Atherosclerosis – Hyperlipidemia

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AS/Hyperlipidemia - Lecture Outline

1. AS
   • Gross and microscopic pathology
   • Pathogenesis – ‘Response to Injury’ hypothesis

2. AS Risk Factors
   • Major and minor
   • RF assessment – role of the clinical laboratory
   • Clinical practice guidelines from the ATPs of the NCEP

3. AS/Hyperlipidemia Review Questions
   • Audience response system and discussion

Case History – Patient Y.G. in Clinic

Patient Y.G. is a 35 y/o Caucasian male seen in clinic after starting a new job. Y.G. tells the physician that he’s not seen a doctor for almost 15 years. But Y.G. explains that relatives from both sides of his family have had heart attacks and strokes in their 50’s and 60’s. He lost an older brother to a heart attack at the age of 43.

The physician explains she will order a lipid profile on Y.G. to evaluate his lipid levels, whether he has hyperlipidemia and if he’s at increased risk for early development of heart disease due to atherosclerosis (AS).

• What is AS?
• What are the major clinical features and manifestations of AS?
• What are the significant pathological features of AS?
What is Atherosclerosis (AS)?

AS is a disease of formation and growth of intimal lesions (atheromas) which protrude into and obstruct vascular lumens as well as weaken the underlying media. As a consequence, pathologic changes to blood vessels lead to:

• Wall dilatation (aneurysm) & rupture
• Damage to endothelium causing thrombosis
• Alteration in blood flow which may also cause thrombosis
• Narrowing of the vessel lumen which may lead to ischemia and infarction downstream

> AS is also a chronic inflammatory disease

Fatty streaks and ‘foam’ cells

Lipid staining near ‘branch points’
AS natural history, morphologic features, main pathogenic events, and clinical complications

Figure 9-14 Summary of the natural history, morphologic features, main pathogenic events, and clinical complications of atherosclerosis.

Atherogenesis – ‘Response to Injury’

Response to injury in atherogenesis:
1. Normal
2. Endothelial injury with monocyte and platelet adhesion
3. Monocyte and smooth muscle cell migration into the intima, with macrophage activation
4. Macrophage and smooth muscle cell uptake of modified lipids and further activation
5. Intimal smooth muscle cell proliferation with ECM elaboration, forming a well-developed plaque

Key Pathological Features of AS
One week later, a concerned Y.G. returns to clinic to discuss his lab test results with the doctor. He is not ‘too’ overweight, doesn’t have high blood pressure, exercises 1-2 times a week and believes he is in good health. Especially since he gave up cigarette smoking a few months back after being a half a pack per day smoker for almost 15 years.

The doctor discusses Y.G.’s lab results with him. Some are abnormal:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>287 mg/dL</td>
<td>Very increased risk</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>193 mg/dL</td>
<td>Very increased risk</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>170 mg/dL</td>
<td>Increased risk</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>38 mg/dL</td>
<td>Increased risk</td>
</tr>
</tbody>
</table>

- The doctor explains to Y.G. that the results indicate positive risk factors for AS and that Y.G. could be a ‘carrier’ for familial hypercholesterolemia.
- Y.G. asks what being a ‘carrier’ for that disease means and are there other risk factors for AS he should be concerned about?

![Risk of Coronary Heart Disease and Serum Cholesterol Levels](image)

* Castelli et al, 1977
Total Cholesterol – The Earliest R.F.

Abundance of evidence links AS to a well-known major risk factor — hypercholesterolemia:

- In animals, high cholesterol diets produce AS plaques
- Plaques are rich in cholesterol and cholesterol esters (both shown to come from blood lipoproteins)
- Direct relationship between cholesterol, LDL and AS
- Genetic defects and acquired diseases that cause high cholesterol lead to early and rampant AS
- Plaque progression slowed, reversed with diet & drugs

Atherosclerosis Risk Factors

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor (selected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Non-modifiable’</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Age</td>
<td>Obesity</td>
</tr>
<tr>
<td>Male gender</td>
<td>Stress (type A)</td>
</tr>
<tr>
<td>Family history</td>
<td>Postmenopausal estrogen deficiency</td>
</tr>
<tr>
<td>Genetic abnormalities*</td>
<td>Alcohol</td>
</tr>
<tr>
<td>‘Modifiable’</td>
<td>Hardened (trans)saturated fat intake</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Chlamydia pneumoniae</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>Cigarette Smoking</td>
<td>Lipoprotein (a)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Lipoprotein particle analysis</td>
</tr>
<tr>
<td>Inflammation</td>
<td>High sensitivity C-reactive protein or hsCRP</td>
</tr>
</tbody>
</table>

