Cardiovascular System

DYSLIPEDIMA

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CAUSATION?

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Cholesterol/Dyslipidemia

The over focus on cholesterol as the sole cause of heart disease is one of the greatest scams in history.

What's the first score patients want to know on their blood test?

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Cholesterol/Dyslipidemia

And yet Cholesterol is essential :
Cell membrane integrity.
Substrate for all adrenal/gonadal hormones
To utilize Vitamin D
To make Bile salts fat/mineral absorption
To Make myelin sheath, memory, neurotransmitters like serotonin
Innate Immune system..

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Cholesterol/Dyslipidemia

- Statin drugs are marketed to the public and given like candy;
- There has been a debate whether they should be added to drinking water.
- The number of individuals in the general population who reported taking any statin climbed from 31 million (12%) in 2008–2009 to 92 million (35%) in 2018–2019, representing a 197% increase

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Cholesterol /Dyslipidemia

New heart disease prevention guidelines suggests that "Almost half of Americans ages 40 to 75 and nearly all men over 60 qualify to consider cholesterol-lowering statin drugs"

New England Journal of Medicine, March 2014 online publication

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Cholesterol/Dyslipidemia

Statin drugs can cause:

- Muscle weakness,
- Sexual dysfunction,
- Reduced thyroid function by inhibiting the conversion of T4 to T3,
- Memory reduction,
- Reduced immunity

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Cholesterol/Dyslipidemia

Statin drugs can also cause:

- Depletions of key nutrients:
- CoQ 10,
- Carnitine,
- Zinc,
- Selenium,
- Vitamin E, D,
- Omega 3 Fatty Acids

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Cholesterol/Dyslipidemia

Statin drugs:

If patients are on statins…

replete the nutrients that the statins deplete Carnitine, CoQ 10, Zinc, Selenium, Vitamins D& E ,

ProMultiPlus 2 tid, CoQ plus 100, Acetyl-L-Carnitine

Or Vasculo Sirt 3 bid

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Cholesterol/Dyslipidemia

BIGGER PICTURE

Use the awareness or fear of Cholesterol to educate or motivate patients to make the lifestyle changes they really need to make

And

Do more testing to find out what else is going on

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WHAT IS CHOLESTEROL?

- Cholesterol is a STEROID because it shares the chemical structure of 4 fused carbon rings with other steroids.
- Specifically, it is a sterol, which is a class of lipid with an unsaturated alcohol (hydroxyl) or -OH group. This makes it a molecule with both hydrophobic and hydrophilic — meaning water-attracting — properties. It needs carrier proteins to take it around the body

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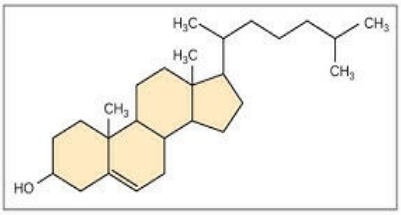
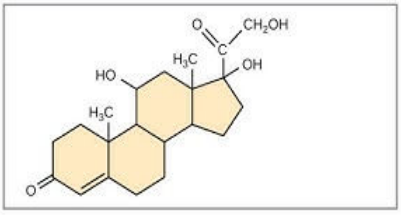
CHOLESTEROL – STEROID – STEROL

Steroids

- Steroids are hydrophobic and insoluble in water.
- Steroids have a fused ring structure (all steroids have four linked carbon rings and several of them, like cholesterol, have a short tail).
- Many steroids also have the –OH functional group, which puts them in the alcohol classification (sterols).



Cholesterol



Cortisol

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PLASMA LIPOPROTEIN PARTICLES

1. Cholesterol
2. Triglycerides
3. Phospholipids and specific proteins called
4. Apoproteins (A, B, C, D, E.)

- The varying composition of these elements determines the density, size, and electrophoretic mobility of each particle. These factors in turn have been used for the clinical and biochemical classification of lipoprotein disorders.

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- ATHEROSCLEROSIS – "**apoB more accurately measures the atherogenic risk owing to the apoB lipoproteins than does low-density lipoprotein cholesterol or non-high-density lipoprotein cholesterol.**"

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- **Triglycerides** - body converts any calories it doesn't need to use right away into triglycerides and stores them in fat cells. Hormones release triglycerides for energy between meals. Triglycerides and cholesterol are both fatty substances called lipids. But triglycerides are fats; cholesterol is not.

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Lipoproteins used to transport lipids in the body are:

- **Chylomicrons**: These large particles transport dietary triglycerides and cholesterol from the intestine to the liver and other body tissues.
- **Very low-density lipoproteins (VLDL):** The liver produces these particles. Muscle and adipose tissues metabolize VLDL into low-density lipoproteins (LDL).
- **LDL**: Small dense LDL particles carry most of the cholesterol in the body's circulation to the tissues. LDL enters the arteries, and free radicals can oxidize it, causing atherosclerosis.
- **High-density lipoproteins (HDL):** These particles play an important role in transporting cholesterol back to the liver, which helps prevent it from being deposited in arteries. HDL has antioxidant and anti-inflammatory properties, which can inhibit atherosclerosis.

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STEROLS

- **ANIMAL & PLANTS**
- **Consume phytosterols**
- Phytosterols are plant compounds that some people use to lower their cholesterol. People can consume phytosterols from whole foods, fortified foods, or supplements.
- Plant sterols and stanols have a similar chemical structure to cholesterol, thereby preventing the intestine from absorbing cholesterol. In addition, foods such as fruits, vegetables, oils, and cereals naturally contain phytosterols.

