Lipid Management in Children

Finding the ‘soft spot’...

...between a rock and a hard place.

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UCSF Center for Health and Community
Healthy Hearts Clinic, Pediatric Cardiology Medical Group-East Bay

Pediatric Lipids - Overview

I. The rock
- CVD risk factors erode the vascular protection of youth
- Dyslipidemia is one of the more modifiable risks
- Atherosclerosis becomes less reversible with increasing age

II. The hard place
- Proven heart-healthy lifestyle guidelines are not ‘a piece of cake’
- Few pharmacologic options exist in kids—none are risk-free
- Starting treatment in youth may mean lifelong drugs

III. Life’s “catch 22” & the metabolic solution suggest a ‘soft spot’
CATCH: Depending upon toxic energy
SOLUTION: Global regulation of lipids, energy (aka weight) & immunity
- Why the “metabolic syndrome” links dyslipidemia, insulin resistance, obesity, and inflammation
- Why we can, conversely, link optimal lipid metabolism, insulin sensitivity, ideal body weight, and robust immunity

Atherosclerosis is an Age-Dependent Disease

From birth... From ~ 2nd decade... Variable onset...

Fatty streak | Raised lesion | Thrombotic plaque
Cardiovascular risk factors accelerate the aging of our vessels

THE ROCK: Cardiovascular Disease is a Pediatric Problem

Calcification of the LCA—density similar to bone (compare with sternum)

Evidence for CVD on our Pediatric Watch

- Autopsy data show advanced atheroma in teens & young adults
- Four major epidemiologic studies have linked CVD risk factors, (esp LDL-c & obesity) with atherosclerosis in young adults
  - Muscatine, Bogalusa, CARDIA, STRIP
  - CIMT, coronary calcium and/or endothelial function
- Hopkins med students with a TC >207 had 5x greater risk of MI in the next 40 yr than students with TC < 172
- Three offspring studies have linked premature parental CVD with dyslipidemia in the children

Pathological Determinants of Atherosclerosis in Youth (PDAY study)

- 1500 men and women autopsied, aged 15-34 yr
- Atherosclerosis quantified in RCA and aorta
- Premorbid risk factors inferred
  - Post-mortem lipoprotein analysis
  - Smoking by thiocyanate levels
  - Adiposity by BMI and abdominal panniculus
  - Hypertension by renal pathology
  - Diabetes by glycosylated hemoglobin levels


**PDAY Multivariable-Adjusted Associations Between Risk and Lesions**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coronaries</th>
<th>Abdominal Aorta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (q 5 y)</td>
<td>2.25 (1.76-2.86)</td>
<td>3.63 (2.58-5.12)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.80 (0.44-1.45)</td>
<td>1.51 (0.95-2.44)</td>
</tr>
<tr>
<td>Non-HDL-c</td>
<td>1.41 (1.21-1.65)</td>
<td>1.23 (1.06-1.45)</td>
</tr>
<tr>
<td>HDL-c</td>
<td>0.80 (0.61-1.05)</td>
<td>1.05 (0.77-1.41)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.26 (0.81-1.95)</td>
<td>2.93 (1.74-4.96)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.91 (1.11-3.26)</td>
<td>1.93 (1.13-3.28)</td>
</tr>
<tr>
<td>Obesity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>3.36 (1.31-4.34)</td>
<td>0.89 (0.41-1.92)</td>
</tr>
<tr>
<td>Women</td>
<td>0.91 (0.28-2.98)</td>
<td>0.89 (0.41-1.92)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2.57 (1.10-6.00)</td>
<td>2.28 (0.91-5.70)</td>
</tr>
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</table>

*McMahan et al, Arch Intern Med. 2005;165:883*

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**Yes and No...**

- **Is age an immutable risk factor?**
  - Yes
  - No

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**Why age may contribute to CAD?**

**Loss of Endothelial Progenitor Cells (EPC)**

- EPC - A unipotent bone marrow reserve to repair vascular wear & tear
- CVD risk factors (dyslipidemia, BMI, stress, smoking) diminish EPCs

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**“I never think of the future. It comes soon enough.”**

Albert Einstein

- The earlier therapy begins, the less carotid intima-medial thickening
  - Longitudinal data on pediatric FH managed with statins
  - Rodenburg et al, Circulation. 2007;116:664
- Once apoB-Lp are retained in the subendothelial space, further retention is amplified
  - Takas et al, Circulation. 2007;116:1832
- In adults, even aggressive LDL lowering can only reduce the incidence of CVD endpoints by 30-45%
  - La Rosa et al, NEJM. 2005;352:1425

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**This just in...**

- Urbina et al, downloaded from circ.ahajournals.org

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- cIMT by age and group. P for slope was 0.002 for obese and T2DM. NS for lean group
The risk-benefit ratio is stacked against Pharma in healthy kids. 

