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Physiologic Approach to Cholesterol Regulation: Cholesterol Homeostasis and Steroidopenia

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Goals and objectives:

- to test a new hypothesis concerning the association of steroidopenia and hypercholesterolemia
- to investigate the role of hormonorestorative therapy in hypercholesterolemia management
- to evaluate the effect of restoration of multiple steroid hormones to youthful levels in hypercholesterolemia treatment
## Leading causes of death in the US 2013

<table>
<thead>
<tr>
<th>Rank</th>
<th>Causes of death</th>
<th>All persons</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All causes</td>
<td>2,596,993</td>
<td>1,306,034</td>
<td>1,290,959</td>
</tr>
<tr>
<td>1.</td>
<td>Diseases of heart</td>
<td>611,105</td>
<td>321,347</td>
<td>289,758</td>
</tr>
<tr>
<td>2.</td>
<td>Malignant neoplasms</td>
<td>584,881</td>
<td>307,559</td>
<td>277,322</td>
</tr>
<tr>
<td>3.</td>
<td>Chronic lower respiratory diseases</td>
<td>149,205</td>
<td>70,317</td>
<td>78,888</td>
</tr>
<tr>
<td>4.</td>
<td>Accidents (unintentional injuries)</td>
<td>130,557</td>
<td>81,916</td>
<td>48,641</td>
</tr>
<tr>
<td>5.</td>
<td>Cerebrovascular diseases</td>
<td>128,978</td>
<td>53,691</td>
<td>75,287</td>
</tr>
<tr>
<td>6.</td>
<td>Alzheimer’s disease</td>
<td>84,767</td>
<td>25,836</td>
<td>58,931</td>
</tr>
<tr>
<td>7.</td>
<td>Diabetes mellitus</td>
<td>75,578</td>
<td>39,841</td>
<td>35,737</td>
</tr>
<tr>
<td>..10.</td>
<td>Intentional self-harm (suicide)</td>
<td>41,149</td>
<td>32,055</td>
<td>9,094</td>
</tr>
</tbody>
</table>

According to Journal of Patient Safety - between 210,000 and 440,000 Americans per year have died as a result of their medical treatments:  
- 106,000 deaths per year due to negative effects of drugs  
- 80,000 deaths per year due to infections in hospitals  
- 20,000 deaths per year due to other errors in hospitals  
- 12,000 deaths per year due to unnecessary surgery  
- 7,000 deaths per year due to medication errors in hospitals  

Iatrogenic causes
despite decades of research on prevention, detection and management of coronary heart disease (CHD), it is still a number one cause of mortality and morbidity in the developed world for both men and women\textsuperscript{4-6}

women tend to develop CHD later in life than men do, experiencing a greater risk after their reproductive years; after menopause, women have heart problems as often as men do; at least a third of the individuals that die of CHD are younger than 55 years of age\textsuperscript{7}

hypercholesterolemia is a major risk factor for coronary atherosclerosis and myocardial infarction (MI) and is also prevalent in the US and in most developed countries\textsuperscript{2,3,8}

incidence/prevalence in USA: 120 million people have a cholesterol level more than 200 mg/dL, and 60 million - more than 240 mg/dL\textsuperscript{9}

most developed countries currently have many treatment guidelines for hypercholesterolemia\textsuperscript{10}
### Cholesterol – Age axis
(mean standard deviation of cholesterol)\(^ {170}\)

<table>
<thead>
<tr>
<th>Age</th>
<th>Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>188.37</td>
</tr>
<tr>
<td>30-39</td>
<td>204.75</td>
</tr>
<tr>
<td>40-49</td>
<td>221.43</td>
</tr>
<tr>
<td>50-59</td>
<td>232.10</td>
</tr>
<tr>
<td>60-69</td>
<td>236.55</td>
</tr>
<tr>
<td>70-79</td>
<td>227.53</td>
</tr>
<tr>
<td>80+</td>
<td>218.18</td>
</tr>
</tbody>
</table>

Starting in childhood, blood cholesterol level rises progressively with each ten-year period until age 70, when cholesterol level begins to stabilize and then decline. By age 80 there is a significant drop to the values noted in much younger age group.\(^ {171}\)
Hypercholesterolemia and cholesterol-lowering drugs (CLD):

**Cholesterol-Lowering Drugs:**
- Statins (also known as HMG CoA reductase inhibitors) – atorvastatin, simvastatin
- Selective cholesterol absorption inhibitors - ezetimibe
- Resins (also known as bile acid-binding drugs) – cholestyramine
- Fibrates (fibric acid derivatives) – gemfibrozil, clofibrate
- Niacin (nicotinic acid)

- currently, statins play a leading role in the treatment of hypercholesterolemia\textsuperscript{11,12}
- a number of studies show that although primary prevention is effective, long-term tolerability is still a matter of controversy\textsuperscript{13,14}
- the reduction of total cholesterol (TC) in the blood by these drugs is associated with a decrease in the incidence of CHD, but also with an increase of noncardiovascular mortality; CLD have not been proven to extend a person's life span\textsuperscript{15-19}
- the results clearly demonstrated that statins reduce lipid levels but do not prevent restenosis after coronary angioplasty\textsuperscript{20}
CLD and mortality

- A meta-analysis of major primary prevention trials shows that the 15% decrease in deaths from heart disease in the cholesterol lowering treatment groups is offset by increases in deaths from other causes\(^{21}\).

- A meta-analysis of cholesterol-lowering trials demonstrated that coronary mortality was not lowered by cholesterol lowering, but total mortality was increased\(^{22,23}\).

- Cholesterol lowering appears to increase the risk for cancer, accidental and violent death, stroke, and oddly enough, CHD when certain medications are used\(^{24,25}\).