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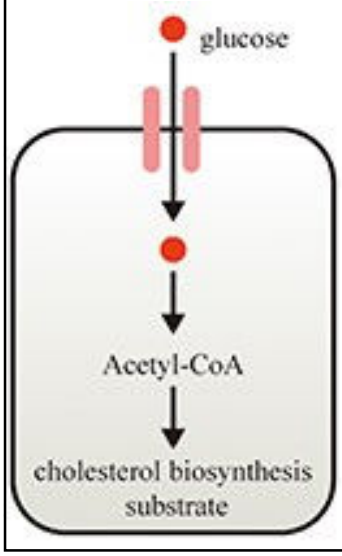
CHOLESTEROL – 80% FROM GLUCOSE, 20% DIETARY INTAKE



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SYNTHESIS

- "Glucose/insulin promotes cholesterol biosynthesis and cholesterol uptake, which indicates that drugs targeting lowering glucose may help to control hypercholesterolemia. On the contrary, cholesterol-lowering drugs or genetic variants could impair glucose homeostasis and lead to diabetes by decreasing pancreatic β-cell insulin secretion or inducing insulin resistance of skeletal muscle cells, adipocytes, or hepatocytes."

Frontiers of Cardiovascular Medicine April 2022

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9098828/

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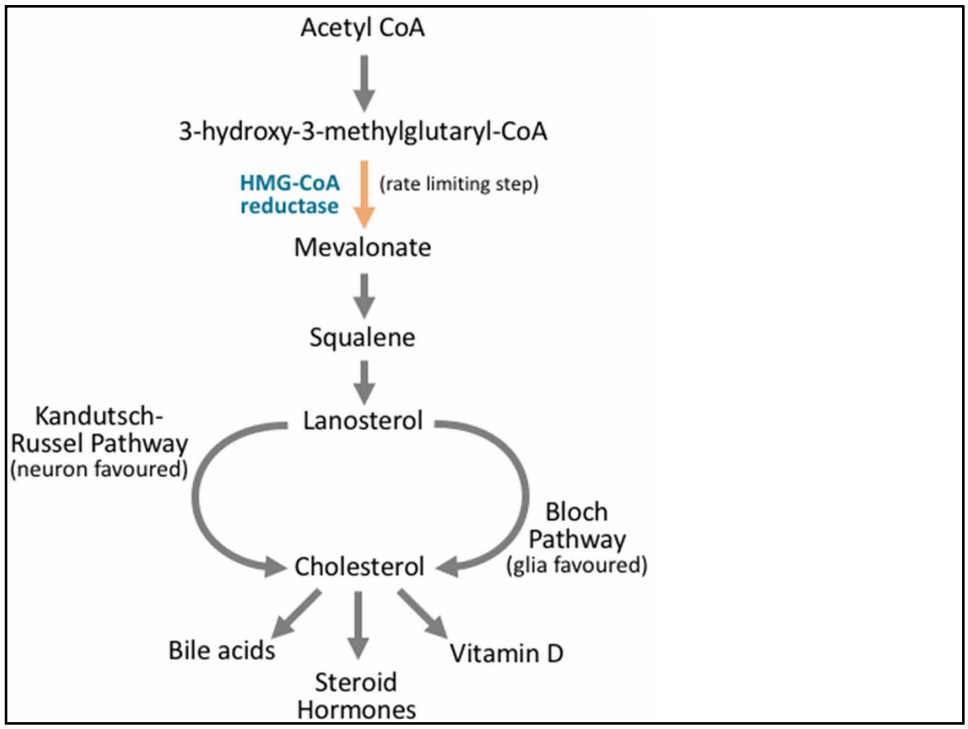

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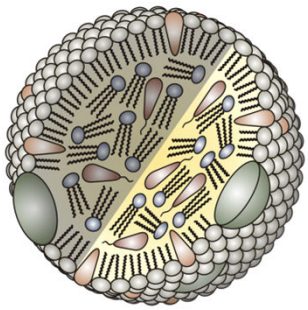
Structure of Lipoprotein



SURFACE COAT
- unesterified cholesterol
- phospholipids
- apolipoproteins

LIPID CORE
- cholesteryl esters
- triglycerides

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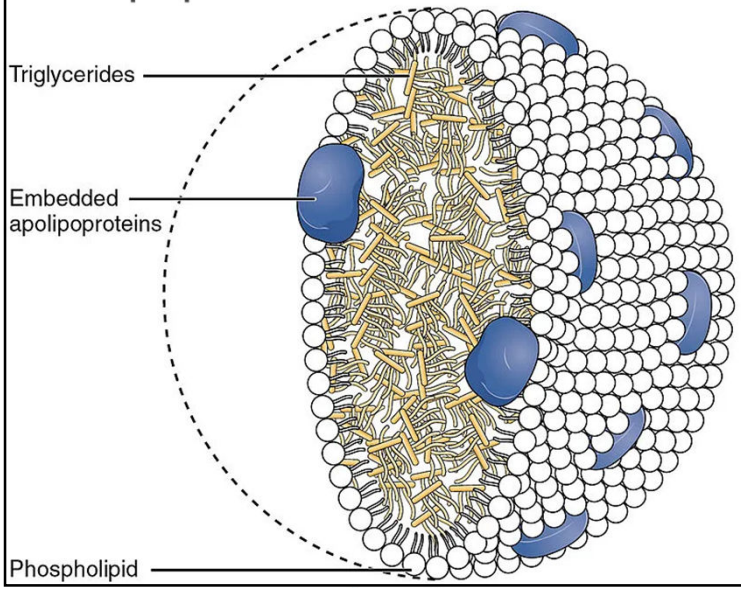
Apolipoprotein is the protein component of the lipoprotein molecule.



