COMBINED DYSLIPIDEMIA IN CHILDHOOD

Rae-Ellen W. Kavey, MD, MPH
COMBINED DYSLIPIDEMIA DEFINITION
(CD aka Atherogenic Dyslipidemia/ Mixed Dyslipidemia)

COMBINED DYSLIPIDEMIA: >2 Abnormal lipid levels:
- TC, TG, LDL-C, non-HDL-C > 95\textsuperscript{th}%ile
- HDL-C ≤ 5\textsuperscript{th}%ile

TYPICAL PATTERN:
+/- \textsuperscript{↑}TC, LDL-C, \textsuperscript{↑}non-HDL-C, \textsuperscript{↑}TG, \textsuperscript{↓}HDL-C
## Normal Plasma Lipid Distributions for Children and Adolescents (mg/dL) (mmol/L)

<table>
<thead>
<tr>
<th></th>
<th>ACCEPTABLE (&lt;=75&lt;95th%ile)</th>
<th>BORDERLINE (75-95th%ile)</th>
<th>ABNORMAL (&gt;95th%ile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;170 (4.39)</td>
<td>170 (4.39)-199 (5.16)</td>
<td>&gt;=200 (5.17)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt;110 (2.85)</td>
<td>110 (2.85)-129 (3.35)</td>
<td>&gt;=130 (3.36)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>&lt;120 (3.11)</td>
<td>120 (3.11)-144 (3.75)</td>
<td>&gt;=145 (3.76)</td>
</tr>
<tr>
<td>TG 0-9y</td>
<td>&lt;75 (0.85)</td>
<td>75 (0.85)-99 (1.12)</td>
<td>&gt;=100 (1.13)</td>
</tr>
<tr>
<td>TG 10-19y</td>
<td>&lt;90 (1.02)</td>
<td>90 (1.02)-129 (1.46)</td>
<td>&gt;=130 (1.47)</td>
</tr>
<tr>
<td>HDL</td>
<td>&gt;45 (1.16)</td>
<td>40 (1.03)-45 (1.16)</td>
<td>&lt;40 (1.03)</td>
</tr>
</tbody>
</table>

**Typical CD FLP:** TC ~200; TG 150-400; HDL-C~40; LDL-C~120; non-HDL-C~160 (mg/dL)
COMBINED DYSLIPIDEMIA

• 6% of Western populations, 20% of CAD pts < 60 y of age, ~70% of children in NA pediatric lipid clinics

• In children, CD pattern is only seen with overweight/obesity

• From 2008 NHANES data, CD is seen in 42% of adolescents with BMI >95th%ile

• Overlap between combined dyslipidemia of obesity (CD) and familial combined hypercholesterolemia (FCHC)
# LIPOPROTEIN DISORDERS MANIFEST IN CHILDHOOD ASSOCIATED WITH CVD

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>% of PREM CVD</th>
<th>LIPID PATTERN</th>
<th>DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hyper-Cholesterolemia</td>
<td>5%</td>
<td>↑ TC, LDL-C</td>
<td>hepatic LDL receptors</td>
</tr>
<tr>
<td>Familial Combined Hypercholesterolemia</td>
<td>2%</td>
<td>↑ TC, LDL-C ↑ TG, ↓ HDL</td>
<td>Unknown</td>
</tr>
<tr>
<td>Familial Hypo-alpha-lipoproteinemia</td>
<td>&lt;1%</td>
<td>↓ HDL</td>
<td>Unknown</td>
</tr>
<tr>
<td>CD</td>
<td>20%</td>
<td>+/- ↑ TC, LDL-C ↑ TG, ↓ HDL</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
LIPID SUBPOPULATION ANALYSIS: NMR SPECTROSCOPY DETERMINES LIPOPROTEIN PARTICLE SIZE (in nanometers) & CONCENTRATION (in nanomoles/L)
CD pattern on traditional lipid profile is represented at the subpopulation level as increased LDL particles (LDL-P), increased small dense LDL (sdLDL), decreased total HDL-C and reduced large HDL particles.
Lipoprotein particles (LDL-P) and Small Dense LDL-C (sdLDL)

- In adults, elevated LDL particle concentration and small dense LDL-C have both been shown to be atherogenic and predictive of CV disease.