- Low or reduced serum cholesterol concentration increases mortality from hemorrhagic stroke\(^{26}\).
CLD and cancer

- all members of the two most popular classes of CLD (the fibrates and the statins) cause cancer and toxic liver damage in rodents\textsuperscript{27}

- a significant increase in the incidence of cancer, especially gastrointestinal, is observed in CLD group\textsuperscript{28}

- CLD increases cancer at the expense of decreasing cardiovascular disease in certain populations, such as the elderly and those treated with immunotherapy for cancer. Furthermore, there may be a relationship between statin dose and cancer.\textsuperscript{29}

Cancer incidence after statin treatment of elderly people.
CLD and hormones

- there is a possibility that CLD treatment is associated with hormonal perturbations\textsuperscript{30}
- a significant association between statin use and total testosterone was observed\textsuperscript{31}
- Simvastatin was found to suppress the synthesis of the androgens androstenediol, total testosterone (-23\%, P < 0.001), free testosterone (-32\%, P < 0.001), androstendione (-20\%, P < 0.01), and dehydroepiandrosterone sulfate (-17\%, P < 0.05)\textsuperscript{194-198}
- mevastatin induced a profound concentration-dependent inhibition of DNA synthesis, decreased production of progesterone (by up to 49\%), and testosterone (by up to 52\%)\textsuperscript{32}
- clofibrate significantly reduced plasma levels of testosterone and cortisol\textsuperscript{33}
- simvastatin significantly decreased secretion of progesterone from the placental explants\textsuperscript{193}
Side effects from CLD

- side effects of CLD were seen in 4-38% of patients resulting in discontinuation and dose reduction;\(^5,34-37\) some studies registered the incidence of adverse events in more than 73% (73.6% for cerivastatin and 74.9% for pravastatin)\(^{38}\)

- most patients who begin lipid-lowering therapy stop it within 1 year, and only about one third of patients reach treatment goals;\(^{39}\) 60% of patients discontinued their medication over 12 months\(^{40}\)

- the most common adverse effects of CLD: abdominal pain, chest pain, dizziness, asthenia/fatigue, fibromyalgia, headache, insomnia, elevations in hepatic transaminase levels, and upper respiratory tract infection\(^{34,41}\)

- statins increase blood glucose levels (hyperglycemia)\(^{200,201}\)

- also, the adverse events from CLD include poor quality of life, eczema, skin rashes, insomnia, cramp, exercise intolerance, fatigability, severe rhabdomyolysis, renal failure, and death\(^{42-49}\)

Statins have a direct effect on the respiratory chain of the mitochondria. Mitochondrial damage leads to a mitochondrial calcium leak and it may account for apoptosis, oxidative stress, and muscle remodeling and degeneration.\(^{47,48}\)
the incidence of congestive heart failure has tripled in the time that statins have been on the market; statins may impair heart pumping function due to their myopathic effect

statins deplete CoQ10 and this could contribute to heart disease. In 1990, Merck received a patent for statin drugs formulated with up to 1,000 mg of coenzyme Q10 to prevent or alleviate cardiomyopathy, that can cause congestive heart failure. However, Merck has not brought these product to market or educated physicians on the importance of supplementing CoQ10 to offset the dangers of these drugs to the heart. Because they hold the patent, other drug companies are prevented from coming out with a statin/CoQ10 product.

cerivastatin was pulled from the market in 2001 because of severe side effects, serious injury, rhabdomyolysis, organ damage and death; worldwide, 100 deaths and 1,600 injuries have been linked to the drug

If you are taking a statin and if you want to avoid becoming a statistic, it is imperative that you take coenzyme Q10 daily. CoQ10 is also called ubiquinone, which means "occurring everywhere".
animal studies showed a possible significant hepatic, testicular atrophy, neurological toxicity, hemorrhages in the gastrointestinal tract, bleeding in the brain stem, fibroid degeneration of vessel walls in choroid plexus, and lens opacity\textsuperscript{52-54}

both statins and fibrates may cause erectile dysfunction (ED)\textsuperscript{55,56}

cognitive impairment, dementia, memory loss, severe irritability, and peripheral neuropathy may occur with statin therapy\textsuperscript{57-62}

restlessness, euphoria, mental confusion, lupus-like syndrome, pleurisy and arthralgia are possible adverse events of statins\textsuperscript{63,64}

all statins at all doses resulted in tachyphylaxis (a decreasing response to physiologically active agents)\textsuperscript{65}

animal models have provided evidence for the teratogenic effects of statins on pregnancy outcome\textsuperscript{193}

Remember that, if you don’t have enough cholesterol, you won’t make enough sex hormones.
The determinant data in the suggestion of a new hypothesis:

- The multiple adverse events from current CLD, including the most severe side effects such as severe rhabdomyolysis, renal failure, and death; all of these facts indicate the need to find the safer and more effective treatment regimen for elevated TC.

- The similarity of symptoms in patients during use of CLD, are as in patients with fibromyalgia and chronic fatigue syndrome (CFS).

- Controversial data about the effect of steroidal hormones on hypercholesterolemia; previously hormone replacement therapy (HRT) was considered as first-line treatment for hypercholesterolemia to prevent CHD in women; recent studies, however, show no benefit of HRT for secondary prevention of coronary events.

- Higher production of cholesterol during increased physiologic demands such as: pregnancy, childhood growth, stress, during the immune response or tissue repair, starvation, and exercise.

- Diminished concentrations of TC in women with threatened abortion.

- Changed cholesterol production during infection, trauma, and surgery.

- High TC was not predictive after age 47 in Framingham study.

TC, LDL and TRG increase significantly during pregnancy in all women. TC rises up to 43% (mean 314 mg/dL) in the third trimester; hypercholesterolemia was found in up to 53.1% of school children in different studies.
The determinant data in the suggestion of a new hypothesis (cont.):

- the fact that up to 70% of patients with CHD or MI had a normal level of TC\(^4,110-116\)
- the association between low TC level and higher mortality rates from cancer, liver disease, respiratory disorders, and injuries\(^117-125\)
- inverse relationship between TC and LDL levels and cancer incidence\(^29,126-130\)
- altered TC level (usually low) in patients with psychiatric disorders: depression, changed personality, suicidal ideation, impulsive aggressive behavior, schizophrenia, etc.\(^131-139\)
- a significantly lower values of TC in individuals with adverse health characteristics, including alcohol use, substance abuse, heroin addiction and depression with suicide tendency\(^121,140-143\)
- information that patients with low TC levels had the highest rates of death from CHD,\(^144,145\) whereas those with elevated TC seemed to have a lower risk for death from CHD\(^145\)
- changed TC and LDL levels were registered in individuals with autism,\(^146\) intracranial hemorrhage,\(^125,147\) cataract,\(^148\) celiac disease,\(^149\) ED,\(^150-153\) CFS\(^154\)
- our clinical experience with the use of hormonorestorative therapy (HT) for hypercholesterolemic patients and immunorestorative therapy for cancer patients\(^155-161\)
Guilt by definition?