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Cholesterol/Dyslipidemia

Particle Size and Particle number are important

CD by Dr. Mark Houston LipidSirt

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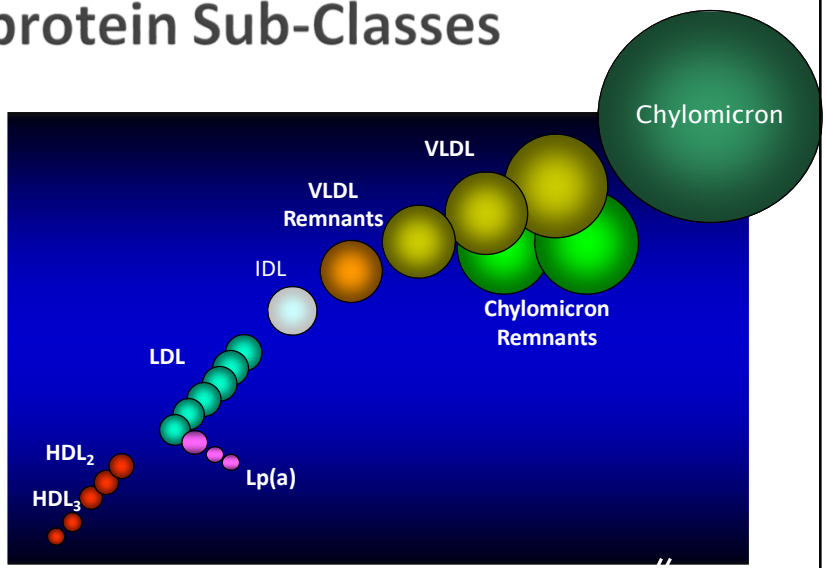
Lipoprotein Sub-Classes



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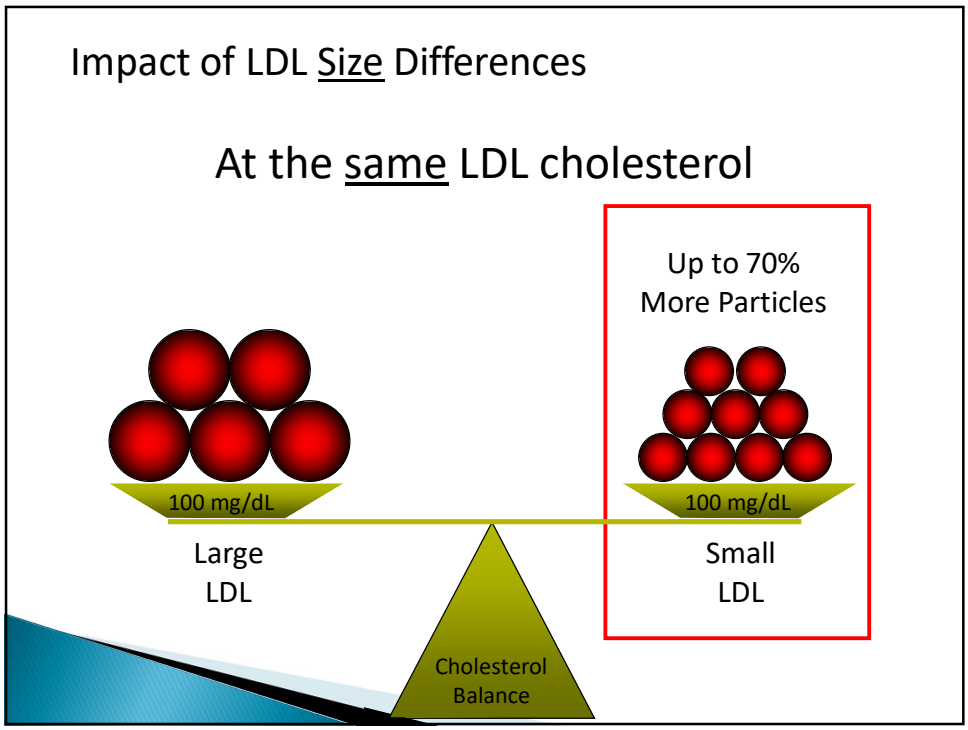

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Cholesterol/Dyslipidemia

Examples of updated testing for Cardiovascular Disease include:

- CRP,
- Fasting Insulin,
- HgbA1c,
- Vitamin D,
- Size and Number…Cholesterol Particles.
- Modified or Oxidized LDL

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Atherosclerosis Process:

1. Fatty streak formation in 4 steps:
   - a. apoB trapping
   - b. Activation of endothelial cells
   - c. Leukocyte activation
   - d. Formation of foam cells
2. Atheroma formation
3. Atherosclerotic plaque formation

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CVD

- Big drivers of CVD:
- LDL-C (cholesterol contained in the LDL-P)
- LDL-P (particle #) – better able to predict CVD than LDL-C
- APO-B
- 5 subgroups of LDL: IDL, I, II, III, IV
- IDL = largest and least dense
- LDL IV – smallest and most dense
- LDL III and LDL IV are 3 times more atherogenic than LDL I and II
- There is an apoB molecule attached to every VLDL, IDL, LDL, and Lp(a)
- Start with apoB, then look at others.