**The Hard Place:** Treating CVD ‘risk factors’ may create new risks

### Cholesterol-Lowering Rx Approved in Peds: Bile-acid resins, cholesterol absorption blockers & statins

- **Bile-acid resins** are safe but uncomfortable; compliance is poor
  - Bind intestinal cholesterol in bile acids, prevent reuptake
  - Cramping, bloating, and constipation are common
  - 10-20% ↓ LDL possible (if taken); TG often rises

- **Cholesterol absorption blockers** (Ezetimibe); tolerable but untested
  - Used with statins in adults → ↓ LDL additional 20%; but NO additional ↓ in CAD
  - Unlike resins, systemically absorbed; potential side effects still unknown

- **HMG-CoA reductase inhibitors - statins; relatively good track record**
  - Inhibit rate-limiting step for cholesterol synthesis, ↓ intracellular cholesterol and ↑ LDL receptors → ↑ plasma cholesterol clearance
  - Generally well tolerated
  - 20-50% ↓ in LDL possible with additional anti-inflammatory benefits
  - Additional benefits in TG; if there is also hypertriglyceridemia
  - Long-term follow-up in adults suggests good safety profile—but not risk-free

### Downside of statins - hepatic inflammation, muscle wasting & more?

- Increased hepatic transaminases
  - Usually reversible with drug withdrawal; rare progression to liver failure

- Elevation of creatinine kinase
  - May rarely be associated with rhabdomyolysis and renal failure

- Potential concerns to cholesterol-dependent tissues in youth
  - Contraindicated in pregnancy; may be teratogenic
  - Pass through breast milk; not recommended if breast feeding
  - Theoretical concern about neurological deficits, compromised cognitive function
  - Possible psychiatric fallout; depression is associated with excessively low cholesterol

- Statins may be particularly problematic for the brain
  - BBB does not permit passage of lipoprotein, either LDL or HDL
  - Statins do pass – may deplete CNS cholesterol reserves

### Predictive Value of Inflammatory Markers with a “normal” LDL

**Risk-Benefit Assessment Complicated by Imperfect Cholesterol Cutoffs**

- TC = 225 in more persons without than with CAD
  - The same TC level may be problematic or not, in a point **

**Lipid Screening Recommendations - WHO?**

<table>
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<th>Risk Category</th>
<th>Rationale</th>
<th>Disease condition</th>
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<td>Coronary artery disease, renal disease, premature vascular aging</td>
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<tr>
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<td>At-risk for accelerated atherosclerosis by epidemiologic evidence</td>
<td>Congenital heart disease, infection, renal disease, premature vascular aging</td>
</tr>
<tr>
<td><strong>At Risk</strong></td>
<td>At-risk for accelerated atherosclerosis by epidemiologic evidence</td>
<td>Cardiovascular risk factors, infection, renal disease, premature vascular aging</td>
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*Image credits:† Ridker et al, NEJM, 2000;342:836"
Advances and Controversies 2009
Pediatric Lipid Management

**Lipid Levels in Kids- WHAT?** (Target is “Acceptable”)

<table>
<thead>
<tr>
<th>Category</th>
<th>&lt;90</th>
<th>90 - 120</th>
<th>&gt;120</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;110</td>
<td>110 - 120</td>
<td>&gt;120</td>
</tr>
<tr>
<td>LDL-c</td>
<td>&lt;110</td>
<td>110 - 140</td>
<td>&gt;144</td>
</tr>
<tr>
<td>ApoB</td>
<td>&lt;90</td>
<td>90 - 120</td>
<td>&gt;120</td>
</tr>
<tr>
<td>TG 0-9 y</td>
<td>&lt;110</td>
<td>90 - 120</td>
<td>&gt;120</td>
</tr>
<tr>
<td>TG 10-19 y</td>
<td>&lt;90</td>
<td>90 - 120</td>
<td>&gt;120</td>
</tr>
<tr>
<td>HDL-c</td>
<td>&gt;40</td>
<td>35 - 45</td>
<td>&gt;50</td>
</tr>
<tr>
<td>ApoA1</td>
<td>&gt;120</td>
<td>110 - 120</td>
<td>&gt;120</td>
</tr>
</tbody>
</table>

Taken from the NCEP Expert panel on cholesterol levels in children. Apo A and apoB levels are from NHANES III.