- we know that low cholesterol is bad, and so is high cholesterol.
- everyone knows that cholesterol can deposit in the arterial wall and can be a factor in atherosclerotic plaque, which can lead to the blockage of arteries. Cholesterol does a bad job in this case. But is it as at fault as appears at first glance?
- if a person gets a bruise, is it necessary to remove all the blood in the body to remove the bruise, because the presence of blood in this instance causes the bruise?!
Lipid hypothesis history

- The lipid hypothesis was proposed by Rudolph Virchow in 1856 and suggested that blood lipid accumulation in arterial walls causes atherosclerosis\textsuperscript{162}.

- There are many players in the “discovery” of cholesterol’s link to heart disease:
  - John Gofman hypothesised in 1950 that blood cholesterol was the main cause of CHD\textsuperscript{163,164}.
  - Duff and McMillian formulated the lipid hypothesis in its modern form in 1951\textsuperscript{165}.
  - Ancel Keys published paper that discussed saturated fats and cholesterol as the cause of heart disease in 1953\textsuperscript{166}.

- It was found that people who died of heart disease often had high level of cholesterol in their blood.

- Many studies have confirmed that elevated cholesterol levels are \textit{associated} with an increased risk of atherosclerosis. The key word is “associated”.

My question is:
- Did patients die from high cholesterol level? or
- Cholesterol level was elevated due to serious physiological malfunctions and patients died from them?
interpretation of data allowed the lipid hypothesis to be “established” in as scientific fact by the end of the last century.  

a survey was conducted in 1978 and found that a large majority of researchers and practitioners were supportive of the validity of the lipid hypothesis.

in this survey, 211 prominent researchers in the field were questioned about the association of the plasma cholesterol biomarker and the link of disease to diet. 90% (193) responded with the following answers:

- do you think there is a connection between plasma cholesterol level and the development of coronary heart disease?
- do you think that our knowledge about diet and coronary heart disease is sufficient to recommend a moderate change in the diet for the population of an affluent society?

My question is:  
- Is a consensus based on survey results the real Scientific Method?
Cholesterol misconception

- Cholesterol is an important part of the blocked arteries story, but...blockages develop because of many other factors.

- Everyone knows only that cholesterol is a major component of atherosclerotic plaques.

- But... how many of us understand the absolutely vital role of cholesterol in our body?!

- No one cardiologist or heart surgeon has mentioned the significant cholesterol contributions to the proper functioning of a human body.

- Because of the propaganda, you may thinking that cholesterol is a harmful alien substance that should be avoided at all costs. In fact, nothing could be further from the truth.

In the animation "bad" cholesterol is shown being deposited in the blood vessel walls, while "good" cholesterol takes it away.

The truth cannot be suppressed by the majority or decreed by consensus!
Multi-function, blood-processing “factory”

- 85-95% of cholesterol in our blood is “endogenous” or manufactured by our own cells (mostly liver)
- 5-15% comes from the food we eat
- so, is zero-cholesterol good...or even healthy?
What's Cholesterol?
What is cholesterol?

- Cholesterol is a peculiar molecule. It is often called a lipid, steroid, fat or a sterol (a combination steroid and alcohol, although it doesn’t behave like alcohol), but the chemical term for the cholesterol molecule does not defined exactly yet.

- Cholesterol is absolutely essential for life. It is found in all cells of the body.

- 25% of cholesterol is localized in the brain.\(^\text{167,187}\) All cholesterol in the brain is a product of local synthesis since lipoproteins are unable to cross the blood-brain barrier.\(^\text{168,188-192}\)

- Cholesterol is:
  - a major building block from which cell membranes are made
  - used to make a number of important substances: steroid hormones, bile acids, and, in conjunction with sunlight, vitamin D3.

- only seven percent of the body’s cholesterol is found in the blood
Cholesterol role in brain function\textsuperscript{202,203}

- cholesterol itself plays essential role in the mechanisms of synaptic function, plasticity and neurodegeneration

- central neurodegeneration features in a number of neurodegenerative diseases may represent functional consequences of abnormal neural cholesterol misregulation
Cholesterol has four hydrocarbon rings. Three of them are six-carbon rings, and one of them is a five-carbon ring. All steroid hormones have a similar chemical structure. Definitely, cholesterol is not fat.

Saturated fatty acids have a similar form to unsaturated fatty acids, but do not contain any double bonds.
Cholesterol carriers

- most fats are transported around the body and stored as TRG
- neither cholesterol nor TRG can be dissolved in a blood; they have to be wrapped up in a sphere known as a lipoprotein in order to transport them out of the gut.

In other words, lipoproteins are the transport for insoluble cholesterol and TRG.
Lipoproteins are classified according to their density.
5 basic types of lipoproteins: 169

- **chylomicron** (contains about 85-88% of TRG, ~3% cholesteryl esters and ~1% cholesterol, ~8% phospholipids, and 1-2% of protein) – are largest in size (1000 nm) in size and least dense (<0.95)

- **very low-density lipoprotein (VLDL)** (carries mostly TRG - 50-55%, 12-15% cholesteryl esters and 8-10% cholesterol, 18-20% phospholipids, and 5-12% protein) – 25-90 nm in size with a density of ~0.98

- **intermediate-density lipoprotein (IDL)** (contains about 32-35% cholesteryl esters and 8-10% cholesterol, 24-30% TRG, 25-27% phospholipids, 10-12% protein) - 40 nm in size and more dense (~1.0)

- **low-density lipoprotein (LDL)** (composition: 37-48% cholesteryl esters and 8-10% cholesterol, 10-15% TRG, 20-28% phospholipids, and 20-22% protein) - 26 nm in size and more dense (~1.04)

- **high-density lipoprotein (HDL)** (composition: 15-30% cholesteryl esters and 2-10% cholesterol, 3-15% TRG, 26-46% phospholipid, and 55% protein) – 6-12.5 nm in size and most dense (~1.12)
Chylomicron transports TRG from the intestines to the liver, skeletal muscle, and to adipose tissue. Liver then reconstructs component parts into VLDL and sends them into the bloodstream.

