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Steroidopenia, Hormonorestorative Therapy and Cholesterol Homeostasis

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Goals & Objectives

- to present a new hypothesis concerning the association of steroidopenia and hypercholesterolemia
- to evaluate the importance and effect of hormonorestorative therapy in the restoration of cholesterol homeostasis

Science behind of Cholesterol

- unfortunately, we ignore thousands of studies that are not in favor of the "main stream" hypothesis
- unsupportive trials were not practically cited after 1970, although their number almost equaled the number considered supportive[10]
- only one of six randomized cholesterol-lowering trials with a negative outcome were cited and only in one of the reviews. In contrast, each review cited two, four, and six non-randomized trials with a positive outcome, respectively. It appears as fundamental parts of the diet-heart idea are based on biased quotation.[11]

Range of normal cholesterol level

- prior to 1980, hypercholesterolemia was defined as any value above the 95th percentile for the population.
  - 1970 - normal range for cholesterol - 150-280 mg/dL[12]
  - 1995 - normal range for cholesterol - 150-250 mg/dL[13]
  - 1996 - recommended interval - less than 200 mg/dL[14]
- as many as 5% of the population in Western countries has TC higher than 300 mg/dL, which is supposed to be the real hypercholesterolemia per the definition of normal ranges.

REMEMBER:
A reference range for a particular test is usually defined as the values that 95% of the population fall into.

Hypercholesterolemia and cholesterol-lowering drugs:

Cholesterol-Lowering Drugs (CLD):
- 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)

- statins play a leading role in the treatment of hypercholesterolemia[15,16]

Problems with CLD

- statins have a major impact on the very basic mechanisms of cholesterol synthesis
- a number of studies show that although primary prevention is effective, long-term tolerability is still a matter of controversy[17,18]
- the reduction of total cholesterol (TC) 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[19-23]

Problems with CLD (cont.)

- the results clearly demonstrated that statins reduce lipid levels but do not prevent restenosis after coronary angioplasty[24]
- statin therapy is associated with decreased myocardial function[183]

CLD and mortality

- a meta-analysis of cholesterol-lowering trials demonstrated that coronary mortality was not lowered by cholesterol lowering, but total mortality was increased[25,26]
- cholesterol lowering appears to increase the risk for cancer, accidental and violent death, mortality from hemorrhagic stroke[27], and oddly enough, CHD[28,29]

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[30]
- a significant increase in the incidence of cancer, especially gastrointestinal, is observed in CLD group[31]
- CLD increase cancer at the expense of decreasing cardiovascular disease in certain populations. Furthermore, there may be a relationship between statin dose and cancer.[32]

CLD and hormones

- there is a possibility that CLD treatment is associated with hormonal perturbations[33]
- a significant association between statin use and total testosterone was observed[34,35]
- mevastatin induced a profound concentration-dependent inhibition of DNA synthesis, decreased production of progesterone by up to 49%, and testosterone by up to 52%[36]
- clofibrate significantly reduced plasma levels of testosterone and cortisol[37]

Side effects from CLD

- side effects of CLD were seen in 4-38% of patients resulting in discontinuation and dose reduction;[2,38-41] some studies registered the incidence of adverse events in more than 73% (73.6% for cerivastatin and 74.9% for pravastatin)[42]
- most patients who begin lipid-lowering therapy stop it within 1 year, and only about one third of patients reach treatment goals;[43] 60% of patients discontinued their medication over 12 months[44]
- 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[38,45]
- 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[46-53]

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.[51,52]

Side effects from CLD (cont.)

- the incidence of congestive heart failure has tripled in the time that statins have been on the market;[54] statins may impair heart pumping function due to their myopathic effect[55]
- statins deplete CoQ10 and this could contribute to heart disease.
- animal studies showed a possible significant hepatic and testicular atrophy, neurological toxicity, hemorrhages in the gastrointestinal tract and brain stem, fibroid degeneration of vessel walls in choroid plexus, and lens opacity[56-58]
- both statins and fibrates may cause erectile dysfunction (ED)[59-61] and primary hypogonadism[35]

Side effects from CLD (cont.)

- cognitive impairment, dementia, memory loss, severe irritability, and peripheral neuropathy may occur with statin therapy[62-67]
- restlessness, euphoria, mental confusion, lupus-like syndrome, pleurisy and arthralgia are possible adverse events of statins[68,69]
- statin use was significantly associated with the development of advanced age-related macular degeneration[70]
- hair loss and alopecia were associated with stanins use[71-73]
- all statins at all doses resulted in tachyphylaxis (a decreasing response to physiologically active agents)[74]

Why do we need a new method?