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ox-LDL

- Oxidized LDL – major factor leading to activation, dysfunction and injury of endothelial cells. Uptake of oxLDL causes development of foam cells. OxLDL can trigger inflammation, platelet aggregation.
- Reduce role of oxidized LDL:
- Magnesium 300mg/day
- Curcumin 180 mg/day
- Red yeast rice, 2400mg/day

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apoB

- To lower apoB:
- Lose weight.
- Replace carbs with olive oil.
- BioFiber Complete – 8-20 g/day
- Phytosterols 2-4g/day : Lipid-Sirt
- Nuts 30-70g/day
- Fish oil reduces apoB – 3-4 grams/day

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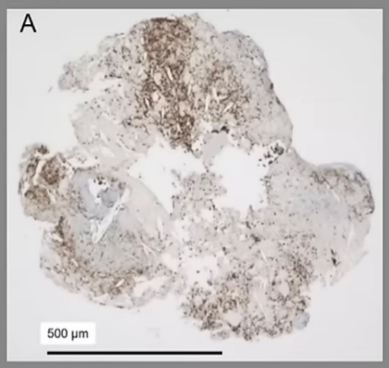
GLYCOPHERIN A



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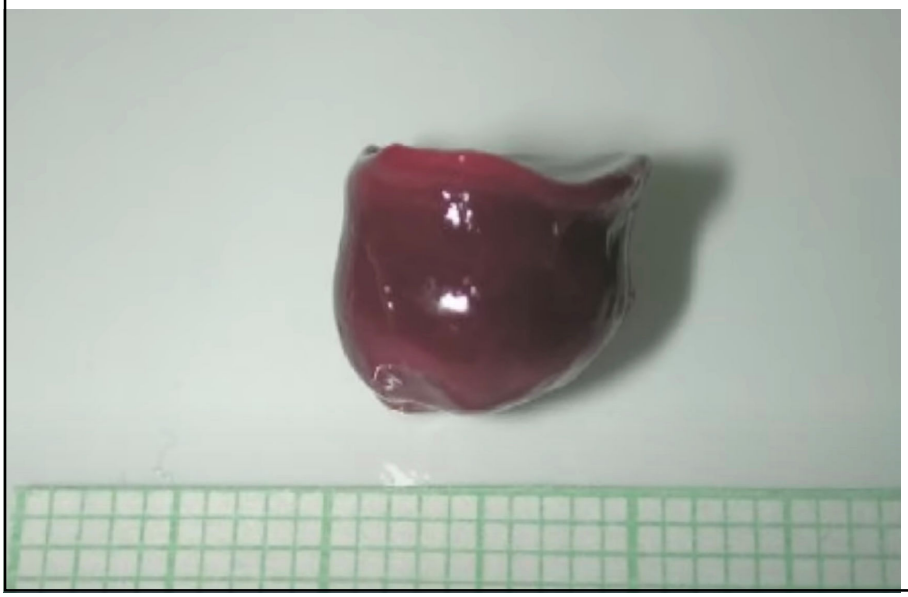
BLOOD CLOT



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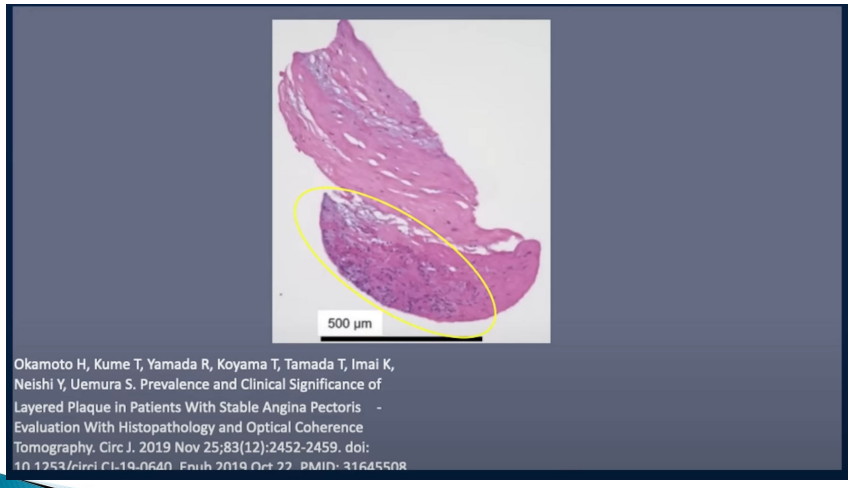
GLYCOPHERIN A



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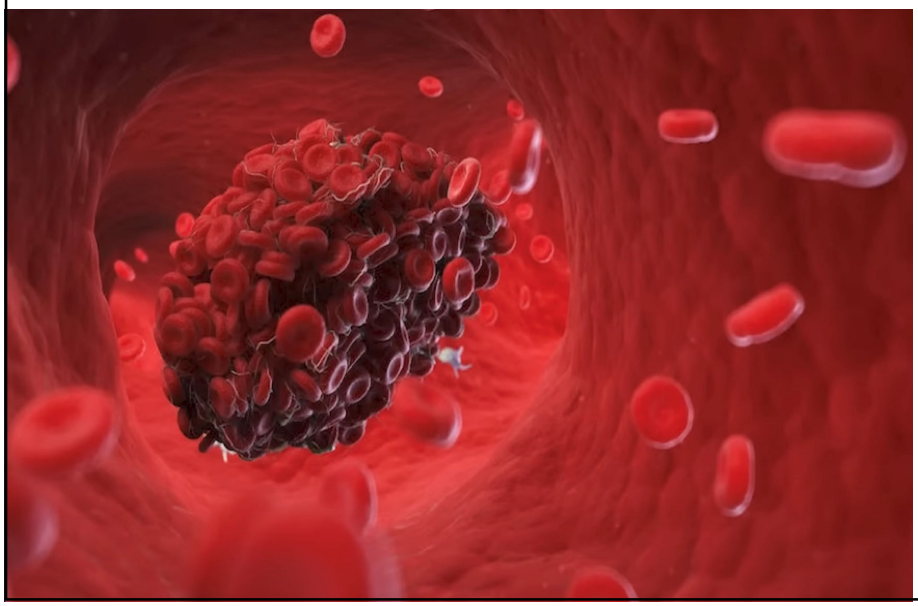