VLDL carries newly synthesized TRG from the liver to adipose tissue. VLDL becomes a IDL particle after it has lost its TRG content.

IDL is a short-lived lipoprotein, converts in the liver to LDL and usually is not detectable in the blood.

LDL is the primary plasma carrier of cholesterol for delivery from the liver to all tissues. Cholesterol is then absorbed by the cells of the body.

LDL particles are involved in the formation of plaques in the walls of the arteries.

HDL molecules are made in the intestine and the liver. HDL collects cholesterol from the body's tissues, and brings it back to the liver.

Excess cholesterol is reabsorbed by the liver and reused or excreted into bile.

LDL is known as “bad cholesterol” (even though LDL is not cholesterol)

HDL is known as “good cholesterol” (even though HDL is not cholesterol)
## Composition of the Major Lipoprotein Complexes

<table>
<thead>
<tr>
<th>Complex</th>
<th>Source</th>
<th>Density (g/ml)</th>
<th>%Protein</th>
<th>%TG&lt;sup&gt;a&lt;/sup&gt;</th>
<th>%PL&lt;sup&gt;b&lt;/sup&gt;</th>
<th>%CE&lt;sup&gt;c&lt;/sup&gt;</th>
<th>%C&lt;sup&gt;d&lt;/sup&gt;</th>
<th>%FFA&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicron</td>
<td>Intestine</td>
<td>&lt;0.95</td>
<td>1-2</td>
<td>85-88</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>VLDL</td>
<td>Liver</td>
<td>0.95-1.006</td>
<td>7-10</td>
<td>50-55</td>
<td>18-20</td>
<td>12-15</td>
<td>8-10</td>
<td>1</td>
</tr>
<tr>
<td>IDL</td>
<td>VLDL</td>
<td>1.006-1.019</td>
<td>10-12</td>
<td>25-30</td>
<td>25-27</td>
<td>32-35</td>
<td>8-10</td>
<td>1</td>
</tr>
<tr>
<td>LDL</td>
<td>VLDL</td>
<td>1.019-1.063</td>
<td>20-22</td>
<td>10-15</td>
<td>20-28</td>
<td>37-48</td>
<td>8-10</td>
<td>1</td>
</tr>
<tr>
<td>*HDL&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Intestine, liver</td>
<td>1.063-1.125</td>
<td>33-35</td>
<td>5-15</td>
<td>32-43</td>
<td>20-30</td>
<td>5-10</td>
<td>0</td>
</tr>
<tr>
<td>*HDL&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Intestine, liver</td>
<td>1.125-1.21</td>
<td>55-57</td>
<td>3-13</td>
<td>26-46</td>
<td>15-30</td>
<td>2-6</td>
<td>6</td>
</tr>
<tr>
<td>Albumin-FFA</td>
<td>Adipose tissue</td>
<td>&gt;1.281</td>
<td>99</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

<sup>a</sup> Triacylglycerols, <sup>b</sup> Phospholipids, <sup>c</sup> Cholesteryl esters, <sup>d</sup> Free cholesterol, <sup>e</sup> Free fatty acids

* HDL2 and HDL3 derived from nascent HDL as a result of the acquisition of cholesteryl esters
Lipoprotein Structure

- **Apoprotein**
- **Nonpolar Lipid Core**
  - Cholesterol Ester
  - Triglyceride
- **Polar Surface Coat**
  - Phospholipid
  - Cholesterol

Adapted from Treatment of Heart Diseases: 1992, Etiologies and Treatment of Hyperlipidemia - Scott Grundy, MD, PhD
# Apoprotein Classifications

<table>
<thead>
<tr>
<th>Apoprotein - MW (Da)</th>
<th>Lipoprotein Association</th>
<th>Function and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>apoA-I - 29,016</td>
<td>Chylomicrons, HDL</td>
<td>major protein of HDL, activates lecithin:cholesterol acyltransferase, LCAT</td>
</tr>
<tr>
<td>apoA-II - 17,400</td>
<td>Chylomicrons, HDL</td>
<td>primarily in HDL, enhances hepatic lipase activity</td>
</tr>
<tr>
<td>apoA-IV - 46,000</td>
<td>Chylomicrons and HDL</td>
<td>present in triacylglycerol rich lipoproteins</td>
</tr>
<tr>
<td>apoB-48 - 241,000</td>
<td>Chylomicrons</td>
<td>exclusively found in chylomicrons, derived from apoB-100 gene by RNA editing in intestinal epithelium; lacks the LDL receptor-binding domain of apoB-100</td>
</tr>
<tr>
<td>apoB-100 - 513,000</td>
<td>VLDL, IDL and LDL</td>
<td>major protein of LDL, binds to LDL receptor; one of the longest known proteins in humans</td>
</tr>
<tr>
<td>apoC-I - 7,600</td>
<td>Chylomicrons, VLDL, IDL and HDL</td>
<td>may also activate LCAT</td>
</tr>
<tr>
<td>apoC-II - 8, 916</td>
<td>Chylomicrons, VLDL, IDL and HDL</td>
<td>activates lipoprotein lipase</td>
</tr>
<tr>
<td>apoC-III - 8,750</td>
<td>Chylomicrons, VLDL, IDL and HDL</td>
<td>inhibits lipoprotein lipase</td>
</tr>
<tr>
<td>apoD, 33,000</td>
<td>HDL</td>
<td>closely associated with LCAT</td>
</tr>
<tr>
<td>cholesterol ester transfer protein, CETP</td>
<td>HDL</td>
<td>exclusively associated with HDL, cholesteryl ester transfer</td>
</tr>
<tr>
<td>Apoprotein - MW (Da)</td>
<td>Lipoprotein Association</td>
<td>Function and Comments</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>apoE - 34,000 (at least 3 alleles [E₂, E₃, E₄] each of which have multiple isoforms)</td>
<td>Chylomicron remnants, VLDL, IDL and HDL</td>
<td>binds to LDL receptor, apoE₄ allele amplification associated with late-onset Alzheimer's disease</td>
</tr>
<tr>
<td>apoH - 50,000 (also known as b-2-glycoprotein I)</td>
<td>Chylomicrons</td>
<td>triacylglycerol metabolism</td>
</tr>
<tr>
<td>apo(a) - at least 19 different alleles; protein ranges in size from 300,000 - 800,000</td>
<td>LDL</td>
<td>disulfide bonded to apoB-100, forms a complex with LDL identified as lipoprotein(a), Lp(a); strongly resembles plasminogen; may deliver cholesterol to sites of vascular injury, high risk association with premature coronary artery disease and stroke</td>
</tr>
</tbody>
</table>
Total cholesterol:

Total Cholesterol = HDL + LDL + TRG/5

How many apples? 35 pineapples + 130 pears + 150 peaches/5

= 195 apples

This formula provides an approximation

- The lipid profile does not measure LDL particles directly but instead estimates them using the Friedewald equation, which estimates LDL from measurements of TC, triglycerides, and HDL
- LDL cannot be calculated if plasma triglyceride is >400 mg/dL
• LDL: “bad”
  • associated with high risk of heart attack
• HDL: “good”:
  • protective effect for heart
HDL is NOT a good cholesterol anymore

- increase CHD on high HDL
- HDL has been described as a "chameleon-like" lipoprotein; it is anti-inflammatory in the basal state and pro-inflammatory during an acute phase response
- “good” HDL becomes “bad” due to conversion of anti-inflammatory HDL into pro-inflammatory HDL. It increases risk of atherosclerosis
Cholesterol Biosynthesis
(simplified version)

1. acetyl CoA + acetoacetyl CoA → acetoacetyl CoA
2. acetoacetyl CoA → 3-hydroxy-3-methylglutaryl CoA (HMG CoA)
3. HMG CoA Reductase
4. Mevalonic acid
5. much more steps there
6. Cholesterol
Statin drugs are structural analogs of HMG-CoA
Regulation of HMG CoA Reductase

- negative feedback regulation
- hormonal regulation
- transcriptional regulation

HMG CoA → Mevalonic acid → Cholesterol

insulin: (+) → HMG CoA Reductase

glucagon: (−) → HMG CoA Reductase

progesterone: (+) → HMG CoA Reductase

LDL: (−) → HMG CoA Reductase

Transcription of HMG CoA mRNA: (−)
Effect of various hormones on lipase

- Growth hormone
- Cortisol
- Insulin
- Glucagon
- TRG* (triglycerides)
- FFA* (free fatty acids)
- Glycerol

Glucose production linkage:
- (+) Positive effect
- (-) Negative effect

* TRG – triglycerides
* FFA – free fatty acids
Cholesterol Biosynthesis

SREBP-2

Acetyl CoA
- ATP-citrate lyase
- Acetoacetyl CoA thiolase

Acetoacetyl CoA
- HMG CoA synthase
- HMG CoA reductase

HMG CoA
- Mevalonate kinase
- Phosphomevalonate kinase
- Mevalonate PP decarboxylase
- GPP synthase
- IPP isomerase
- IPP synthase
- Squalene synthase

Mevalonate
- Squalene epoxidase
- Lanosterol synthase
- CYP51
- Lathosterol oxidase
- DHCR

Squalene
- Cholesterol

SREBP-1c

Acetyl CoA carboxylase

Malonyl CoA
- Fatty acid synthase
- Long chain fatty acyl elongase

NADPH

Fatty acyl CoA
- StearoylCoA desaturase

Monounsaturated fatty acids

NADPH

G6PD

Glucose-6-P

6-P-gluconate

PGDH

Saturated fatty acids
Bisphosphonates

- Bisphosphonates are commonly used to prevent and treat osteoporosis\(^{180,181}\)

- Bisphosphonates inhibit key enzymes of the intracellular mevalonate pathway that are essential for the bone-resorbing activity and survival of osteoclasts\(^{180-182}\)

- Bisphosphonates therapy suppresses normal bone remodeling to such an extent that endogenous bone repair is decreased leading to significantly increased “atypical” fracture risk\(^{183}\)
Bisphosphonate side-effects^184

- upper gastrointestinal tract adverse events
- renal toxicity
- ocular adverse events
- acute phase response - fever, chills, bone pain, myalgias and arthralgias
- hypocalcaemia and secondary hyperPTH
- musculoskeletal pain
- osteonecrosis of the jaw
- atrial fibrillation
- atypical fractures of the femoral diaphysis
Metabolism of Cholesterol
(simplified version)

The body uses over sixty steroids derived from cholesterol.

Cholesterol
  → pregnenolone
     /\      \
    /         \
  DHEA      progesterone
    \       /  \
      \   /    \
  androstenediol androstenedione cortisol aldosterone
    \       /  \
      \   /    \
  testosterone estrone
    \       /  \
      \   /    \
  estradiol estriol
New hypothesis of hypercholesterolemia:
(hormonodeficit hypothesis of Hypercholesterolemia)

- this hypothesis implies that hypercholesterolemia is the reactive consequence of enzyme-dependent down regulation of steroid hormone biosynthesis and their interconversion

- in short, hypercholesterolemia is the compensatory mechanism for declined production of steroidal hormones

Note!
We believe that:
- a high cholesterol level is a consequence of a low production of steroid hormones
- a low cholesterol level is a cause of a low steroid hormones production
All steroid hormones have a similar chemical structure.
Cholesterol is our Body’s “Thermostat”

High cholesterol (as well as low cholesterol) is a sign that something is wrong.

TREATING CHOLESTEROL LIKE TREATING A FEVER DOES NOT TREAT THE CAUSE.
The Relationship Between Cholesterol Lowering Drugs and Hormones

Diminished hormone production -> increased cholesterol

Diminished hormone production -> increased cholesterol + CLD

What do we have left?

Diminished hormone production

To sum up:
the original problem remains in full swing, but the cholesterol has been decreased.
Remember: cholesterol is not the cause, it is the effect.
Side effect of statin drugs due to their method of effect

- CLD often lower cholesterol past the point where it was originally under the optimal system
- The effect on the chain of conversion for the creation of steroid hormones

Example to illustrate this:
X being the progenitor (for our example cholesterol). Now let’s say that unit D is malfunctioning, in this case we designate this condition with r.