- the fact that CLD have multiple adverse events, including the most severe side effects such as severe rhabdomyolysis, renal failure, and death;[46-52] indicates the need to find the safer and more effective treatment regiment for elevated TC
- the fact that statins have an extremely high cytotoxic potency and were used as an effective anticancer drug for several types of cancer[75,76]
- intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-dose statin therapy[300]
- our clinical experience of the use of hormonorestorative therapy (HT) for patients with high cholesterol[77-82] shows a possible safe approach to correction of hypercholesterolemia

Why do we need a new method? (cont.)

Taking potent cholesterol-lowering medications to achieve a "risk reduction" has never been shown in clinical research to actually improve a total mortality. In fact, in the biggest trials, significantly more people who took drugs died than those who did not. They didn't die of a heart attack, but dead is dead whatever the cause.

Is physiologic medicine a possible solution?

Physiologic medicine concentrates on causes of physiology malfunction and does not undertake to treat disease, but patient.

- we know that when a person suffers from any disease our body tries to restore normal physiology or in other words, it struggles to restore vital equilibrium
- the luck of equilibrium leads to development of different symptoms and diseases;
- therefore, disease should not be a primary object of treatment

Homeostatic regulation of cholesterol

- interest in possible age-related changes in homeostatic regulation of cholesterol, and in hypothalamic-pituitary-adrenal (HPA) functioning in particular, has been stimulated by the fact that men and women who are 65 and over represent one of the fastest segments of the population[180]
- in population studies, dyslipidemia, diabetes, hypertension, and obesity, overlap to a significant degree, often in multiple combinations.[181,182] That is why we need the safe method of physiology correction that can affect all those conditions simultaneously.

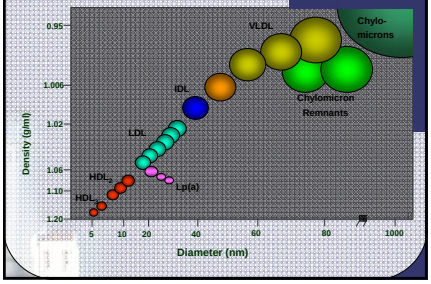
What is cholesterol?

- Cholesterol is a peculiar molecule. It is often called a lipid, steroid, fat or a sterol, 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.[83] All cholesterol in the brain is a product of local synthesis since lipoproteins are unable to cross the blood-brain barrier.[84]
- 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.

Cholesterol carriers

- 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.*

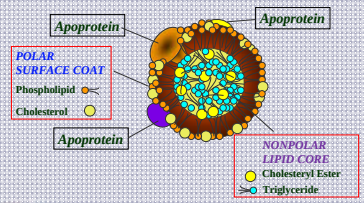
Lipoproteins are classified according to their density



5 basic types of lipoproteins:[85]

- **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, and 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% phospholipids, and 55% protein – 6-12.5 nm in size and most dense (~1.12)

Lipoprotein Structure



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

Function of Lipoproteins:

- **Chylomicron** transports TRG from the intestines to the liver, skeletal muscle, and to adipose tissue.
- **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 is known as " bad cholesterol" (even though LDL is not cholesterol)
- **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.**

  HDL is known as " good cholesterol" (even though HDL is not cholesterol)

Is HDL NOT a good cholesterol anymore?

- many patients with CHD have high levels of 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

Navab M, Van Lenten BJ, Reddy ST, Fogelman AM. High-density lipoprotein and the dynamics of atherosclerotic lesions. Circulation. 2001 Nov 13;104(20):2386-7.

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

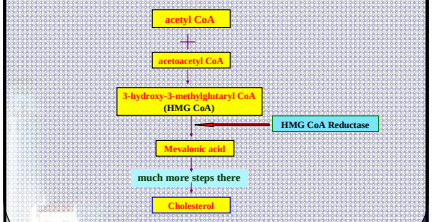
- The lipid profile does not measure LDL particles directly but instead estimates them using the Friedewald equation, which estimates LDL from measurements of TC, triglycerides, and HDL.
- LDL cannot be calculated if plasma triglyceride is >400 mg/dL.

Statins deficiency

- "As it relates to cholesterol, most physicians feel that everyone over the age of 50 has is suffering from an acute Lipitor/Zocor/Crestor deficiency."
- "We are measuring the wrong thing. We treat with the wrong medicines. Statins are toxic. And we wonder why large numbers of people are still dropping over dead with heart attacks."