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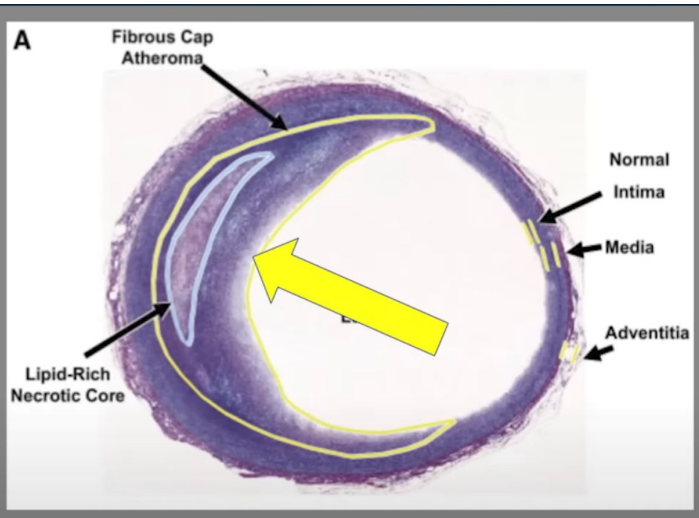
SINGLE LAYER



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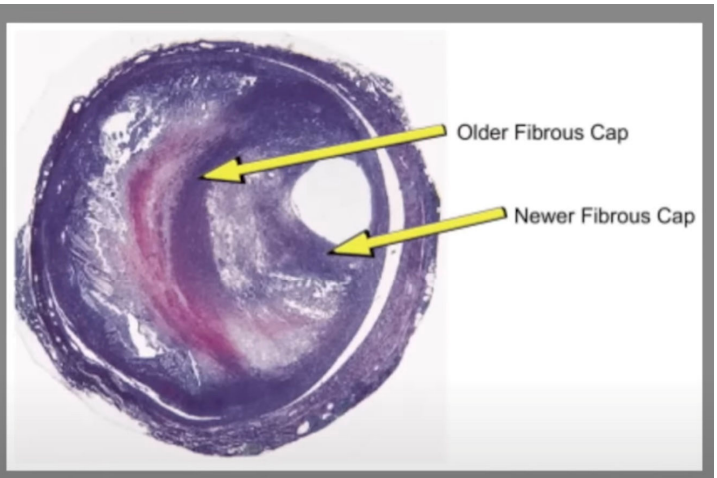
DUAL LAYER



Insull W Jr. The pathology of atherosclerosis: plaque development and plaque responses to medical treatment. Am J Med. 2009 Jan;122(1 Suppl):S3-S14.

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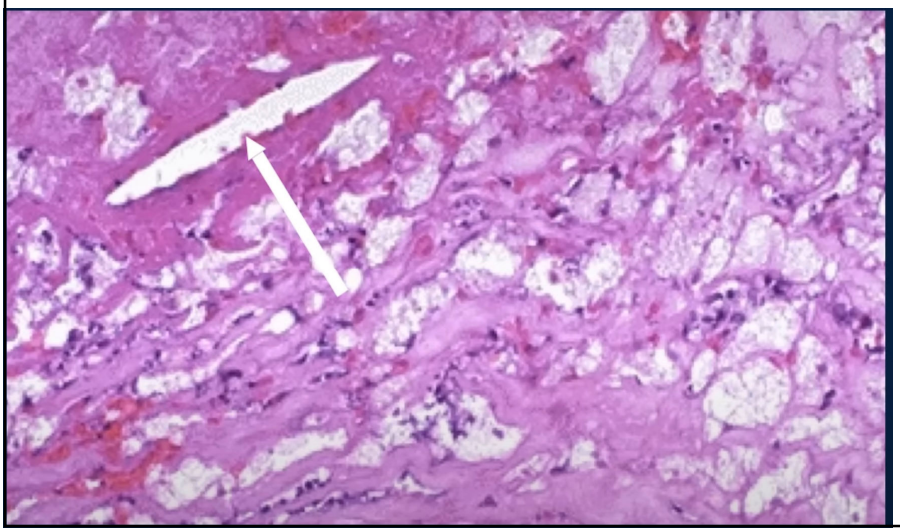
CRYSTALIZATION… IS IT REALLY CHOLESTEROL?