- REFERENCE values: Total LDL particle concentration:

<table>
<thead>
<tr>
<th>Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 nmol/L</td>
<td>Optimal</td>
</tr>
<tr>
<td>1300-1599 nmol/L</td>
<td>Borderline high</td>
</tr>
<tr>
<td>1600-2000 nmol/L</td>
<td>High</td>
</tr>
<tr>
<td>&gt; 2000 nmol/L</td>
<td>Very high</td>
</tr>
</tbody>
</table>


Otvos JD et al. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the VA HDL Intervention Trial. Circulation 2006;1134:1556-1563.
LIPID ATEROGENESIS: Small lipoprotein particles (< 70 nm) linked to ApoB can enter arterial walls and potentially initiate atherosclerosis.

Response to Retention Hypothesis, Tabas et al, Circulation, 2007;116:1832
ATHEROGENIC MECHANISMS: High LDL-P and sdLDL

- Exposure of vascular endothelium to high concentration of circulating LDL particles
- Decreased binding of sdLDL particles to LDL receptors → prolonged residence time in plasma
- Greater binding of sdLDL to the sub endothelial matrix molecule proteoglycans
- Increased sdLDL susceptibility to oxidation

- Reduced HDL-C affects reverse cholesterol transport and efflux capacity but specific mechanisms related to reduced large HDL particles are not yet clarified.
With lipoprotein sub-population analysis, high LDL-C subjects (FH) and high TG/low HDL-C subjects (CD) each have high LDL-P → COMMON ATEROGENIC PATHWAY FOR FH & CD
TG/HDL-C Ratio: A Surrogate Index of Atherogenicity

- In adults, TG/HDL-C is a strong predictor of CAD events.
- In obese black and white adolescents, TG/HDL-C is a marker for elevated LDL-P and sdLDL: TG/HDL-C ratio >3 in white subjects, > 2.5 in black subjects strongly predicted elevated LDL-C & sdLDL.
- The HEALTHY study characterized lipids in a diverse population of 2384 6th grade children. 33% of overweight/obese children had TG/HDL-C ratio > 3.0 → this identified the lipid subpopulation pattern of increased total LDL-P & sdLDL.
- 16% of children had LDL-P>LDL-C and this group had significantly greater BMI, WC, Ins R, TGs & BP than those with LDL-P = LDL-C or LDL-P < LDL-C

PATHOPHYSIOLOGY OF COMBINED DYSLIPIDEMIA

- CD is strongly linked to visceral adiposity, insulin resistance, non-alcoholic fatty liver disease (NAFLD) and the metabolic syndrome
VISCERAL ADIPOSITY & COMBINED DYSLIPIDEMIA
Visceral Adiposity + NAFLD + Insulin Resistance + CD

Visceral adipose tissue → Portal circulation

Subcutaneous adipose tissue → Systemic circulation

↓ Lipid storage capacity

Portal circulation

Excess FFA

VLDL-TG → Insulin Resistance

↓ Lipotoxicity
↓ Gluconeogenesis

NAFLD

Liver

Skeletal Muscle

↓ Fat oxidation
↓ Insulin action
↓ Glucose uptake
Association Between Visceral Fat and Insulin Resistance

Metabolic Syndrome

- Visceral Obesity
- Insulin Resistance
- High Triglycerides
- Low HDL-Cholesterol
- Hypertension

+ NAFLD
Metabolic Syndrome and Dyslipidemia

Mean adjusted total LDL-P and LDL-C

- LDL-C (mg/dL)
- LDL-P (nmol/L)

# of metabolic syndrome criteria

0 1 2 3 4 5
Familial/Racial/Ethnic Predisposition to Metabolic Dysregulation

Metabolic Healthy Obese
- Insulin sensitivity
- Ectopic fat (Fatty liver, IMCL)
- Adipocyte size (homogen)
- Adipogenic/Lipogenic Genes
- AT Inflammation

Metabolic Unhealthy Obese
- Insulin resistance
- Ectopic fat (Fatty liver, IMCL)
- Adipocyte Hyper trophy (heterogen)
- Adipogenic/Lipogenic Genes
- AT Inflammation

Low VAT/SAT ratio

High VAT/SAT ratio
ETIOLOGY OF THE CARDIOMETABOLIC COMPLEX

Single Primary Initiating Factor
vs
Expression of multiple environmental and genetic factors mediated by metabolic and inflammatory reactions.
Evidence linking CD in childhood to accelerated atherosclerosis/early CVD

- Pathologic
- Vascular
- Epidemiologic
PDAY STUDY: At autopsy, atherosclerotic extent correlates with pre-morbid lipid levels.

Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking
PDAY Research Group; JAMA 1990;264:3018-24
Vascular Imaging:
CAROTID INTIMA MEDIA THICKNESS (CIMT)

- Normative values for CIMT for children & adolescents by age/race
- Increased with obesity, hypercholesterolemia, hypertension & diabetes
- Has been used to assess response to risk reduction
Association of dyslipidemias from childhood to adulthood with cIMT in adulthood:
The Cardiovascular Risk in Young Finns Study.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Combined dyslipidemia</th>
<th>FH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1980 Age</strong></td>
<td><strong>10.6+/-.5</strong></td>
<td><strong>11.4+/-.4.9</strong></td>
<td><strong>10.9+/-.5</strong></td>
</tr>
<tr>
<td><strong>2001 Age</strong></td>
<td><strong>31.6+/-.5</strong></td>
<td><strong>32.4+/-.4.9</strong></td>
<td><strong>31.9+/-.5</strong></td>
</tr>
<tr>
<td><strong>TC</strong></td>
<td><strong>199+/-.38</strong></td>
<td><strong>226+/-.37</strong></td>
<td><strong>258+/-.27</strong></td>
</tr>
<tr>
<td><strong>TG</strong></td>
<td><strong>53+/-.21</strong></td>
<td><strong>103+/-.39</strong></td>
<td><strong>61+/-.21</strong></td>
</tr>
<tr>
<td><strong>HDL-C</strong></td>
<td><strong>63+/-.11</strong></td>
<td><strong>54+/-.9</strong></td>
<td><strong>62+/-.29</strong></td>
</tr>
<tr>
<td><strong>LDL-C</strong></td>
<td><strong>127+/-.26</strong></td>
<td><strong>138+/-.29</strong></td>
<td><strong>184+/-.29</strong></td>
</tr>
<tr>
<td><strong>CIMT 2001</strong></td>
<td><strong>0.578+/-.09</strong></td>
<td><strong>.621+/-.15</strong>**</td>
<td><strong>0.592+/-.10</strong></td>
</tr>
</tbody>
</table>

** p<.001
Triglyceride to HDL-C Ratio & Increased Arterial Stiffness in Children, Adolescents & Adults

- Arterial stiffness assessed in 893 subjects aged 10-26y by carotid-femoral pulse wave velocity (PWV)
- ↑TG/HDL-C → Progressive rise in PWV; associated with increasing levels of BMI, BP, LDL-C, glucose, insulin & CRP
- PWV increased across TG/HDL-C tertiles
- In MVA, TG/HDL-C = Significant independent determinant of PWV after adjustment for BP, HR & demographics.
- Relationship strongest in overweight /obese subjects
Pediatric triglycerides predict cardiovascular disease events in the fourth to fifth decade of life

Princeton Follow-Up Study (PFS):

- 1973-1978: Multistage family survey of lipids
- 1998: All eligible former schoolchildren from initial study invited to participate in PFS – 53% (n=808) participated.
- No contact in the 22-31 yr interval between studies
- Current CV risk factor status + history of CVD
- 19 live subjects with CVD events at mean 37.1+/−4.9y
- 789 subjects CVD event-free
## PRINCETON STUDY: BASELINE

<table>
<thead>
<tr>
<th>Baseline</th>
<th>CVD Cases N=19</th>
<th>No CVD n=789</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>15.3 +/- 2.5</td>
<td>12.3 +/- 3.3</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>24.3 +/- 5.7</td>
<td>20.0 +/- 4.3</td>
<td>0.012</td>
</tr>
<tr>
<td>TC</td>
<td>186 +/- 25</td>
<td>174 +/- 33</td>
<td>0.094</td>
</tr>
<tr>
<td>TG</td>
<td>127 +/- 75</td>
<td>76 +/- 45</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>53 +/- 17</td>
<td>55 +/- 12</td>
<td>0.93</td>
</tr>
<tr>
<td>LDL-C</td>
<td>112 +/- 25</td>
<td>107 +/- 30</td>
<td>0.40</td>
</tr>
<tr>
<td>SBP</td>
<td>114 +/- 13</td>
<td>104 +/- 13</td>
<td>0.27</td>
</tr>
<tr>
<td>DBP</td>
<td>68 +/- 11</td>
<td>62 +/- 12</td>
<td>0.75</td>
</tr>
<tr>
<td>Glucose</td>
<td>87 +/- 9</td>
<td>86 +/- 8</td>
<td>0.60</td>
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### PRINCETON STUDY: FOLLOW-UP