**Life’s metabolic “catch 22”** - dependence on a toxic form of energy -

**LIPIDS (TG and cholesterol)**

- essential for every living cell membrane
- building blocks for steroid hormones and bile acids
- valuable source of concentrated caloric energy
- required for the synthesis of Vit D & absorption of fat soluble vitamins A, E, & K

- insoluble
- highly inflammatory; shares molecular epitopes with endotoxin
- molecularly unstable; readily oxidized to toxic free radicals
- excess accumulation is the root cause of atherosclerosis

**Metabolic Solution: Interconnectedness**

- Lipid metabolism, energy homeostasis/weight, and immunity are all controlled by global transcriptional regulators
- Peroxisome proliferator-activated receptors (PPARs)
  - Part of the body’s quick-response mechanism to respond to the environment
  - PPAR DNA response elements respond to heterodimers of PPAR/RXR receptor
  - Environmental ligands arguably more important than drugs

**Lifestyle PPAR Activators**

- Balanced body and brain nutrition: increased omega 3's and monounsaturates
- Physical activity and stress reduction: aerobic exercise, weight loss, and reduced stress levels
- Environmental factors: reduced exposure to endotoxins and inflammation

**Therapy for Pediatric Dyslipidemia**

1) Lifestyle Modification- Heart Healthy Nutrition & Exercise, Stress Reduction & NO SMOKING

- **“Eat food, not too much. Mostly plants.”**
- Upgrade fats (omega 3’s and monounsaturates)
- Upgrade carbs (70% or less F&W & increase whole grains)
- Upgrade protein (lean meats, beans, nuts, eggs, & fibers in more plant protein)

- Smoking
- Unhealthy diets (high fats, high sugars, high fiber, high refined, high acid ratios)
- Unhealthy fats (low fiber, low sugar, low fat, high acid ratio)
- Lack of Exercise
- Stress (and ethanol)
Therapy for Pediatric Dyslipidemia

When necessary as an adjunct to a heart-healthy lifestyle:

2) Nutraceuticals
   - esp. soluble fiber (oatmeal and oat bran or beans); 8-10 g/d lowers LDL 10-15%
   - plant stanols and sterols – essential components of plant membranes so present in all fruits, vegetables, seeds, and nuts- concentrated in commercial spreads & dressings; 2-3 g/d lowers LDL 5-15%
   - omega 3 fatty acids; 1-2 g/d lowers TG 10-20% with benefits to LDL size

3) Medication- post puberty (earlier only in highest risk children)
   - Rarely necessary in pediatrics
   - Works best in conjunction with lifestyle

Pharmacologic Treatment Thresholds-WHEN?

for children 10 yrs and older, already on optimal lifestyle

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Patient Characteristics</th>
<th>Cut Point (mg/dl)</th>
<th>Modulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-c*</td>
<td>No other CVD risk factors</td>
<td>&gt;180</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVD risk factors present, including obesity, hypertension,</td>
<td>&gt;160</td>
<td></td>
</tr>
<tr>
<td></td>
<td>smoking, heavy alcohol use, positive family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prems of premature CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes Mellitus (Type 1 or 2)</td>
<td>&gt;130</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No other CVD risk factors</td>
<td>&gt;160</td>
<td></td>
</tr>
<tr>
<td>TG**</td>
<td>Control high LDL &amp;/or low HDL</td>
<td>&gt;400</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVD risk factors present (as above)</td>
<td>&gt;180</td>
<td></td>
</tr>
</tbody>
</table>

* Daniels et al, Peds. 2008;122:198-208
** Manlhiot et al, Peds. 2009;123:458-465

Treatment Algorithm for Pediatric Dyslipidemia

- **FIRST PRIORITY ALWAYS:** Healthy Eating, Active Living

  - LDL Cholesterol lowering- aiming to preserve large buoyant LDL
    - Second: HMG CoA Reductase inhibitor (statin)
    - Third: Bile acid binding resin (or better, just up dietary fiber, esp soluble)

  - Triglyceride Lowering
    - Second: Glycemic control
    - Third: Fish oil (always molecularly distilled)
    - Fourth: Statins (moderately effective, esp if there is accompanying ↑ LDL)

  - HDL Cholesterol raising- aiming for large AI containing HDL
    - Second: Behavioral interventions (fitness, endurance exercise, smoking cessation)
    - Second: Fish oil

Summary

I. Atherosclerosis is prevalent, age-dependent, and preventable
II. Vascular age & atherosclerosis are accelerated by CVD risk factors
III. Dyslipidemia is one of the more modifiable risk factors
   - A readily identified marker for dysmetabolic changes
   - Think quality as well as quantity of lipoproteins
IV. Heart-Healthy Lifestyle (rarely with adjunct pharmacotherapy) can find the PPAR-activating, ‘age-defying’ metabolic soft-spot