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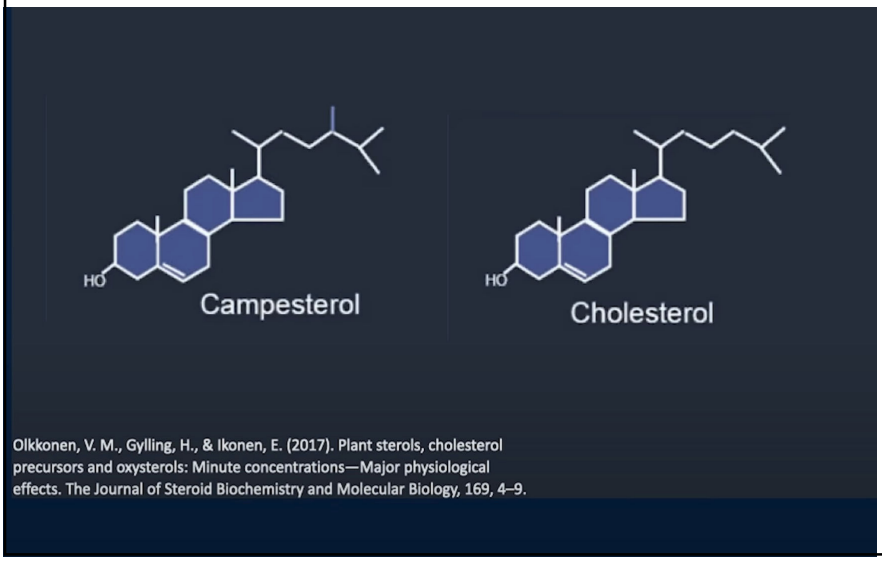
CAMPESTEROL VIRTUALLY INDENTICAL TO CHOLESTEROL



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Plant Sterols in Serum and in Atherosclerotic Plaques of Patients Undergoing Carotid Endarterectomy

Non-cholesterol sterols in serum and endarterectomized carotid arteries after a short-term plant stanol and sterol ester challenge

Steroids

Increased plant sterol deposition in vascular tissue characterizes patients with severe aortic stenosis and concomitant coronary artery disease

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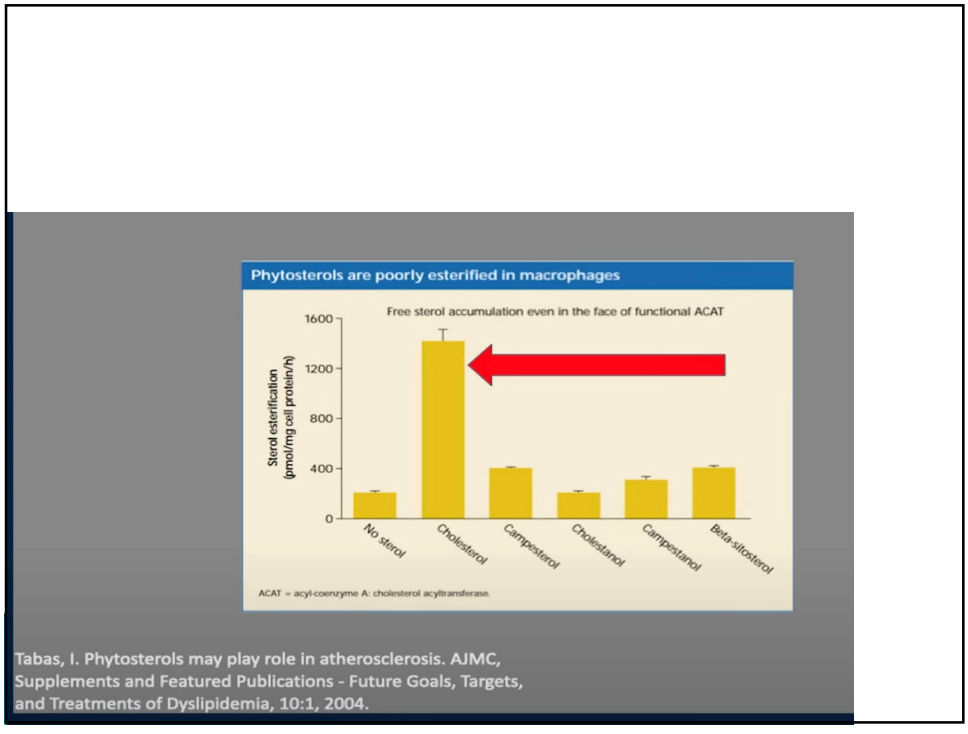

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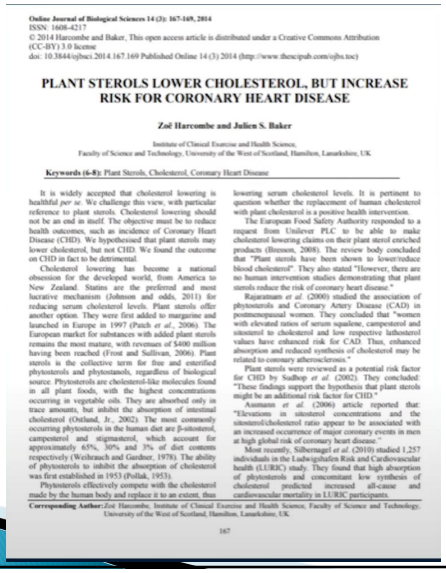
PLANT STEROLS



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doi: 10.3844/ojbsci.2014.167.169 Published Online 14 (3) 2014 (http://www.thescipub.com/ojbs.toc)

PLANT STEROLS LOWER CHOLESTEROL, BUT INCREASE RISK FOR CORONARY HEART DISEASE

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Keywords (6-8): Plant Sterols, Cholesterol, Coronary Heart Disease

It is widely accepted that cholesterol lowering is healthful *per se*. We challenge this view, with particular reference to plant sterols. Cholesterol lowering should not be an end in itself. The objective must be to reduce health outcomes, such as incidence of Coronary Heart Disease (CHD). We hypothesised that plant sterols may lower cholesterol, but not CHD. We found the outcome on CHD in fact to be detrimental.