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>CVD Cases (n=19)</th>
<th>No CVD (n=789)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>33.2 +/- 6.2</td>
<td>28.6 +/- 6.8</td>
<td>.0078</td>
</tr>
<tr>
<td>TC</td>
<td>196 +/- 24</td>
<td>194 +/- 42</td>
<td>.79</td>
</tr>
<tr>
<td>TG</td>
<td>251 +/- 186</td>
<td>135 +/- 133</td>
<td>.0016</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40 +/- 15</td>
<td>46 +/- 15</td>
<td>.16</td>
</tr>
<tr>
<td>LDL-C</td>
<td>110 +/- 31</td>
<td>121 +/- 36</td>
<td>.098</td>
</tr>
<tr>
<td>SBP</td>
<td>128 +/- 16</td>
<td>120 +/- 15</td>
<td>.062</td>
</tr>
<tr>
<td>DBP</td>
<td>85 +/- 11</td>
<td>79 +/- 11</td>
<td>.080</td>
</tr>
<tr>
<td>T2DM</td>
<td>32%</td>
<td>4%</td>
<td>.0001</td>
</tr>
<tr>
<td>Never Smoker</td>
<td>37%</td>
<td>61%</td>
<td>.016</td>
</tr>
</tbody>
</table>

In MVA, childhood TG & TG/HDL = Independent predictors of CVD after correction for adult lipids, BMI, BP & DM (HR=5.85)
TREATMENT OF COMBINED DYSLIPIDEMIA

Lifestyle interventions:
• Weight loss
• Diet composition
• Exercise

Drug treatment
Separate effects of reduced carbohydrate and weight loss on atherogenic dyslipidemia

• 178 men with mean BMI of 29.2±2 kg/m² & atherogenic dyslipidemia randomized for 3 wks to diets with carbohydrate content of 54%, 39% or 26% of total calories with low saturated fat content. A 4th group had a 26% carbohydrate/high saturated fat diet. All X 3 wks

• Weight loss induced by 1000 kcal/d decrease in total calories X 5 wks → 4 wks of wt stabilization
Separate effects of reduced carbohydrate and weight loss on atherogenic dyslipidemia

Krauss RM et al.

Am J Clin Nutr 2006;83:1025-1031.

RESULTS:

• 26% carb/low sat fat diet significantly decreased TG, TC, apo B, TC:HDL-C with decrease in mass of small LDL & increased LDL peak diameter vs 54% carb group

• In the reduced calorie stage, weight loss led to further reductions in these variables but changes were significantly greater for the 54% carb diet group.

• Linear reduction in the proportion of subjects with LDL subclass pattern B(high sdLDL) with reduced carb diets

• Findings suggest that either moderate reduction in carb intake or weight loss impact CD separately and significantly.
Role of Carbohydrate Modification in Weight Management among Obese Children

- 102 obese children aged 7-12 yrs randomized to a 3m diet intervention:
  
  **Low CHO vs Reduced GL vs Low cal/Low fat**

- Intensive weekly child and parent training with dietitians X 12 wks, F/U X 12 m

- All groups significantly reduced caloric intake X12 m

- All groups decreased BMI, waist circumference & % body fat but improvements dwindled over time

- Only the low CHO group decreased TG and raised HDL
Change in Anthropometrics and Diet Adherence

Figure 2: Graphs showing the change in BMI Z-score, waist circumference, and percentage body fat over 12 months for three groups (LC, RGL, PC). The graphs demonstrate significant differences in anthropometric measures over time, with group LC showing the most consistent improvement.
<table>
<thead>
<tr>
<th></th>
<th>LC B/L</th>
<th>12m</th>
<th>RGL B/L</th>
<th>12m</th>
<th>LF B/L</th>
<th>12m</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>162±4</td>
<td>161±5</td>
<td>158±5</td>
<td>153±4</td>
<td>159±5</td>
<td>160±6</td>
</tr>
<tr>
<td>TG</td>
<td>100±7</td>
<td>83±7*</td>
<td>87±6</td>
<td>82±6</td>
<td>102±7</td>
<td>89±7</td>
</tr>
<tr>
<td>HDL</td>
<td>47.6±1.4</td>
<td>52.7±1.8**</td>
<td>49.8±1.4</td>
<td>50.3±1.5</td>
<td>48.2±2.1</td>
<td>51.7±2.1**</td>
</tr>
<tr>
<td>LDL</td>
<td>95.0±3.9</td>
<td>91.7±4.6</td>
<td>91.1±4.0</td>
<td>86.1±3.5</td>
<td>90.8±4.6</td>
<td>89.9±4.7</td>
</tr>
</tbody>
</table>
DIET COMPOSITION, WEIGHT LOSS & C-V RFs IN ADOLESCENTS

