

CHD Mortality

- 12 million Americans have CHD
- ~800K Americans die each year of CHD
 - 1 death every 33 seconds
 - Leading cause of death in America
- **The failure of primary prevention!**

Serum Lipoprotein Classes

Chylomicrons

VLDL Very Low Density Lipoprotein

IDL Intermediate Density Lipoprotein

LDL Low Density Lipoprotein

HDL High Density Lipoprotein

Dietary Factors Influencing Serum Cholesterol Levels

- Average adult requires about 1.1 g/d of cholesterol for maintenance of cell membranes and serving as precursor of steroid hormones and bile acids
- ~10% of this obtained from diet
- average American man's daily cholesterol intake is 327 mg
- average American woman's intake is 221 mg
- about half (or more) is excreted (i. e., not absorbed)
- ⟨ NOTE: absorption of cholesterol from diet is highly variable and is affected by dietary composition and genetics

Major sources of dietary cholesterol

- egg yolks
- meats, especially red meats and liver
- dairy products
- plants do NOT synthesize cholesterol, but do synthesize other sterols and similar compounds (e.g., stanols)

In vivo sources of cholesterol

- ~80-90% of daily cholesterol needed obtained from *de novo* synthesis
- liver accounts for ~1/2 of synthesis
- gut accounts for ~15%
- skin accounts for significant portion of remainder
- all carbons of cholesterol derived from acetyl-CoA *via* isoprenoid pathway
- since cholesterol synthesis occurs during absorptive phase, glucose is a major source of acetyl-CoA for fatty acid & cholesterol biosynthesis

Because of regulation of cholesterol synthesis at level of HMG-CoA reductase by cholesterol entering liver from LDL or chylomicron remnants, effect of ingested cholesterol on serum cholesterol level is minimal at best in most normal individuals. For example if one goes from dietary intake of 500 mg cholesterol/day to one having 200 mg/day, would expect no more than a 10 - 15% reduction in serum cholesterol level, absent some other intervening factor

- Number of studies found that going from one or more eggs per day to fewer or no eggs, or vice versa, no significant change in serum cholesterol, except in a fraction of population that is "cholesterol sensitive"

- Extent of cholesterol sensitivity in U. S. and other countries unclear, except not predicted by cholesterol intake, body weight or levels of HDL
- amount of cholesterol synthesized in liver and non-hepatic tissues regulated by the amount of cholesterol that enters from LDL, derived from VLDL *via* IDL
- you already know that uptake of LDL is receptor mediated event and that one cause of CHD is caused by genetic factors affecting the LDL receptor

Dietary Fiber & Cholesterol

- One factor involved in determining amount of cholesterol utilized daily is amount of bile acids returned to liver from GI tract
- One dietary factor involved in influencing this is the amount of fiber ingested

Dietary Fiber

Total fiber: dietary fiber + functional fiber

- Current (2002) IOM-FNB DRI for Total Fiber
- * AI = 38g/d for men ages 14 - 50 y
- * AI = 25g/d for women ages 19 - 50 y

Viscous Fiber

- Intake of even moderate amounts of viscous fiber is associated with lowering plasma cholesterol levels
- Viscous fiber apparently interferes with absorption of dietary fat and cholesterol and enterohepatic circulation of bile acids and cholesterol

↳ **Tables for Total Fiber DRI (AI) and sources of fiber on p. 9, Macronutrient I handout**

Types of Fat & Serum Cholesterol Levels

- In addition to genetics and fiber intake another major factor influencing serum cholesterol levels is amount & type of fat in diet
- In general, the more saturated fat in the diet, the higher the serum cholesterol
- There appear to be differences between types of saturated fats
- diets high in stearate (18:0) and oleate (18:1) cause lower cholesterol levels than diets high in palmitate (16:0), myristate (14:0) or laurate (12:0)
- stearate or oleate not as effective as n-3 PUFA
- n-6 PUFA fall between stearate/oleate and n-3 fats, or are closer to the latter (n-3)

Adult Treatment Panel III (ATP III)

- ATP III issued in 2001 by National Cholesterol Education Program (NCEP)
- NCEP is unit of National Heart, Lung & Blood Institute of NIH
- ATP III provides guidance to physicians on treatment of hypercholesterolemia

Effects of Saturated Fatty Acids (SFA) on LDL Cholesterol (ATP III)

- Positive dose response between intake of (most) saturated fatty acids and LDL cholesterol levels
- Reduction in intakes of (most) SFA reduces LDL cholesterol levels
- Epidemiological evidence that high intakes of SFA associated with high population risks for CHD

Effects of Monounsaturated Fatty Acids (MUFA) and Polyunsaturated Fatty Acids (PUFA) on LDL Cholesterol (ATP III)

- MUFA lower LDL cholesterol relative to SFA

- MUFA do NOT lower HDL cholesterol nor raise TAG
- n-6 PUFA lower LDL cholesterol relative to SFA
- n-6 PUFA also cause a slight drop in HDL cholesterol relative to MUFA
- Epidemiological evidence that substitution of PUFA for SFA reduces risks for CHD

Effect of *Trans* Fatty Acids (TFA) on Serum Cholesterol Levels (ATP III)

- Convincing evidence that *trans* fatty acids increase LDL:HDL ratios
- Indeed, they appear to increase the ratio more than do saturated fatty acids
- They not only increase LDL, they also markedly lower HDL
- There appears to be a positive association between higher intakes of *trans* fatty acids and CHD incidence
- Mean TFA intake (1999) estimated at 2.6% of daily total energy intake
- IOM 2002 Macronutrient guidelines recommends that *trans* fats be reduced to lowest level feasible.

Which foods contribute to trans fatty acids (TFA) intake?

Recent survey found following contributions (%) of various foods to TFA intake

| Food | % | Source |
|-----------------------|------------|----------------------|
| milk (whole) & cheese | 18.8 | Natural |
| butter | 6.9 | Natural |
| eggs | 0.9 | Natural |
| meats & meat products | 10.3 | Natural |
| oils & fats | 35.5 | Mainly hydrogenation |
| biscuits & cakes | 16.5 | Mainly hydrogenation |
| savory pies, etc | 3.5 | Mainly hydrogenation |
| chips, french fries | 4.5 | Mainly hydrogenation |
| other | 4.1 | Mainly hydrogenation |
| TOTAL | 100 | |

Effects of Carbohydrate Intake on LDL & HDL Cholesterol Levels (ATP III)

- When carbohydrate is substituted for SFA, LDL cholesterol falls
- Very high carbohydrate intake ($\geq 60\%$ of total calories), HDL cholesterol falls and TAG increases
- Lower carbohydrate intake ($\leq 50\%$ of calories) should be considered for persons with elevated TAG or low HDL cholesterol
- Most of carbohydrate intake should come from whole grains, fruit and vegetables, and fat-free and low-fat dairy products

ATP III Lipid and Lipoprotein Classification

Total Cholesterol (mg/dL)

- <200 Desirable
- 200–239 Borderline high
- ≥ 240 High

LDL Cholesterol (mg/dL)

- <100 Optimal
- 100–129 Near optimal/above optimal
- 130–159 Borderline high
- 160–189 High
- ≥ 190 Very high

Major focus of ATP III is on lowering LDL Cholesterol

ATP III Lipid and Lipoprotein Classification – Update

Modified Goals for LDL Cholesterol (mg/dL)

- * <100 For those at high risk
- * <70 For those at very high risk
- * Based on 5 clinical trials of statin therapy completed since ATP III was published
- * From NCEP update to ATP III guidelines published by Scott M. Grundy *et al. Circulation*, 110: 227 - 239; July 13, 2004

ATP III Lipid and Lipoprotein Classification

HDL Cholesterol (mg/dL)

<40 Low

≥60 High

\ **In general, the higher HDL, the better**

Initiate ATP III Therapeutic Lifestyle Changes (TLC) if LDL is above goal

TLC Features:

\ **TLC diet**

- υ Saturated fat <7% of calories, cholesterol <200 mg/day
- υ Consider increased viscous (soluble) fiber (10 - 25 g/day) and plant stanols/sterols (2 g/day)

\ **Weight management**

\ **Increased physical activity**

Mediterranean Diet and CVD

- Main characteristics are:
- Abundance of plant food (fruits, nuts, vegetables, whole-grain cereals, legumes)
- Olive oil (and/or canola oil) as principal source of fat
- Fish and poultry in low-to-moderate amounts
- Relatively low consumption of red meat
- Moderate consumption of wine, normally with meals

The Lyon Diet Heart Health Study

Michel de Lorgeril, et al. *Circulation* p. 779; Feb 16, 1999

- This was designed and funded as 5-yr study comparing a “Mediterranean diet” to control diet similar to the old AHA Step I diet
- All 605 participants had had a myocardial infarction
- After 27 m, the Scientific and Ethics Committee terminated the trial because the benefits of the experimental diet were so favorable
- 70% reduction in all-cause mortality and 73% reduction in rate of coronary events
- Dr. de Lorgeril informed participants of the above and they agreed to continue the diets

- The longer term follow-up (mean 46 m) showed the same positive cardioprotective effect of the Med diet compared to the AHA Step I diet
- True for cumulative survival without nonfatal MI
- True for cumulative survival without nonfatal MI and without major secondary end points
- True for cumulative survival without nonfatal MI, without major secondary end points, and without minor secondary end points

Low Density Lipoprotein (LDL)

- LDL derived from VLDL as TAG in VLDL (and IDL) removed by lipoprotein lipase
 - \ LDL major cholesterol-carrying lipoprotein (levels correlate more strongly with CHD than total serum cholesterol levels)
- LDL taken up by liver via LDL receptor which recognizes apo B100
- High levels of LDL, small LDL size and oxidized LDL increase risk of atherosclerosis

High Density Lipoprotein (HDL)

- HDL functions in reverse cholesterol transport – removal of cholesterol from peripheral tissues
- Nascent HDL is newly synthesized from apo A-I and phospholipid and accepts cholesterol from cell membranes
- LCAT (lecithin-cholesterol acyltransferase) converts HDL cholesterol to cholesterol ester
- CETP (cholesterol ester transfer protein) transfers cholesterol ester from HDL to VLDL remnants in exchange for triacylglycerol
- Hepatic lipase degrades HDL
- HDL can also be taken up without degradation by HDL receptor
- Thus, peripheral cholesterol is transferred to liver either after transfer to LDL or via HDL receptor
- Low levels of HDL correlate with increased risk of CHD

Atherosclerosis – Pathogenesis

- Endothelial injury/dysfunction
 - \ Smoking (hypoxia, carbon monoxide)
 - \ Hypertension/hemodynamic factors
- Platelet/Monocyte adhesion
 - \ Release of growth factors, chemo attractants
 - \ Smooth muscle proliferation – extracellular matrix production
 - \ Macrophage infiltration and lipid uptake (oxidized LDL, ?remnants) – Foam cell formation
 - \ Cell death – necrotic center, extracellular lipid accumulation, calcification
- Plaque formation
 - \ Plaque rupture, thrombosis, arterial occlusion, infarction, death.

* **Now recognized that atherosclerosis has a significant inflammatory component, and, in parallel, statins appear to inhibit inflammatory processes directly**

* Recent evidence* that statins not only inhibit cholesterol synthesis, but independently reduce circulating levels of C-reactive protein (CRP), a stable biomarker of inflammation

* This has implications for a dual role for statins

- \ Reduces level of LDL cholesterol

- \ Decreases inflammatory component of atherosclerosis

*Ricker, P.M. *et al.*, *N. Engl. J. Med* 352:1, 20 - 28; 01/06/2005; Nissen, S.E. *et al.*, *ibid*, 29 – 38; Ehrenstein, M.R., *ibid*, 73 - 75 (editorial)