Cholesterol lowering has become a national obsession for the developed world, from America to New Zealand. Statins are the preferred and most lucrative mechanism (Johnson and odds, 2011) for reducing serum cholesterol levels. Plant sterols offer another option. They were first added to margarine and launched in Europe in 1997 (Puch *et al*., 2006). The European market for substances with added plant sterols remains the most mature, with revenues of $400 million having been reached (Frost and Sullivan, 2006). Plant sterols is the collective term for free and esterified phytosterols and phytostanols, regardless of biological source. Phytosterols are cholesterol-like molecules found in all plant foods, with the highest concentrations occurring in vegetable oils. They are absorbed only in trace amounts, but inhibit the absorption of intestinal cholesterol (Ostland, Jr., 2002). The most commonly occurring phytosterols in the human diet are β-sitosterol, campesterol and stigmasterol, which account for approximately 65%, 30% and 3% of diet contents respectively (Weihrauch and Gardner, 1978). The ability of phytosterols to inhibit the absorption of cholesterol was first established in 1953 (Pollak, 1953).

Phytosterols effectively compete with the cholesterol made by the human body and replace it to an extent, thus lowering serum cholesterol levels. It is pertinent to question whether the replacement of human cholesterol with plant cholesterol is a positive health intervention.

The European Food Safety Authority responded to a request from Unilever PLC to be able to make cholesterol lowering claims on their plant sterol enriched products (Brenson, 2008). The review body concluded that "Plant sterols have been shown to lower/reduce blood cholesterol". They also stated "However, there are no human intervention studies demonstrating that plant sterols reduce the risk of coronary heart disease."

Rajaratnam *et al*. (2000) studied the association of phytosterols and Coronary Artery Disease (CAD) in postmenopausal women. They concluded that "women with elevated ratios of serum squalene, campesterol and sitosterol to cholesterol and low respective lathosterol values have enhanced risk for CAD. Thus, enhanced absorption and reduced synthesis of cholesterol may be related to coronary atherosclerosis."

Plant sterols were reviewed as a potential risk factor for CHD by Sudhop *et al*. (2002). They concluded: "These findings support the hypothesis that plant sterols might be an additional risk factor for CHD."

Assmann *et al*. (2006) article reported that: "Elevations in sitosterol concentrations and the sitosterol/cholesterol ratio appear to be associated with an increased occurrence of major coronary events in men at high global risk of coronary heart disease.".

Most recently, Silbernagel *et al*. (2010) studied 1,257 individuals in the Ludwigshafen Risk and Cardiovascular health (LURIC) study. They found that high absorption of phytosterols and concomitant low synthesis of cholesterol predicted increased all-cause and cardiovascular mortality in LURIC participants.

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SEED OILS DANGER

Seed oil	Phytosterol content (mg/100 g)
Rice bran oil	1891.82
Corn oil	990.94
Rapeseed oil	893.84
Sesame oil	637.60
Flaxseed oil	466.73
Peony seed oil	367.19
Soybean oil	355.67
Peanut oil	319.75
Olive oil	288.02

Yang R, Xue L, Zhang L, Wang X, Qi X, Jiang J, Yu L, Wang X, Zhang W, Zhang Q, Li P. Phytosterol Contents of Edible Oils and Their Contributions to Estimated Phytosterol Intake in the Chinese Diet. Foods. 2019 Aug 9;8(8):334.

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Open Access Research

BMJ Open

Randomised trial of coconut oil, olive oil or butter on blood lipids and other cardiovascular risk factors in healthy men and women

Kay-Tee Khaw,[1] Stephen J Sharp,[2] Leila Finikarides,[3,4] Islam Afzal,[5] Marleen Lentjes,[1] Robert Luben,[1] Nita G Forouhi[2]

ABSTRACT

Introduction High dietary saturated fat intake is associated with higher blood concentrations of low-density lipoprotein cholesterol (LDL-C), an established risk factor for coronary heart disease. However, there is increasing interest in whether various dietary oils or fats with different fatty acid profiles such as extra virgin coconut oil may have different metabolic effects but trials have reported inconsistent results. We aimed to compare changes in blood lipid profile, weight, fat distribution and metabolic markers after four weeks consumption of 50 g daily of one of three different dietary fats, extra virgin coconut oil, butter or extra virgin olive oil, in healthy men and women in the general population.

Design Randomised clinical trial conducted over June and July 2017.

Setting General community in Cambridgeshire, UK.

Participants Volunteer adults were recruited by the British Broadcasting Corporation through their websites. Eligibility criteria were men and women aged 50–75 years, with no known history of cancer, cardiovascular disease or diabetes, not on lipid lowering medication, no contraindications to a high-fat diet and willingness to be randomised to consume one of the three dietary fats for 4 weeks. Of 192 individuals initially expressing an interest and assessed for eligibility, 96 were randomised to one of three interventions; 2 individuals subsequently withdrew and 94 men and women attended a baseline assessment. Their mean age was 60 years, 67% were women and 98% were European Caucasian. Of these, 91 men and women attended a follow-up assessment 4 weeks later.

Intervention Participants were randomised to extra virgin coconut oil, extra virgin olive oil or unsalted butter and asked to consume 50 g daily of one of these fats for 4 weeks, which they could incorporate into their usual diet or consume as a supplement.

Main outcomes and measures The primary outcome was change in serum LDL-C, secondary outcomes were change in total and high-density lipoprotein cholesterol (TC and HDL-C), TC/HDL-C ratio and non-HDL-C; change in weight, body mass index (BMI), waist circumference, per cent body fat, systolic and diastolic blood pressure, fasting plasma glucose and C reactive protein.

