Fat: Friend or Foe? An Overview of Pediatric Hyperlipidemia and Current Treatment Options

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Disclosure

Elia Nila Escamena, MD, has no relationships with commercial companies to disclose.

Learning Objectives

At the end of this presentation, the participant will be able to:
- Demonstrate an understanding of lipoprotein metabolism
- Understand current screening guidelines
- Demonstrate an understanding of pediatric dyslipidemias
- Distinguish current treatment options.

Friend

Fats and oils are important forms of stored energy and insulators.
Major structural elements of membranes.

Precursors for:
- Enzyme cofactors
- Electron carriers
- Light absorbing pigments
- Intracellular messengers
- Emulsifying agents
- Hormones

<image of bear>
Or Foe?
- Heart disease is the leading cause of death for both men and women in the US.
- In every 4 Americans die of heart disease a year.
- High blood cholesterol is a major risk factor for CVD.
- Longitudinal studies have found relationships of risk factors measured in youth with atherosclerosis in adulthood.

Historical Context
- In the 1960s, the Framingham study helped identify risk factors for cardiovascular disease.
- Late 1970s, the federal government started promoting the low-fat diet.
- In the 1980/90’s, ‘low-fat foods’ heavily promoted in popular culture.

What is a Lipoprotein?
Lipoproteins are lipid carriers through lymph or plasma.
Apolipoproteins (‘apo’ means separated) designates the protein in its lipid free form.

Important Lipoproteins, Apolipoproteins and Function
- Chylomicrons and their remnants: Apo B-48, (Apo C-II, C-III and E)
- VLDL: B-100 (C-II, CIII, E)
- LDL: B-100, Apo E
- HDL: A-I, A-II, (C-I, C-II, E)
  "Reverse transfer of cholesterol via various apolipoproteins"
Lipoprotein Lipase

- A triglyceride hydrolase found on the capillary endothelium with its highest concentration in the muscle and adipose tissue.
- ApoC-II activates LPL to release triglycerides to FFA.
- Insulin promotes the synthesis of LPL and stimulates the uptake of fatty acids released from triglyceride hydrolysis by LPL itself.

FH: No FH of hyperlipidemia. Paternal grandparents w/ T2DM. PGF/PGM with T2DM. No early heart disease. Grandparent with HTN.
Social: Likes to eat Whataburger. In college.
PE: BMI 25.4, no xanthomas or skin tags
Labs:
AST 72 U/L
ALT 147 U/L
Triglycerides 1554 mg/dl
Total Cholesterol 273 mg/dl

Case 1
20 yr old male w/ pre B-cell ALL currently receiving maintenance chemotherapy. Previously had received pegaspargase and cytarabine. Consulted for persistently elevated triglycerides 1504 mg/dl ->1564 mg/dl over the past 2 weeks.
R/O: (-) abdominal, emesis or epigastric pain. (+) nausea
PMH: No h/o elevated triglycerides or cholesterol. Pre B cell ALL, transaminitis.

Management
He was started on insulin drip because of risk of pancreatitis (triglycerides >1000 mg/dl) and concern that fibrates may worsen liver function.
Triglycerides 1554 mg/dl prior to starting drip @ 8/11 15:48 PM
8/12 4AM -> 8/12 12PM -> 8/13 9AM
739 mg/dl -> 500 mg/dl -> 290 mg/dl
Cholesterol 273 mg/dl -> 196 mg/dl
Counseled on low fat diet and discharged with omega 3 FA.

Lipoprotein Metabolism
Lipid transport occurs in 3 ways:
- Exogenous
- Endogenous
- Reverse cholesterol
Endogenous Pathway

Reverse HDL

Who should be screened?

- Birth to 2 y no routine lipid screening.
- 2-8 y Family History of early CVD, parent with dyslipidemia (TC≥240 mg/dl) or presence of additional risk factor or high risk condition. Fasting lipid profile (FLP x 2 (avg)
- 9-10 y Universal Screening with non-fasting HDL= TC-HDL or FLP x 2 (avg)

What are the other risk factors?

- 12-16 No routine screening unless new risk factors. Measure FLP x 2 (avg).
- 17-21 Universal Screening with non-fasting HDL= TC-HDL or FLP x 2 (avg)
### Familial Hypercholesterolemia

AD single gene d/o in lipoprotein metabolism. High among Lebanese, French Canadians, and South Africans. Heterozygous form: 1/4000
- LDL 2-3x higher than normal
- Homozygous: 1/1,000,000
- Plasma LDL 4-6x higher than normal

### Autosomal Dominant Hypercholesterolemia

- Inherited d/o with marked elevations or low levels of LDL
- Caused by mutations in protepan convertase subtilisin/kexin type 9 (PCSK9) involved in the degradation of LDLR

### Dyslipidemias

- Case 1
- Case 2

### Autosomal Recessive Hypercholesterolemia

- Caused by mutations in the ARH (LDLRAP1) gene, which encodes the adaptor protein required for normal LDLR-mediated endocytosis in hepatocytes
- TC are 5-6X higher than normal
- Similar to homozygous FH with usually normal lipoprotein profiles in their parents
Familial ligand-defective apoB-100

- Clinically resembles heterozygous FH
- Moderate to markedly high plasma LDL levels, normal triglycerides, and tendon xanthomas
- Poor binding of the LDL particle to the LDLR due to a mutation in apoB-100, resulting in a decreased clearance of LDL from plasma.

Familial Combined Hyperlipidemia (FCHL)

- AR disorder
- Prevalence of 1-2% in Western populations
- Increased production of hepatic VLDL
- Can have hypercholesterolemia, hypertriglyceridemia and/or elevated apo B levels; lipid profile can vary throughout time
- In: increased cholesterol, triglyceride or apoB in patients and their 1st degree relatives
- Often in conjunction with insulin resistance, central obesity, HTN and have increased risk of CAD.

Secondary Causes of Dyslipidemias

Endocrine: Hypothyroidism, Diabetes, Pregnancy
Exogenous: Drugs, Obesity, Alcohol
Renal: Nephrotic Syndrome, Chronic renal failure
Hepatic: Cholestasis, Biliary Atresia, Hepatitis, Biliary cirrhosis
Immunologic: HIV infection/AIDS

Case 2

14 5/12 y/o F with abnormal weight gain (30 lbs over the last year), dry skin, fatigue, and abnormal menses.
ROS: fatigue, excessive weight gain, fatigue, dryness, acanthosis, irregular menses, obesity.
FH: Sister hypothyroidism and Type I DM. PGM, paternal aunt have hypothyroidism. Mother, MGM, and MGF, PGM, PA, PGGM have Type II DM. MGM elevated cholesterol and HTN.

Drinks: flavored milk, regular coke, gatorade. Shakes at fast food restaurants in place of drink. Starbucks’s drink
PE: Weight 90 kg (57th %ILE), BMI 43.1 (57th %ILE), BP 115/59
Flat affect, no thyromegaly, dry skin, dry brittle hair, acanthosis, no HSM

Initial Labs:
AST 105 U/L, ALT 183 U/L
Cholesterol 252 mg/dl, Triglycerides 248 mg/dl, HDL 46 mg/dl, VLDL 60 mg/dl, LDL 166 mg/dl
TSH 213 uiU/mL

Started on 75 mcg levothyroxine and met with nutritionist.

Labs 5 months after treatment
Cholesterol 181 mg/dl, Triglycerides 160 mg/dl, LDL 102 mg/dl, HDL 47 mg/dl, VLDL 32 mg/dl
Free T4 0.77 ng/dl L TSH 10.37 ul/mL H
**CHILD 1**

- Birth to 6 mo: Exclusively BF
- 6-12 mo: Continue BF without fat restriction (limit juice, sweetened beverages)
- 12-24 mo: Total fat 30% of daily kcal of estimated energy req (EER)
  - Saturated fats 8-10% of kcal/EER
  - Avoid trans fats
  - Mono/Poly unsaturated up to 20% of daily kcal/EER
  - Cholesterol <300 mg/d
2-10 y/o: Total fat 25-30% of daily kcal/EEER
  Saturated fats 8-10% of kcal/EEER
  Avoid trans fats
  Mono/Poly unsaturated up to 20% of daily kcal/EEER
  Cholesterol <300 mg/d
  Encourage high fiber (age - 5 g/day)

11-21 y/o: Same as above with increased fiber 14 g/1000 kcal

CHILD-2

If LDL > or = 130 mg/dl after 3-6 months of dietary adherence to CHILD-1 then further restriction recommended.
  • < 7% of Total calories from saturated fat
  • Cholesterol < 200 mg/day

Other dietary strategies

Plant based diets
  • 4 wk prospective randomized trial
  • Large Midwestern hospital
  • 30 children (9-18 yrs old) + parent pairs
  • Child BMI > 95th percentile
  • Child cholesterol > 169 mg/dL
  • Randomized to PB or AHA + weekly 2-hour classes of nutrition education

Pharmacological Tx

• In 1985, Nobel Prize awarded to Michael Brown and Joseph Goldstein for their discovery of the LDL receptor and regulation of cholesterol metabolism.

• Concept of feedback regulation of receptors helps explain the cholesterol-lowering effects of statins.

• By 1992, 4 statins were commercially available on the market.

• This class of drugs are remarkably effective in lowering plasma LDL levels, reducing heart attacks, and prolonging life.
Pharmacologic

**Drugs Affecting Lipoprotein Metabolism**

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<thead>
<tr>
<th></th>
<th>LDL-C (%)</th>
<th>HDL-C (%)</th>
<th>TG (%)</th>
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<tbody>
<tr>
<td>Statins</td>
<td>10-85</td>
<td>10-100</td>
<td>20-40</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>10-50</td>
<td>10-100</td>
<td>10-20</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>10-50</td>
<td>10-200</td>
<td>10-200</td>
</tr>
<tr>
<td>Fibric Acids</td>
<td>10-50</td>
<td>10-200</td>
<td>20-400</td>
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<tr>
<td>Ezetimibe</td>
<td>10-30</td>
<td>10-200</td>
<td>10-200</td>
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<tr>
<td>Omega-3 fatty acids</td>
<td>10-20</td>
<td>10-70</td>
<td>10-40</td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>10-70</td>
<td>10-150</td>
<td>10-170</td>
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*Primary for hypertriglyceridemia

Side Effects

Statins: Raise liver enzymes, can increase creatinine kinase, myopathy possible progressing to rhabdomyolysis.

Bile acid sequestrants: GI upset.

Fibrates: Dyspepsia, constipation, anemia, myositis, raise liver enzymes.

Nicotinic Acid: Flushing, hepatic toxicity, increase fasting glucose and uric acid.

What’s approved in kids?

- Most statins are approved in children >10 yrs (Pravastatin approved for >8 yrs)
- Bile acid sequestrants such as colesvelam indicated as monotherapy or with statin >10 yrs
- Nicotinic Acid not recommended in children < 2 y/o

Case 4

5 year old H female referred for elevated total cholesterol and LDL. PCP screened lipids b/c complaints of HA and FH of hyperlipidemia. Initial fasting labs with TC of over 300. Parents were counselled on diet modification. F/u with PCP, fasting TC 287, Trig 78, HDL 48, LDL 229.

ROS: (-) HA 3-4 times a week x 4 months (-) No abdominal pain. No tachycardia, no palpitation and no chest pain.

PMH: None

FH: Mom and MGM both have high cholesterol (on statins). Maternal obesity. Denied any h/o of early cardiac disease or stroke.

SH: Family originally from Mexico. In kinder.

Nutrition: Drinks 1 glass of whole milk a day and 2 cups of juice per day.

W: 18.3 kg (50th) H: 105.6 cm (25th) BMI: 16.4 kg/m2 (75th)

PE: Tanner I female. no xanthomas or skin tags

Seen by Lipid Specialist at OSH Dx with Familial hypercholesterolemia.

Started on red rice yeast extract.
Red Yeast Rice Extract

- Red yeast rice is made by culturing rice with various strains of the yeast Monascus purpureus.
- Used in food products in Chinese cuisine.
- Monacolins block the production of cholesterol.

"Not FDA approved in children."

Side effects:
- Similar to statins including myopathy, rhabdomyolysis and liver toxicity.
- Concerns for contamination of product.

Fish Oil (Omega 3 FA)

An essential fatty acid (needs to be derived from food)

Omega 3 comes in three flavors: (ALA, EPA, DHA)

Rich sources come from marine oils including fatty fish (such as cold water salmon) and plant sources such as flaxseed oil and canola oil.

Side effects:
- Occasional nausea more so at higher doses 4g/day.
- Raisin ALT/AST.
- Fish taste.

Not FDA approved for children.

Supplements

Fish Oil (Omega 3 FA)
Decrease hepatic fatty acid (FA) and triglyceride (TG) synthesis.
Enhance FA oxidation
Reduce VLDL cholesterol release
May increase LDL or LDL particle size

FDA has approved fish oil supplements at a dose of 4 g/day for prescription therapy of hypertriglyceridemia in adults.

Rx Brand: Lovaza 1g capsule contains 465 mg EPA + 375 DHA

Fun Fact

USDA egg has a omega 6 to omega 3 ratio of 9 while a free range eggs is 1:3.
In summary...

"Cholesterol is a Janus-faced molecule. The very property that makes it useful in cell membranes, namely its absolute insolubility in water, also makes it lethal."

Nobel lecture, December 9, 1966, by Michael Brown and Joseph Goldstein