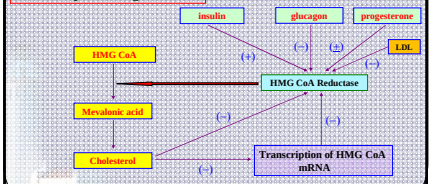
R. Miller, MD

Cholesterol Biosynthesis
(simplified version)

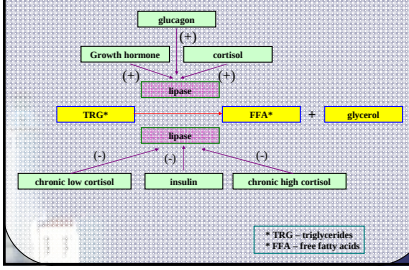


Regulation of HMG CoA Reductase

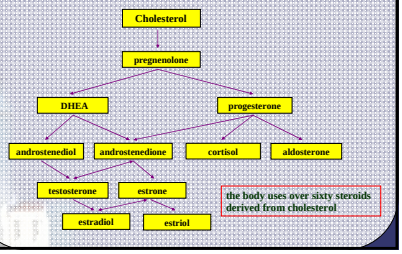
- negative feedback regulation
- hormonal regulation
- transcriptional regulation



Effect of various hormones on lipase



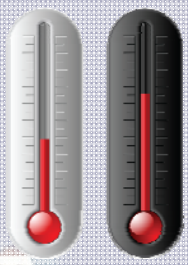
Metabolism of Cholesterol
(simplified version)



New hypothesis of the etiology and pathogenesis 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 interconversions
- in short, hypercholesterolemia is the compensatory mechanism for declined production of steroidal hormones

Dzugan SA, Smith RA. Hypercholesterolemia treatment: a new hypothesis or just an accident. Med Hypotheses. 2002;59:753-8.



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.

Material and Method:

- we retrospectively analyzed the results of two studies that included 155 patients with hypercholesterolemia.

Dzugan SA, Rozakis GW, Dzugan SS, Smith RA. Hormonorestorative therapy is a promising method for hypercholesterolemia treatment. Approaches to Aging Control. 2009;13:12-19.

Dzugan SA, Rozakis GW, Dzugan KS, Embol L, Dzugan SS, Xydas C, Michaelides C, Chene J, Medvedovsky M. Correction of Steroidopenia as a New Method of Hypercholesterolemia Treatment. Neuroendocrinology Letters (NEL). 2011;32(1):77-81.

Material and Method:

- we analyzed 112 patients with hypercholesterolemia
- mean age – 54.2 (from 22 to 81yr)
- male to female ratio – 1:2.3 (34-78)
- follow up duration – 3-144 months

Dzugan SA, Rozakis GW, Dzugan SS, Smith RA. Hormonorestorative therapy is a promising method for hypercholesterolemia treatment. Approaches to Aging Control. 2009;13:12-19.

Hormonorestorative therapy (definition)

In 1996 we employed the term hormonorestorative therapy (HT) into our practice for the regimen that was used for our patients.

Hormonorestorative therapy is the multi-hormonal therapy with the use of a chemically identical formula to human hormones and is administered in physiologic ratios with dose schedules intended to simulate the natural human production cycle and allows to restore the optimal level of hormones.

One of the most significant age-related events is an alteration in amplitude and pulsatile pattern of hormone release.[60] Hormone restoration should provide a serum hormone profile similar to that found in normal physiology.

Basic Hormonorestorative therapy

HT includes a combination of several bio-identical hormones:

- pregnenolone
- dehydroepiandrosterone (DHEA)
- triestrogen (women)
- progesterone
- testosterone
- Armour thyroid
- melatonin
- hydrocortisone
- aldosterone

Vitamin D-3 is a part of optimization therapy for cholesterol

Dosage

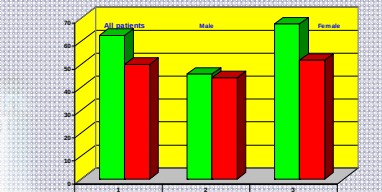
the recommended doses were determined by clinical data, serum hormonal levels, and the so-called the optimal range that was defined as a level of hormones in one third of the highest normal range for all steroid hormones for healthy individuals between the age of 20 and 30.

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%)
- serum TC normalized in 71 patients (63.4%)
- 41 patients (36.6%) still have serum TC levels slightly higher then normal

Total Cholesterol Before and After Hormonorestorative therapy

HDL Before and After Hormonorestorative Therapy



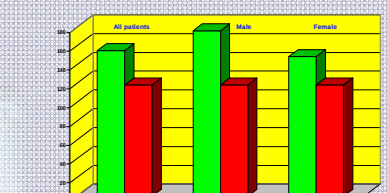
Why decreasing HDL is a good sign during HT?

- 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!

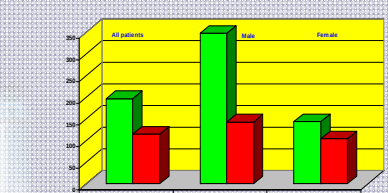
Our results can explain the failure of a new drug for the elevation of HDL from Pfizer – torcetrapib. As you know, this drug raised the risk of death by 59% and heart problems by 25%. It looks like elevated HDL is stealing supply of cholesterol from plants that must produce hormones.