Units A, B, and C are maintaining their status quo. Unit D is not. Units E and F are impaired in their production because their point of origin is a conversion from unit D. The chain can now be updated to reflect this.

X is increased to repair the link of D. That is the situation as we know it currently. What happens when statins, in this case S, are introduced?

Suddenly, the entire chain is compromised.
we retrospectively analyzed the results of two studies that included 155 patients with hypercholesterolemia
we analyzed 112 patients with hypercholesterolemia

- mean age – 54.2 (from 22 to 81 yr)
- male to female ratio – 1:2.3 (34-78)
- follow up duration – 3-144 months
Results:

- acute morbidity of HT was zero
- the mean serum TC decreased from 252.9 mg/dL before treatment to 190.7 mg/dL after intervention (dropped 24.6%)
Total Cholesterol Before and After Hormone-restitorative therapy

- All patients
  - Before Treatment: 252.9
  - After Treatment: 190.7
- Male
  - Before Treatment: 268.3
  - After Treatment: 188.6
- Female
  - Before Treatment: 246.1
  - After Treatment: 191.6
HDL Before and After Hormonorestorative Therapy

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Treatment</td>
<td>62.7</td>
<td>45.8</td>
<td>67.6</td>
</tr>
<tr>
<td>After Treatment</td>
<td>50.1</td>
<td>44.2</td>
<td>51.9</td>
</tr>
</tbody>
</table>
Why decreasing HDL is a good sign during HT?

- If we normalize the level of TC, what reason is there for extra production of HDL? If there is nothing to transport back to the liver, why produce the extra carrier?
- HDL, by this logic, should decrease!

Our results can explain the failure of a new drug for the elevation of HDL from Pfizer – torcetrapib. As you know, this drug raised the risk of death by 59% and heart problems by 25%. It looks like elevated HDL is stealing supply of cholesterol from plants that must produce hormones.
### LDL Before and After Hormonorestorative Therapy

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Treatment</td>
<td>154.9</td>
<td>176</td>
<td>148.5</td>
</tr>
<tr>
<td>After Treatment</td>
<td>118.6</td>
<td>118.4</td>
<td>118.7</td>
</tr>
</tbody>
</table>

**Legend:**
- Green: Before Treatment
- Red: After Treatment
Correction of Steroidopenia

- we analyzed 43 patients
- mean age - 58.4 years
- 12 males and 31 females
Results:

- The mean serum TC decreased from 228.8 mg/dL before treatment to 183.7 mg/dL after intervention (dropped 19.7%).
- HT was associated with statistically significant elevations in pregnenolone, DHEA Sulfate, testosterone, progesterone, but not in total estrogen, cortisol, or vitamin D-3 in both men and women.
Total Cholesterol Before and After Hormonorestorative therapy
Steroid hormone levels in males before and after Hormonorestorative Therapy

![Graph showing steroid hormone levels before and after treatment]

- Pregnenolone (ng/dL)
- DHEA S (ug/dL)
- Testosterone (ng/dL)
- Total Estrogens (pg/mL)
- Progesterone (ng/mL)
- Cortisol (ug/dL)
- Vitamin D3 (ng/mL)
Steroid hormone levels in females before and after Hormonorestorative Therapy

- Pregnenolone (ng/dL)
- DHEA S (ug/dL)
- Testosterone (ng/dL)
- Total Estrogens (pg/mL)
- Progesterone (ng/mL)
- Cortisol (ug/dL)
- Vitamin D3 (ng/mL)
<table>
<thead>
<tr>
<th>Study</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCMRCC (our study)(^{157})</td>
<td>252.0</td>
<td>192.8</td>
</tr>
<tr>
<td>FDIM, Osaka University (Japan)(^{176})</td>
<td>269.9</td>
<td>215.2</td>
</tr>
</tbody>
</table>
we know that, plasma cholesterol level increases with age, as does the incidence of CHD

- the most myocardial infarctions occur in patients who have normal TC levels; the mean serum TC levels did not differ between the MI patients and the normal population

- hypercholesterolemia was observed in 31-70% of patients with CHD

But how can we explain that up to 70% of patients with CHD or MI have documented “normal” level of cholesterol?
<table>
<thead>
<tr>
<th>Age</th>
<th>25</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (nl &lt;200 mg/dl)</td>
<td>130</td>
<td>190</td>
</tr>
<tr>
<td>Patient 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (nl &lt;200 mg/dl)</td>
<td>180</td>
<td>240</td>
</tr>
</tbody>
</table>

Life cycle related elevation of TC is 60 mg/dl in both cases.

We hypothesize: TC elevation over time is a critical determinant of risk for CHD or MI.
“Relative Hypercholesterolemia”
(total cholesterol before and after hormonorestorative therapy)

<table>
<thead>
<tr>
<th></th>
<th>before treatment</th>
<th>after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>198</td>
<td>168</td>
</tr>
<tr>
<td>2</td>
<td>202</td>
<td>162</td>
</tr>
<tr>
<td>3</td>
<td>195</td>
<td>138</td>
</tr>
<tr>
<td>4</td>
<td>196</td>
<td>113</td>
</tr>
<tr>
<td>5</td>
<td>189</td>
<td>153</td>
</tr>
<tr>
<td>6</td>
<td>198</td>
<td>173</td>
</tr>
<tr>
<td>7</td>
<td>185</td>
<td>170</td>
</tr>
<tr>
<td>8</td>
<td>198</td>
<td>178</td>
</tr>
</tbody>
</table>
Mechanism of action of HT

From our point of view HT restores a normal condition of all 3 regulation mechanisms:

- feedback regulation (through restoration of youthful level of basic steroidal hormones)
- hormonal regulation (through correction of insulin/glucagon balance)
- transcription regulation (through improvement of anabolic reactions)
Summary on hypercholesterolemia

- hypercholesterolemia is a risk factor, not a cause of CHD
- steroidopenia is central to the mechanism of hypercholesterolemia related clinical disease
- cholesterol is an important marker of the health condition
- the purpose of cholesterol elevation is:
  - to increase production of steroid hormones and vitamin D3
  - to repair damaged cell structure (membrane); healing of damaged endothelium by the “plaquing” of tears and holes
  - to provide a normal response to physiologic demand (growth, pregnancy, stress, etc.)
- high concentration of cholesterol can lead to vascular damage with stenosis or occlusion of arteries if reason for elevation of cholesterol will not be corrected in time
- method of correction of elevated cholesterol with the use of CLD is wrong at the origin of the concept and has no physiologic foundation; CLD “fight” with consequence (high cholesterol) not a cause of hypercholesterolemia (low level of steroid hormones).
In 1858 Virchow clearly showed that cholesterol does not start the process but that it is the end product of degeneration. Damage to the tissue became evident first, and then came an accumulation of fat, and finally, as the scar tissue was formed, a high content of cholesterol appeared. It was part of the healing process of a wound from damage caused by something else.