- Randomized trial of low carb vs low fat diet, each with self-selected energy intake in overweight adolescents X 12 wks
  - **Low carb (LC):** \( \leq 20 \text{ g/d of carbs} \times \text{first 2 wks} \rightarrow 40\text{g/d for remainder; ab lib protein, fat, calories} \)
  - **Low fat (LF):** < 40g/d of fat + 5 servings of starch/d, ab lib fat free dairy, F & V
  - No SSB in either group

# DIET COMPOSITION AND CD IN ADOLESCENTS

<table>
<thead>
<tr>
<th></th>
<th>LOW CARB</th>
<th>LOW FAT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALORIES (kcal)</td>
<td>1830+/−615</td>
<td>1100+/−297</td>
<td>.03</td>
</tr>
<tr>
<td>% Carb</td>
<td>8.0+/−7.6</td>
<td>56.1+/−25</td>
<td>.02</td>
</tr>
<tr>
<td>% Fat</td>
<td>59.6+/−10</td>
<td>12.3+/−1.6</td>
<td>.001</td>
</tr>
<tr>
<td>% Sat Fat</td>
<td>22.0+/−16</td>
<td>6.8+/−6.3</td>
<td>.001</td>
</tr>
<tr>
<td>Cholesterol (mg/d)</td>
<td>667+/−216</td>
<td>164+/−57</td>
<td>.005</td>
</tr>
</tbody>
</table>

BMI (kg/m²): LC: -3.3+/−3.0 vs LF: -1.5+/−1.7; p<.05

Weight (kg): LC: -9.9+/−9.4 vs LF: -4.1+/−4.9; p<.04
## DIET COMPOSITION AND CD IN ADOLESCENTS: LIPID PROFILE RESPONSE

<table>
<thead>
<tr>
<th>(mg/dL)</th>
<th>LOW CARB</th>
<th>LOW FAT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>-3.7+/-18</td>
<td>-17.3+/-15.8</td>
<td>NS</td>
</tr>
<tr>
<td>TG</td>
<td>-48.3+/-29</td>
<td>-5.9+/-70</td>
<td>.07</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+3.8+/-7.2</td>
<td>+1.8+/-7.7</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>+3.8+/-13</td>
<td>-25.1+/-25.3</td>
<td>.006</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-26+/-22</td>
<td>-13.6+/-13.4</td>
<td>.036</td>
</tr>
</tbody>
</table>
Moderate to Vigorous Physical Activity & Sedentary Time and Cardiometabolic Risk Factors in Children
Ekelund U et al. JAMA 2012;307(7):7040712

• Meta-analysis of 14 studies of physical activity and sedentary time measured by accelerometry, correlated with cardiometabolic RFs; TG/HDL in 8/14.
• Physical activity (PA) monitoring for mean of 5.2d
• Total PA was significantly inversely associated with WC, fasting insulin & TG after adjustment for age, sex & WC (with insulin & TGs as outcomes).
• Higher levels of MVPA were associated with significantly lower WC, SBP, insulin & TGs and higher levels of HDL-C across tertiles for sedentary time.
NO DIRECT APPROACH TO WEIGHT LOSS: Weight loss stated to be effective treatment but as a long term goal – initial approach: diet composition & activity.

DIET:
- Elimination of SSB
- Shift starches from simple to complex carb form
- Fat free milk + low fat for all dairy

ACTIVITY
- ½ hr of activity every day of the week outside of school, vigorous enough that child is slightly SOB throughout
- Limit leisure screen time to < 2 hrs/d
Follow-Up:
• Visits at ~4month intervals with FLP in advance
• Cardiologist reviews FLP results and progress towards diet and activity goals → goal restatement / reinforcement by MD +/- RD
• No improvement by visit 3 → Weight loss.

