for whom statins were available much later in life. This landmark report emphasizes the safety, effectiveness and benefit of long-term statin therapy initiated in childhood for treatment of FH (189). Dolt!, an ongoing Pediatric Heart Network trial is evaluating the clinical and vascular responses to statin therapy in adolescents with obesity and CD. Enrollment is ongoing with a planned sample size of more than 300 subjects. Results are anticipated soon (190).

Omega-3 Fish Oil

Omega-3 fish oil therapy has been shown to be safe in adults, with some reports that TG levels decreased by as much as 30–45%, with associated increases in HDL-C (191). However, more recent reports including a Cochrane systematic review of 25 randomized, controlled trials have shown no conclusive benefits of standard fish oil treatment (usually 1 gram per day) on serum lipids or cardiovascular disease outcomes (192-194). Two randomized, controlled trials of omega-3 fish oil in adolescents showed statistically insignificant decreases in TGs and no change in LDL particle number or size (195,196). Evidence from multiple trials in adults with established CV risk shows conflicting results for benefit from omega-3 fatty acids and/or EPA. A detailed discussion of the potential benefits of omega-3-fatty acids on cardiovascular outcomes are discussed in detail in other Endotext chapters. There is as yet no information on use of EPA in children or adolescents.

PPAR-Alpha Agonists (Fibrates)

In adults, fibrates have been used effectively and safely to lower TG levels, alone and in combination with statins (fenofibrate should be used in combination as gemfibrozil increases the risk of muscle disorders) (197). Fibrates reduce cholesterol synthesis and lower plasma TGs by 30-50% with an increase in HDL-C of 2-20%. Fibrate therapy beneficially alters LDL subclass distribution with an increase in LDL size and a decrease in LDL particles (198).

In children, treatment with fibrates in a single small randomized trial (n=14) and 3 case series (n=7, n=17, n=47) was associated with significant TG lowering by as much as 54% with an associated 17% increase in HDL-C (199-202). One child was thought to have myositis on clinical grounds with no lab changes and there were mild, transient elevations in liver enzymes in 2 subjects but no other potentially adverse effects were reported. There are no long-term-trials of fibrates in children and no studies of the vascular or clinical response to treatment.

Summary

Evidence for drug therapy of moderate hypertriglyceridemia or CD in childhood is limited. Statins improve LDL-C subpopulation characteristics on NMR analysis in children with FH (184,185). There is substantial evidence that statins as a group are safe and effective for long-term treatment of hypercholesterolemia beginning in childhood (189). Despite concern about hepatic side-effects, current evidence indicates that statins are safe in patients with NAFLD and may improve liver function tests (203). Statin therapy therefore appears to be the logical theoretical choice for treatment of CD if drug therapy is needed. The possibility of eicosapentaenoic acid (EPA) as secondary treatment for adults with established CVD and residual risk due to high TGs represents a theoretical treatment option but results are controversial and there is no reported experience for use in youth (204). There are no current trials of any other medication in children with combined dyslipidemia.- A large body of evidence indicates that lifestyle therapy is highly effective for management of CD in youth and that a decision to initiate drug treatment should only be made in an adolescent with multiple additional high-level risk factors after intensive long-term efforts at lifestyle modification.

CONCLUSION

In youth, CD is a prevalent, highly atherogenic lipid disorder, almost always associated with obesity. High TGs and CD are strongly associated with a complex of related risk factors including visceral adiposity, insulin resistance/T2DM, NAFLD, and the metabolic syndrome complex which significantly exponentiate risk for CVD. Primary therapy is lifestyle change focused on weight loss, change in diet composition, and increased activity. These interventions are usually very effective. Drug therapy is only rarely needed in the multiple risk adolescent with CD with statin medications as the theoretical drug of choice.

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