Total Cholesterol = HDL + LDL + TRG/5

LDL Before and After Hormonorestorative Therapy



Triglycerides Before and After Hormonorestorative Therapy



Correction of Steroidopenia

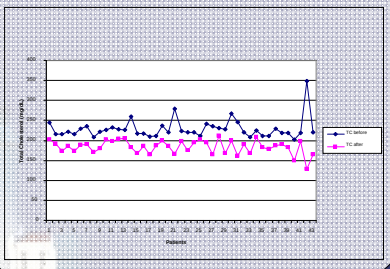
- we analyzed 43 patients
- mean age - 58.4 years
- 12 males and 31 females

Dzugan SA, Rozalis GW, Dzugan KS, Embof L, Dzugan SS, Xydas C, Michaelides C, Cherne J, Medvedovsky M. Correction of Steroidopenia as a New Method of Hypercholesterolemia Treatment. Neuroendocrinology Letters (NEL). 2011;32(1):77-81.

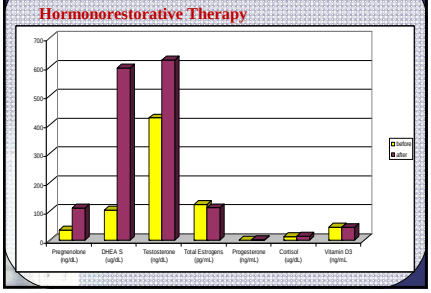
Results:

- the mean serum TC decreased from 228.8 mg/dL before treatment to 183.7 mg/dL after intervention (dropped 19.7%)
- 7 patients still had cholesterol levels ranging from 202 mg/dL to 211 mg/dL but all of these patients had a beneficial drop in TC
- 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

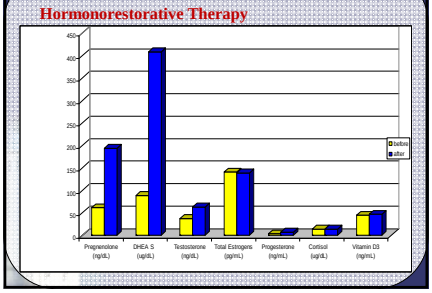
Total Cholesterol Before and After Hormonorestorative therapy



Steroid hormone levels in males before and after Hormonorestorative Therapy



Steroid hormone levels in females before and after Hormonorestorative Therapy



Summary on hypercholesterolemia

- hypercholesterolemia is a risk factor, not a cause of CHD
- steroidopenia is the main cause of hypercholesterolemia
- 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 structures; to heal of damaged endothelium by the "plaquing" of microtrauma
  - to provide a normal response to physiologic demand (growth, pregnancy, stress, etc.)

Summary on hypercholesterolemia (cont.)

- vascular damage with stenosis or occlusion of arteries can develop if the reason for the elevation of cholesterol was not 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)

Case study

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

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

	TC	TRG	HDL	LDL	VLDL	TC/HDL
08/31/00	330	216	54	233	43	6.1
09/09/03	187	138	40	119	28	4.7

	DHEAS	Pregn	Estradiol	Progest	Test	Cortisol
(nl - age 20-29)	(280-640)	(10-200)	(0-53)	(0.3-1.2)	(280-830)	(4.3-22.4)
08/31/00	93	24	56	0.3	186	0.9
09/09/03	540	159	30	1.3	496	15.6

	DHT	Free Test	PSA
	(30-85)	(9.3-26.5)	(0-4)
08/31/00	44	1.01	1.1
09/09/03	38	19.6	0.8

follow up 09/09/03 – no complaints

Case study

Patient E. 51 yr, female, August 16, 2010

Diagnosis: hypercholesterolemia, anxiety, arthritis, fatigue, insomnia, Crohn's Disease, menopause, sarcoidosis

	TC	TRG	HDL	LDL
07/13/10	254	98	62	172
09/09/10	183	81	60	107

	DHEAS	Pregn	total estrogens	Progest	Test	Cortisol	vit. D-3
	(65-380)	(10-230)	(70-900)	(0.2-28)	(14-76)	(4.3-22.4)	(30-100)
07/13/10	24	46	<50	0.5	17	20.8	25
11/07/10	329	181	276	9.1	43	18.8	44

follow up 01/06/11 – no complaints

Conclusion

- the results of our clinical studies support a new hypothesis concerning the association of steroidopenia and hypercholesterolemia
- hormonorestorative therapy is an effective strategy for normalizing and maintaining cholesterol homeostasis
- hormonorestorative therapy can serve as a decisive physiologic method in the management of hypercholesterolemia

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