* Risk factors assessed by use of the clinical laboratory

The ‘MRFIT’ Study

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Atherosclerosis – Hyperlipidemia

Mechanisms of Human Disease

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Lipoproteins (LP’s):

- **Cholesterol and other lipids are transported in blood by LP’s:**

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Density (g/ml)</th>
<th>Major Lipids</th>
<th>Major Apoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low Density</td>
<td>&lt; 0.94</td>
<td>Triglycerides</td>
<td>B-48, A-I, IV</td>
</tr>
<tr>
<td>(VLDL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Density</td>
<td>0.94 to 1.019</td>
<td>Triglycerides, Cholesteryl esters</td>
<td>B-100, E</td>
</tr>
<tr>
<td>(IDL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Density</td>
<td>1.019 to 1.063</td>
<td>Cholesteryl esters</td>
<td>B-100</td>
</tr>
<tr>
<td>(LDL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Density</td>
<td>&gt; 1.063</td>
<td>Cholesterol, Phospholipids, Proteins</td>
<td>A-I, A-II</td>
</tr>
<tr>
<td>(HDL)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LDL and HDL are Two of the Plasma Lipoproteins (LP’s):**

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**LDL Receptor Defects:**

**Familial Hypercholesterolemia**

The LDL receptor is on chromosome 19

- 5 major domains
- Located on 19p13.1-3
- 839 a.a. protein
- 5 main classes of LDL receptor defects in FH
- > 800 known mutations

Modified from www.people.virginia.edu/~rjh9u/ldlrecelp.html

**Diseased patients are homozygotes while their parents are heterozygotes**
<table>
<thead>
<tr>
<th>Homocysteine</th>
<th>Lp(a) is a LDL-Polypeptide (a) Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Highly reactive sulfhydryl a.a. derived from methionine</td>
<td>- LDL particle with apo-B100 linked to apo (a)</td>
</tr>
<tr>
<td>- Elevations seen in genetic disorders of methionine metabolism and premature AS</td>
<td>- Concentration dependent on apo (a) size and genetics</td>
</tr>
<tr>
<td>- Metabolism involves several cofactors … folic acid, B6, B12</td>
<td>- May inhibit fibrinolysis (&quot;a&quot; structural homologue of plasminogn)</td>
</tr>
<tr>
<td>- May contribute to AS through:</td>
<td>- Commercial assays poorly standardized, sensitive to apo (a) size</td>
</tr>
<tr>
<td>• Platelet activation and increasing platelet adhesiveness</td>
<td>- Links hyperlipidemia to abnormal coagulation (thrombogenic)</td>
</tr>
<tr>
<td>• Promoting proinflammatory response, DVT and directly activates coagulation cascade</td>
<td>- May be most prognostic in those with FH of premature AS</td>
</tr>
</tbody>
</table>
Lipoprotein Particles

Small, dense LDL is the most atherogenic.

High Sensitivity C-Reactive Protein

- CRP a long known marker of chronic inflammation
- Elevated levels may indicate greatest risk for CVD
- CDC/AHA guidelines - tertiles of normal range

Baseline hsCRP and RR of 1st MI

- Baseline Risk of the Atherosclerotic Plaque Erosion and Platelet-Related Plaque Compartment Formation of C-Reactive Protein, Stratified According to Randomized Assignment to Aspirin or Placebo Therapy
Event Free Survival According to Baseline Quintiles

Selected Milestones in Cholesterol Education and AS Awareness

- 1948 Framingham Heart Study Begins
- 1965 First Framingham report on stroke
- 1970’s More Framingham reports: Multiple Risk Factor and Intervention Trial, LRC-COPPT
- 1977 Effects of triglyceride, LDL and HDL cholesterol on AS and CVD first described
- 1985 National Cholesterol Education Program (NCEP) created
- 1988 First Adult Treatment Panel (ATP I) of National Cholesterol Education Program (NCEP) – angiographic trials and metaanalyses
- 1993 ATP II of NCEP
- 2001 ATP III of NCEP
- 2007 Revision of ATP III
- 2014 ATP IV of NCEP