REVIEW
• Retrospective review of 53 pts seen for initial W/U over a 2y period who returned for 2 F/U visits
• Mean age: 12.1 +/- 3.4 yrs
• Baseline BMI: 29.6±4.4 kg/m2 (93% >95th%ile)
# RESULTS:

<table>
<thead>
<tr>
<th></th>
<th>B/L</th>
<th>F/U 1</th>
<th>( p )</th>
<th>F/U 2</th>
<th>( p )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B/L, F/U1</td>
<td></td>
<td>F/U1, F/U2</td>
<td></td>
<td>B/L, F/U2</td>
</tr>
<tr>
<td>TC</td>
<td>209 ± 39</td>
<td>190 ± 37</td>
<td>&lt;.001</td>
<td>181 ± 32</td>
<td>&lt;.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TG</td>
<td>255 ± 119</td>
<td>196 ± 104</td>
<td>&lt;.001</td>
<td>168 ± 99</td>
<td>&gt;.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL</td>
<td>42 ± 14</td>
<td>41 ± 13</td>
<td>&gt;.05</td>
<td>42 ± 13</td>
<td>&gt;.05</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>LDL</td>
<td>121 ± 43</td>
<td>111 ± 40</td>
<td>&lt;.05</td>
<td>106 ± 30</td>
<td>&gt;.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>167 ± 35</td>
<td>150 ± 32</td>
<td>&lt;.001</td>
<td>138 ± 30</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TG/HDL</td>
<td>7.0 ± 4.6</td>
<td>5.4 ± 3.8</td>
<td>&lt;.01</td>
<td>4.5 ± 3.8</td>
<td>&gt;.05</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Combined dyslipidemia in obese children: Response to a focused lifestyle approach

• BMI decreased in 58% of pts
• Mean BMI change: -0.67 kg/m²
• At last F/U, BMI was <95th %ile in 17% of pts
• No difference in lipid profile results between group who decreased BMI and remainder
• In 42% of pts, lipid profile results had improved enough by F/U2 for discharge back to regular pediatric care

BUT
• TG/HDL decreased from 7.0+/-4.6 to 4.5+/-3.8 but ratio still indicates high LDL-P and elevated atherogenic risk
Statin Treatment for Combined Dyslipidemia

In adults, statins are the most prescribed medication in the world:

- HMG-CoA reductase inhibitors limiting endogenous cholesterol synthesis which also leads to a decrease in the intracellular pool of cholesterol, up-regulation of LDL receptors and increased clearance of circulating LDL–C.
- Primarily given for LDL-C lowering effect
- Beneficially alter standard lipid and LDL- particle profiles
- Improve multiple measures of vascular function.
- Reduce the risk of a major vascular event (MI, stroke, bypass surgery, cardiac death) by 21% for each 1 mmol/L reduction in LDL cholesterol achieved.
STATIN THERAPY IN CHILDREN

• Almost exclusively for FH with severe LDL-C elevation
• Systematic review & meta-analysis of statin therapy in children with FH → analyzed studies that included ~800 children.
• Statin therapy decreased LDL-C by 20 to 50% but change in TGs was much less consistent, ranging from an increase of 9% to a decrease of 20%.
• Adverse effects from statins very rare in children and adolescents

STATIN EFFECTS ON LDL PARTICLES

- Statins (HMG-CoA reductase inhibitors) lead to reduced LDL particle concentrations in adults
- Single study in children with FH:

B/L NMR spectroscopy:

<table>
<thead>
<tr>
<th>PARTICLES (nmol/L)</th>
<th>FH (n=144)</th>
<th>Siblings (n=45)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>116±38</td>
<td>51±20</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL</td>
<td>1727±391</td>
<td>955±191</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL</td>
<td>6±3</td>
<td>9±2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

STATIN EFFECTS ON LDL PARTICLES

- FH children randomized to pravastatin or placebo X 1y → Repeat NMR spectroscopy

<table>
<thead>
<tr>
<th>Particles (nmol/L)</th>
<th>PRAVASTATIN</th>
<th>PLACEBO</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>-38±33</td>
<td>-2±36</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL</td>
<td>-275±299</td>
<td>+68±354</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HDL</td>
<td>+2.6±3</td>
<td>+0.4±3</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Omega-3 Fish Oil