Atherosclerosis is a disease primarily involves four cell types, i.e., endothelial and vascular smooth muscle cells, monocytes and platelets. Arterial plaque contains a complex mixture of cholesterol, calcium, lipoproteins, mutated arterial cells, and fibrin.

It is well known that the composition of the atheroma is the same as for many granulation tissues which are interpreted as a healing process.

Cholesterol is important for normal repair of tissues since every cell membrane, and the organelles with the cells, are rich in cholesterol. Cholesterol is present along with fibrin, collagen, and elastin as a part of the repair process of lesions.
- Arterial plaques begin as mutations to smooth muscle cells in the artery, which then proliferate, become fibrous, and eventually manufacture their own cholesterol.

- Anabolic influence in human metabolism decline with age. Age-related weakness of smooth muscle cells or infections may lead to endothelial injury. The process may followed by incomplete healing and lead to permanent damage of arterial wall.

- Endothelial cells impaired easier because weaker arterial muscular response on normal or elevated blood pressure due to increased peripheral vascular resistance and increased arterial wall stiffness because of aging.
Cholesterol and atherosclerosis (cont.)

- why you do not afraid to use calcium for aging patients, but afraid cholesterol?!! … even they both participate in formation of atherosclerotic plaques?!!

- the majority of doctors prescribe calcium even when patient has atherosclerosis, but suppress cholesterol!!

Where is the logic there?!
The Role of Cholesterol in atherosclerosis – new hypothesis

- We hypothesized that:
  - cholesterol is a key component of the repairing process
  - atherosclerosis is a consequence of age-related metabolic shift from anabolic to catabolic, causing tissue degeneration, including sarcopenia
  - healing of endothelial and smooth muscle cells’ microtrauma due to physical or chemical injuries is a cause of atherosclerosis
  - atherosclerosis is a physiologic adaptation to vascular injury

Like any product of bodily metabolism, cholesterol can be overproduced or misutilized with harmful effects.

Q: Why did increase the risk of hemorrhagic stroke during CLD use?
A: Because we suppress a “healing” ability of vascular wall.
Case study 1: hypercholesterolemia

Patient E. 57 yr, male, first visit 08/31/00

Diagnosis: hypercholesterolemia, impotence, depression, insomnia.

Complaints: severe ED (since age 39), hypercholesterolemia, depression, fatigue, insomnia, short-term memory problems.

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>TRG</th>
<th>HDL</th>
<th>LDL</th>
<th>VLDL</th>
<th>TC/HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/31/00</td>
<td>330</td>
<td>216</td>
<td>54</td>
<td>233</td>
<td>43</td>
<td>6.1</td>
</tr>
<tr>
<td>09/09/03</td>
<td>187</td>
<td>138</td>
<td>40</td>
<td>119</td>
<td>28</td>
<td>4.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DHEAS</th>
<th>Pregn</th>
<th>Estradiol</th>
<th>Progest</th>
<th>Test</th>
<th>Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>(nl - age 20-30)</td>
<td>(280-640)</td>
<td>(10-200)</td>
<td>(0-53)</td>
<td>(0.3-1.2)</td>
<td>(280-830)</td>
<td>(4.3-22.4)</td>
</tr>
<tr>
<td>08/31/00</td>
<td>93</td>
<td>24</td>
<td>56</td>
<td>0.3</td>
<td>186</td>
<td>0.9</td>
</tr>
<tr>
<td>09/09/03</td>
<td>540</td>
<td>159</td>
<td>30</td>
<td>1.3</td>
<td>496</td>
<td>15.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DHT</th>
<th>Free Test</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(30-85)</td>
<td>(9.3-26.5)</td>
<td>(0-4)</td>
<td></td>
</tr>
<tr>
<td>08/31/00</td>
<td>44</td>
<td>1.01</td>
<td>1.1</td>
</tr>
<tr>
<td>09/09/03</td>
<td>38</td>
<td>19.6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

follow up 09/09/03 – no complaints
Case study 2: normocholesterolemia ("relative hypercholesterolemia")

Patient G. 24 y.o. male, first visit 12/10/02

Diagnosis: ADHD, social anxiety disorder (SAD), major depression, insomnia.

Complaints: ADHD and SAD, no energy, tiredness, severe depression (in spite of Paxil), severe anxiety, no libido, erection problem, poor sex drive, decreased appetite, poor short-term memory, sleeping problems, frequent sinus infection and sore throat.

TC was 140 mg/dL in 2000. ADHD was diagnosed around age 7 and SAD in age 14. Patient had been using Ritalin for several years. He was also on different antidepressants during the last 10 years.

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>DHEAS</th>
<th>Pregn</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/10/02</td>
<td>195</td>
<td>79</td>
<td>56</td>
<td>678</td>
</tr>
<tr>
<td>08/14/03</td>
<td>152</td>
<td>456</td>
<td>162</td>
<td>730</td>
</tr>
</tbody>
</table>

follow up 08/14/03

Complaints: none.
We want to stress the importance of blood test by demonstration of laboratory results assessment of 6 years old boy with the severe ADHD (this disorder was diagnosed in age 4).

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>108</td>
</tr>
<tr>
<td>&lt;15</td>
<td></td>
</tr>
<tr>
<td>Pregn</td>
<td>41</td>
</tr>
<tr>
<td>&lt;10</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>(0-53)</td>
</tr>
<tr>
<td>Progest</td>
<td>(0.3-1.2)</td>
</tr>
<tr>
<td>Test</td>
<td>(0-20)</td>
</tr>
<tr>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

The test revealed total cholesterol on low side and significantly decreased production of basic steroid hormones. There are no “cooling/calming” effect on testosterone there in matters of aggression and hyperactivity.