Recent Lipid Treatment Clinical Practice Guidelines

- NCEP ATP III (2001 – 2013)
  - Focused on multiple risk factors
  - Used Framingham projections for 10-yr absolute risk
  - More aggressive treatment & support for implementation
  - All cholesterol fractions in mg/dl:
    - Total = < 200 Optimal or Desirable; 200 – 239 Borderline High; 240 High
    - LDL = < 100 Optimal or Desirable; 100 – 129 Near or Above Optimal; 130 – 159 Borderline High; 160 – 189 High; > Very High
    - HDL = > Optimal or Desirable; < 40 Bad; > 60 Very Good
- ACC/AHA Guidelines (2014)
  - Completely revised approach
  - Identifies 4 statin benefit groups
  - Simplifies therapy into high-intensity and moderate-intensity statin therapy
  - Details still being developed by providing institutions
Assessing 10-Year CHD Risk

**General Risk Categorization #1**
- < 10%: Low risk (35% of U.S.)
- Reassurance:
  - All CHD RF to be treated to reduce CHD risk

**General Risk Categorization #2**
- 10–20%: Intermediate risk (40% of U.S.)
- Other public health recommendations. May delay further CV assessment for 5 years
  - Candidates for aggressive management with LDL goals of <100 (vs < 70) mg/dl and aspirin

**General Risk Categorization #3**
- > 20%: High risk (25% of U.S.)
- Do not qualify for most intensive RF interventions
  - Candidate for pharmacotherapy if LDL > 160 mg/dl

**Other public health recommendations**
- Candidates for aggressive management with LDL goals of <100 (vs < 70) mg/dl and aspirin
- Pharmacotherapy if LDL > 190 mg/dl
- Most CVD events occur in intermediate risk pts

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Assessing 10-Year CHD Risk

- **Outcome** – Coronary Heart Disease
- **Duration of follow-up**
  - Maximum of 12 years
  - 10-year risk prediction
- **Population of interest**
  - Individuals 30 to 74 years old and without overt CHD at baseline exam
- **Predictors**
  - Age
  - Diabetes
  - Smoking
  - Blood pressure categories
  - NCEP total cholesterol categories
  - LDL cholesterol categories
- Assign point values and total points = 10 yr risk
- Use different scales for men and women

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Moving Towards hsCRP Modified Risk Scores?

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Quantitating LDL Cholesterol

LDL cholesterol is remains one of the more common targets for therapy and treatment once hyperlipidemia or hyperlipoproteinemia is identified in a patient.

LDL cholesterol can be directly measured, but is more often calculated using the Friedewald Equation:

$$\text{LDL (calculated)} = \text{Total cholesterol} - (\text{HDL cholesterol} + \text{Triglyceride}/5)$$

* Triglyceride/5 approximates VLDL cholesterol if Triglyceride is ≤ 400 mg/dl

Patient Y.G. – 3rd Clinic Visit

3 months later, Y.G. returns to clinic and gets good news. He is not a carrier for familial hypercholesterolemia. But he has been prescribed pharmacologic therapy (rosuvastatin). Fortunately, he has responded and his insurance even covers it. Y.G. is 25 lbs lighter and goes to the fitness center 4 times a week. He hasn't felt this good since before he started smoking.

The doctor discusses Y.G.'s latest lab results. They are much improved:

- Total Cholesterol: 193 mg/dl (Desirable)
- LDL Cholesterol: 104 mg/dl (Desirable)
- Triglyceride: 107 mg/dl (Desirable)
- HDL Cholesterol: 43 mg/dl (Desirable)

Y.G. thanks the doctor telling her all this 'lab stuff' is pretty interesting although a little complicated. He wants to know where he can get more information about these and other lab tests:

www.labtestsonline.org

ATP III Guidelines: 40 Years of Education


In Summary…..

From Robbins

Review Question 1

Following a meal, lipids are digested and absorbed in the GI tract for transport to the liver. Which of the following blood components transports exogenous (dietary) triglyceride from the intestine to the liver?

a. Lipoprotein lipase
b. Chylomicrons
c. High density lipoprotein
d. Low density lipoprotein
e. Oxidized low density lipoprotein

Review Question 2

Gross and microscopic pathologic findings of autopsy studies reveal that atheroma formation can start in early childhood. Which of the following lesions is most likely to be the first (earliest) visible gross evidence for the formation of an atheroma?

a. Calcification
b. Thrombus
c. Fatty streak
d. Hemorrhage
e. Ulceration
Review Question 3

Which of the following apoproteins is required for cell surface recognition of LDL by the LDL receptor?

a. Apo A-1
b. Apo B-48
c. Apo B-100
d. Apo C-2
e. Apo E

Review Question 4

Assuming all other risk factors for AS/CAD are normal, which of the following risk factor changes from normal blood levels increases the risk for a patient to develop AS/CAD?

a. Postprandial increased triglyceride
b. Increased HDL
c. Decreased LDL
d. Increased Lp (a)
e. Decreased high sensitivity CRP

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