- Decrease hepatic FA and TG synthesis while enhancing FA degradation/oxidation, with subsequent reduced VLDL–C release
- Lower TGs, raise HDL–C, increase LDL–C and LDL–C particle size
- In adults, some trials report that TG levels decreased by as much as 30–45 percent, with significant associated increases in HDL–C.
- More recent reports have not shown a conclusive benefit of fish oil treatment.
- In children with CD, 2 recent randomized trials of prescription fish oil.
A double-blind randomized trial of fish oil to lower triglycerides and improve cardiometabolic risk in adolescents

Gidding SS et al

- 42 adolescent with CD & LDL-C<160 mg/dl randomized to 4 gms of prescription fish oil vs placebo, X 8 wks
- TGs decreased in both groups with no significant difference between groups.
- On lipid subpopulation analysis, large VLDL particle number was significantly decreased but there was no significant change in LDL particle number or size.
FIBRATES

• PPAR agonists that act in the liver to reduce cholesterol synthesis, reduce VLDL secretion & increase VLDL removal
• Lower plasma TGs by 30-50% and LDL-C by 0-30%.
• Alter LDL subclass distribution with an increase in LDL size and a decrease in LDL particles plus an increase in small HDL subclass particles.
• 2011 systematic review/meta-analysis of vascular risk reduction in pts treated with fibrates identified 6 trials:
  7389 High TG $\rightarrow$ RR 0.75(0.65,0.86); p<.001
  5068 High TG, low HDL-C $\rightarrow$ RR 0.71 (0.62,0.82); p<.001
  15,303 low HDL-C subjects $\rightarrow$ RR 0.84(0.77,0.91); p<.001
  9872 neither high TG nor low HDL-C $\rightarrow$ RR 0.96 (0.85,1.09)

FIBRATES IN CHILDREN

• Single small randomized trial (n=14) and 3 case series (n=7, n=17, n=47)
• Significant TG lowering by as much as 54% with an associated 17% increase in HDL-C
• No major adverse effects reported.
• No long-term trials of fibrates in children
• No studies of the lipid subpopulation, vascular or clinical response to fibrate treatment.
NIACIN

- Complex mechanism of action: Partial inhibition of FFA release from adipose tissue & increased lipoprotein lipase activity with decreased rate of hepatic synthesis of VLDL & LDL-C.
- Major decreases in TGs and increases in HDL-C; also lowers TC & LDL-C
- In long term studies from the pre-statin era, nicotinic acid significantly reduced the incidence of cardiovascular events and the rate of atherosclerosis progression.
- Recent studies in which niacin was compared to placebo in pts already treated with statin to ideal LDL-C levels showed no efficacy for the primary endpoint of a composite cardiovascular event despite significantly increased HDL-C levels.
- There were significantly more serious adverse events in the niacin group including diagnosis of diabetes, gastrointestinal symptoms, flushing/ itching/rash, infection and bleeding.
FIBRATES IN CHILDREN

• Single case series which demonstrated a very high rate of side effects leading to discontinuation.
• No current recommendations for use of niacin to treat combined dyslipidemia in childhood.
DRUG THERAPY FOR COMBINED DYSLIPIDEMIA IN CHILDREN

- 2011 Expert Panel guidelines recommend consideration of drug therapy for CD after lifestyle change X 6-12 mos if TG> 200 mg/dl, non-HDL-C>145 mg/dL
- Initial drug therapy with omega-3 fish oil *
- Statin
- +/- Fibrate

- In the rare child with severe persistent elevation of TG (>500 mg/dL), at risk for pancreatitis, management by a lipid specialist is recommended. [Low-fat diet (<10 % fat) + Medium-chain TGs. Some response to fibrates, niacin, or statins.]
CONCLUSIONS

- CD is very prevalent in obese children & adolescents and is associated with a high LDL particle burden.
- CD is tightly linked with visceral adiposity, insulin resistance, NAFLD and the metabolic syndrome complex.
- Pathologic, vascular & epidemiologic evidence demonstrate the atherogenicity of CD dating from childhood.
- In children, small studies show that lifestyle change +/- drug therapy can improve traditional lipid profile results.
- RCT evidence for improved lipid subpopulation results, vascular outcomes & clinical endpoints is lacking.

→ DoIt! Trial = 2y RCT of statin vs UC in adolescents with CDO; Primary endpoint = PWV & CIMT with lipid subpopulation analysis; funded by NHLBI/PHN. To begin enrollment, 2015.