Remember:
Imbalance of hormones produced by our glands may happen at any age. Hormones are extremely important for mental health.

Case study 3: hypocholesterolemia (food for thought)
Case study 4: hypocholesterolemia

Patient G. 29 y.o. female, first visit 07/23/99

**Diagnosis**: hypocholesterolemia, obesity, depression, menstrual disorder.

**Complaints**: overweight, fatigue, no energy, depression, anxiety, panic attacks, no libido, poor sex drive, very poor short-term memory, irregular menstrual cycle.

Weight - 242 pounds. Height 5’5”. Body fat percentage (BFP) - 58% (nl 17-24%).

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>DHEAS</th>
<th>Pregn</th>
<th>Estr.(total)</th>
<th>Progest</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/23/99</td>
<td>130</td>
<td>87</td>
<td>30</td>
<td>87</td>
<td>0.4</td>
<td>33</td>
</tr>
<tr>
<td>12/20/01</td>
<td>126</td>
<td>360</td>
<td>157</td>
<td>454</td>
<td>1.8</td>
<td>61</td>
</tr>
</tbody>
</table>

(blood was drawn in one week after menses completion in both cases)

**follow up 12/20/01**

**Complaints**: none. Weight - 146 lb. BFP -18%.
Familial hypercholesterolemia is associated with mutations affecting the LDL receptors. Cells lacking functional LDL receptors cannot take up LDL. As a result, the amount of circulating LDL increases. 

**Case study 5: familial hypercholesterolemia**

Patient G. 38 y.o. male. *(this case we managed “blindly”)*

**Diagnosis:** familial hypercholesterolemia (familial combined hyperlipidemia)

**Complaints:** high total cholesterol (>500 mg/dL) and TRG > 1500 mg/dL

**Diet:** eats no red meat, no eggs, and everything fat free!

Wt - 225 lb     Ht - 5’11”

**Program was initiated** - October 2004 (no base line for hormones)

- After 3 months of taking a 50 mg DHEA, 100 mg pregnenolone, and 100 mg coenzyme Q-10 daily, patient agreed to do a lipid profile (refused to check his hormones). His TC was down to 318mg/dL, TRG – to 1085 mg/dL (01/07/05).

Certain ethnic groups have a much greater incidence of this genetic trait, with Ashkenazic (Eastern European) Jews, Afrikaner, French Canadians, Lebanese Christians, and Finns high up on the list.
Case study 5 (cont.): familial hypercholesterolemia

- We suggested he takes 100 mg DHEA and 200 mg pregnenolone. Two months later (03/10/05), his TC was up to 412, and we asked him if he was taking the supplements regularly. He was not. We agreed to increase the pregnenolone to 300 mg, and after one month to 400 mg because severe short-term memory and joints problems.

- December 4, 2005 he donated blood and the results of his cholesterol test were stunning – 240! That was not even a fasting cholesterol test! He never had such a low level of cholesterol. Later (12/28/05) his hormones were tested, and fasting lipid profile was done:

  TC – 210 mg/dL, TRG – 518 mg/dL, testosterone – 274 ng/dL, estradiol – 55 pg/ml, DHEA-S – 919 ug/dL, pregnenolone - 113 ng/dL

That got me thinking…

it is not familial hypercholesterolemia per se, but rather familial low hormone production.
Familial hypercholesterolemia is a compensatory reaction on a low production of steroid hormones due to congenital defect of the enzymes system responsible for the regulation of steroid hormone biosynthesis or their interconversions.

- malfunction of enzyme system leads to a low ability in production of the steroid hormones in spite of overproduction of cholesterol
- hypercholesterolemia developed as a normal response of feedback mechanism where deficiency of hormones serves as a start point in over production of cholesterol
- a high synthesis of cholesterol requires a significantly larger amount of LDL in the blood
- But…there is no need to increase the number of LDL-receptors on the cells’ surface because of a low ability to produce hormones. Plus…synthesis of LDL receptors is suppressed by high intracellular cholesterol. As a result, the amount of circulating LDL increases.
- The decreased synthesis of LDL receptors prevents excessive cholesterol uptake by cells. Otherwise cells will depot enormous amount of cholesterol without ability to use it for hormonal production due to enzymes failure. It may block a normal cells function.
- We think that this is the one of the possible defensive mechanism that prevents the overflooding of cells with cholesterol by keeping a low number of functioning LDL receptors.
PCSK9 drugs lower LDL. That fact is clear. But our target is not a lab value; it's heart disease.

In the OSLER and ODYSSEY studies new drugs [evolocumab (Repatha, Amgen) and alirocumab (Praluent, Sanofi/Regeneron)] showed a high level of negative neurocognitive effects. But follow-up was only 11 months in OSLER and 78 weeks in ODYSSEY. That's too short. Heart-disease prevention is not a 2-year endeavor.

These drugs are guaranteed to cause harm. An enzyme called PCSK9 causes a degradation of the LDL receptor that rebinds to LDL. If you don't have that receptor, the cholesterol stays in your blood. By blocking this enzyme, you end up with more LDL receptors on the surface of the cell. The LDL can unbind to the cholesterol and bring it inside the cell.

What you're going to end up with are these cells that are going to be chockfull of cholesterol. This drug is going to take cell function out of balance.
the results of our clinical study support a new hypothesis of hypercholesterolemia which implies that elevation of cholesterol is the compensatory mechanism for declined production of steroidal hormones

hypercholesterolemia reflects a serious problem with steroidal hormones production and serves as an excellent marker which can be used to define the time when patients need to begin hormonorestorative therapy

hormonorestorative therapy can serve as a decisive method in the management of hypercholesterolemia

hormonorestorative therapy is an effective strategy for maintaining cholesterol homeostasis in patients characterized by hypercholesterolemia and sub-youthful serum steroidal hormones

hormonorestoration is typically associated with a substantial drop in serum TC and could be a physiologic and inexpensive resource for the healthcare system


References


References


References


References


References


References


169. Available at:


