Cholesterol – a biomolecule
Bad cholesterol – a strange tale
Good cholesterol - indeed

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Myth or Science?

- High cholesterol causes coronary heart disease
- Lowering LDL (“bad cholesterol”) is beneficial
- Exercise and diet are insufficient
- Preventative drug therapy strongly recommended (Statins)
Who is wrong?

Ancel Keys

WHO
Study Flaw 1

- Anitschkow – rabbits fed with very high doses of cholesterol developed “arteriosclerosis”
- Rabbits are herbivores
- Cholesterol is exclusively in animal fats
- Carnivores and omnivores (dogs, rats) do not exhibit arteriosclerosis-like symptoms
The 7 country study was actually a 22 country study.
Same data – different graph
Same data – different graph
Could it get any worse?

Maasai (Kenya)
Inuit (Alaska)
Rendile (Kenya)
Tokelau (New Zealand)
Persistent low cholesterol is strongly associated with increased mortality due to heart disease.
The Framingham Study

- 15,000 individuals, 3 generations
- Dietary cholesterol intake inconsequential for serum cholesterol levels
- High cholesterol does not correlate with increased risk for coronary heart disease

"There is a direct association between falling cholesterol levels over the first 14 years and mortality over the following 18 years."

In other words, as cholesterol fell death rates went up.
The Japan Study

- 47,000 individuals
- The lipid intervention trial

“Changes in Total Serum Cholesterol and Other Risk Factors for Cardiovascular Disease in Japan, 1980–1989


AKIRA OKAYAMA, HIROTSUGU UESHIMA, MICHAEL G. MARMOT, MASAKAZU NAKAMURA, YOSHIKUNI KITA and MASANOBU YAMAKAWA

“The highest death rate observed was among those with lowest cholesterol (under 160mg/dl); lowest death rate observed was with those whose cholesterol was between 200-259mg/dl”

while prevalence in women remained low (from 10.1 to 9.9%) Considerable increases in total serum cholesterol levels do not offer an explanation of the recent decline in mortality from coronary heart disease in Japan. This
The Honolulu Study

The Honolulu Heart Program study, with 8,000 participants, published in 2001:

“Long-term persistence of low cholesterol concentration actually increases the risk of death. Thus, the earlier the patients start to have lower cholesterol concentrations, the greater the risk of death.”

Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study

Prof Dr Irwin J Schatz, MD, Prof Kamal Masaki, MD, Katsuhiko Yano, MD, Randi Chen, MS, Prof Beatriz L Rodriguez, MD, Prof J David Curb, MD

Only the group with low cholesterol concentration at both examinations had a significant association with mortality (risk ratio 1.64, 95% CI 1.13–2.36).
More Interesting Data

- Most Heart Attack Patients' Cholesterol Levels Did Not Indicate Cardiac Risk (2009)
- University of California - Los Angeles
- nearly 75% of patients hospitalized for a heart attack had cholesterol levels that would not indicate a high risk for a cardiovascular disease
- Half of patients had “optimal” LDL cholesterol levels
- Smith-Lemli-Opitz syndrome – children with cholesterol synthesis defect → still birth or infant death (severe brain abnormalities) → severe retardation of survivors
- High cholesterol diet alleviates many syndromes or severity
More Ancel Keys

1955: “It is concluded that in adult men the serum cholesterol level is essentially independent of the cholesterol intake over the whole range of natural human diets.

1997: “There’s NO connection whatsoever between cholesterol in food and cholesterol in blood. And we’ve known that all along. Cholesterol in the diet doesn’t matter at all unless you happen to be a chicken or a rabbit.”
New Facts

- High serum cholesterol does not correlate with increased risk of coronary heart disease
- Dietary cholesterol has little if any influence on serum cholesterol
- High fat diets do not promote coronary heart disease
Low Fat Diet – High Fat Diet

- The percentage of fat in your diet is not linked to disease
- The type of fat matters a lot more
- Avoid trans fats
- Healthy fats include 10% each mono/polyunsaturated and saturated fats
- Olives, canola, sunflower, nuts, seeds, fish
Saturated fatty acid

Cis unsaturated fatty acid

Trans unsaturated fatty acid
**Foods rich in saturated triacylglycerols:**
fatty red meat, cheese, butter, fried foods, ice cream

**Foods rich in unsaturated triacylglycerols:**
plant oils, nuts, soybeans, fish (salmon, herring, mackerel)

**Foods rich in trans triacylglycerols:**
margarine, processed foods, fried foods, some baked goods

- no double bonds in the carbon chains
- solid at room temperature
- increases blood cholesterol level

- one (or more) double bonds in the carbon chains
- liquid at room temperature
- decreases blood cholesterol level

- one (or more) trans double bonds in the carbon chains
- semi-solid at room temperature
- increases blood cholesterol level
Fatty Acids and Food Sources

**TABLE 10–2**

<table>
<thead>
<tr>
<th>Trans Fatty Acids in Some Typical Fast Foods and Snacks</th>
<th>Trans fatty acid content</th>
<th>As % of total fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In a typical serving (g)</td>
<td></td>
</tr>
<tr>
<td>French fries</td>
<td>4.7–6.1</td>
<td>28–36</td>
</tr>
<tr>
<td>Breaded fish burger</td>
<td>5.6</td>
<td>28</td>
</tr>
<tr>
<td>Breaded chicken nuggets</td>
<td>5.0</td>
<td>25</td>
</tr>
<tr>
<td>Pizza</td>
<td>1.1</td>
<td>9</td>
</tr>
<tr>
<td>Corn tortilla chips</td>
<td>1.6</td>
<td>22</td>
</tr>
<tr>
<td>Doughnut</td>
<td>2.7</td>
<td>25</td>
</tr>
<tr>
<td>Muffin</td>
<td>0.7</td>
<td>14</td>
</tr>
<tr>
<td>Chocolate bar</td>
<td>0.2</td>
<td>2</td>
</tr>
</tbody>
</table>


Note: All data for foods prepared with partially hydrogenated vegetable oil in the United States in 2002.
Trans Fats

- Raise LDL and lower HDL
- Desirable flavor to processed foods
- Restricted/banned in some countries (Denmark, Canada, Switzerland, CA, NY city, Baltimore)
- Very rare in raw food sources
- Generated by hydrogenation of oils to stabilize fats
- US guideline – trans fat < 0.5 g per serving → zero trans fat statement allowed
- Linked to heart disease, diabetes, obesity, high blood pressure
Diet and Cholesterol

- Daily cholesterol 1,100 – 1,700 mg
- 25% dietary, 75% synthesized
- Most dietary cholesterol cannot be absorbed
- Most cholesterol in our digestive system was first synthesized by our body
- Cholesterol level is tightly regulated
- Well designed studies show that dietary cholesterol has NO influence on serum cholesterol (75% of population)
- High responders (25% of population) – most increase in LDL paralleled by HLD increase
- Ratio remains constant (!)
Risk Factors for Heart Disease

Multifactorial (genetic, lifestyle, environmental, diet)

- Age
- Smoking
- Poor nutrition - 2% increase in energy intake from trans fatty acids increased CHD incidence by 23%
- Infrequent exercise
- Alcohol (1 -2 units/day reduce the risk of CHD)
- Psychosocial wellbeing - stress, lack of social support, depression, anxiety and personality (particularly hostility)
- Blood pressure
- Overweight and obesity
- Diabetes
- Cholesterol
The real story
Cholesterol – a biomolecule
Bad cholesterol – a strong tale
Good cholesterol - indeed
Good cholesterol: Indeed

- What is good cholesterol?
- What causes ‘bad cholesterol’?
- What causes inflammation in the vascular system?
- What do watch out for?
Good Cholesterol

- Large, fluffy LDLs have no potential to cause atherosclerosis
- Large, fluffy LDL = good “bad” cholesterol
- Large fluffy LDL is GOOD cholesterol
- HLD is still good “good” cholesterol
Bad Cholesterol

- Small, dense LDLs or oxidized LDLs are strongly associated with plaques and increase risk of CVD
- Small, dense LDL = bad “bad” cholesterol
- Triglyceride/HDL ratio is an indication of the level of oxidized LDL in our body
- \textbf{Triglyceride/HDL} < 2 then most LDL is large and fluffy
- \textbf{Triglyceride/HDL} > 4 then most LDL is small and dense
Oxidized LDLs

- Oxidation of LDL is a result of inflammation and oxidative stress.
- Inflammation and oxidative stress alter the properties of endothelial cell membrane.
- oxLDL tend to adhere and invade endothelium more than LDL.
- Recruitment of inflammatory immune cells.
What really matters!

Lower risk

130 mg/dL

Large LDL
(Pattern A)

Higher risk

130 mg/dL

Small LDL
(Pattern B)

LDL Cholesterol Balance
Oxidized Low-Density Lipoprotein

Sampath Parthasarathy, Achuthan Raghavamenon, Mahdi Omar Garelnabi, and Nalini Santanam
The oxidation of LDL-C lipid particles is known to increase their atherogenicity.\(^{56,57}\) (Figures 1 and 4). Oxidized LDL (ox-LDL) is taken up by the arterial walls more rapidly than unoxidized LDL and becomes trapped.\(^{56,58}\) The deposited ox-LDL then induces an increase in the expression of monocyte adhesive membrane proteins in the luminal endothelial cells thereby drawing leukocytes into the subendothelial space (intimal layer).\(^{59}\) The monocytes' scavenger receptors recognize and take up the ox-LDL\(^{56}\) which induces the expression and release of various pro-inflammatory cytokines from the monocyte and promotes their transformation into foam cells.\(^{60}\) The pro-inflammatory cytokines then lead to attraction of more monocytes into the subendothelial space, thereby creating a pro-atherogenic cycle.
Arterial Plaque Formation
Arterial Plaque Formation
Improving Triglycerides/HDL

- Decrease your **insulin** levels (fats/cholesterol regulated by insulin)
- Excessive insulin increase triglyceride
- Triglycerides are lowered fairly easy by reducing **sugar** in your diet
- High doses of ultra refined-grade fish oil
Regulation of Cholesterol and Triglycerides

Acetyl-CoA
multistep
$\beta$-Hydroxy-$\beta$-methyl-glutaryl-CoA

HMG-CoA reductase

Mevalonate
multistep
stimulates proteolysis of HMG-CoA reductase

Cholesterol (intracellular)

Cholesteryl esters
ACAT receptor-mediated endocytosis

LDL-cholesterol (extracellular)

insulin
glucagon
citrate lyase
acetyl-CoA carboxylase
Malonyl-CoA

Acetyl-CoA

insulin triggers activation
glucagon, epinephrine trigger phosphorylation/inactivation

Citrate

400 Å

(a) Palmitoyl-CoA

(b)
What causes heart disease?

SUGAR