Results LDL-C concentrations were significantly increased on butter compared with coconut oil (=0.42, 95% CI 0.19 to 0.65 mmol/L, P<0.0001) and with olive oil (=0.38, 95% CI 0.16 to 0.60 mmol/L, P<0.0001), with no differences in change of LDL-C in coconut oil compared with olive oil (−0.04, 95% CI −0.27 to 0.19 mmol/L, P=0.74). Coconut oil significantly increased HDL-C compared with butter (=0.18, 95% CI 0.06 to 0.30 mmol/L) or olive oil (=0.16, 95% CI 0.03 to 0.28 mmol/L). Butter significantly increased TC/HDL-C ratio and non-HDL-C compared with coconut oil but coconut oil did not significantly differ from olive oil for TC/HDL-C and non-HDL-C. There were no significant differences in changes in weight, BMI, central adiposity, fasting blood glucose, systolic or diastolic blood pressure among any of the three intervention groups.

Conclusions and relevance Two different dietary fats (butter and coconut oil) which are predominantly saturated fats, appear to have different effects on blood lipids compared with olive oil, a predominantly monounsaturated fat with coconut oil more comparable to olive oil with respect to LDL-C. The effects of different dietary fats on lipid profiles, metabolic markers and health outcomes may vary not just according to the general classification of their main component fatty acids as saturated or unsaturated but possibly according to different profiles in individual fatty acids, processing methods as well as the foods in which they are consumed or dietary patterns. These findings do not alter current dietary recommendations to reduce saturated fat intake in general but highlight the need for further elucidation of the more nuanced relationships between different dietary fats and health.

Trial registration number NCT03105947; Results.

Strengths and limitations of this study

- The randomised trial design comparing three dietary fat interventions minimised confounding and bias.
- There was good compliance and participants were from the general community in a 'real life' setting.
- Objective measures of outcome—blood biochemistry and anthropometry—were used, minimising bias.
- Participants were not blinded as to the intervention, and the intervention was relatively short term over 4 weeks.

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► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-020167).

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HYDROGENATION DAMAGING OILS

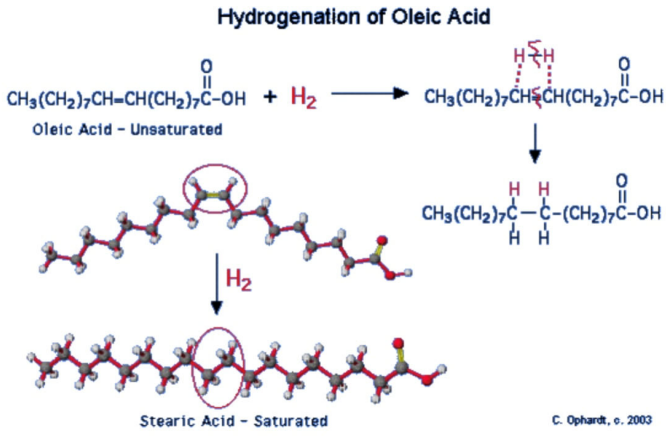

Figure 1: Hydrogenation of a oleic fatty acid

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International Journal of Molecular Sciences

MDPI

Review

Oxidative Stress and Thrombosis during Aging: The Roles of Oxidative Stress in RBCs in Venous Thrombosis

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Abstract: Mid-life stage adults are at higher risk of developing venous thrombosis (VT)/thromboembolism (VTE). Aging is characterized by an overproduction of reactive oxygen species (ROS), which could evoke a series of physiological changes involved in thrombosis. Here, we focus on the critical role of ROS within the red blood cell (RBC) in initiating venous thrombosis during aging. Growing evidence has shifted our interest in the role of unjustifiably unvalued RBCs in blood coagulation. RBCs can be a major source of oxidative stress during aging, since RBC redox homeostasis is generally compromised due to the discrepancy between prooxidants and antioxidants. As a result, ROS accumulate within the RBC due to the constant endogenous hemoglobin (Hb) autoxidation and NADPH oxidase activation, and the uptake of extracellular ROS released by other cells in the circulation. The elevated RBC ROS level affects the RBC membrane structure and function, causing loss of membrane integrity, and decreased deformability. These changes impair RBC function in hemostasis and thrombosis, favoring a hypercoagulable state through enhanced RBC aggregation, RBC binding to endothelial cells affecting nitric oxide availability, RBC-induced platelet activation consequently modulating their activity, RBC interaction with and activation of coagulation factors, increased RBC phosphatidylserine exposure and release of microvesicles, accelerated aging and hemolysis. Thus, RBC oxidative stress during aging typifies an ultimate mechanism in system failure, which can affect major processes involved in the development of venous thrombosis in a variety of ways. The reevaluated concept of the critical role of RBC ROS in the activation of thrombotic events during aging will help identify potential targets for novel strategies to prevent/reduce the risk for VTE or VTE recurrences in mid-life stage adults.

Keywords: VTE; aging; red blood cell; oxidative stress; reactive oxygen species; antioxidant defenses; redox regulation; venous thrombosis

1. Introduction

Aging contributes to an elevated incidence of venous thrombosis (VT)/thromboembolism (VTE) [1,2], the third most common cause of cardiovascular death worldwide. It has been documented that the incidence of VTE is two to seven times higher in patients above the age of 55 as compared to a younger cohort [3]. A large sum of first-time VTE occurs in patients that are ≥ 45 years of age [4]. These epidemiological findings have sparked considerable interest in characterizing changes in the coagulation system as a function of aging, since in light of increasing life expectancy, VTE will become a greater health care issue [5]. Hence, aging is not only an important biological issue, but also a crucial socioeconomic factor affecting an ever-increasing aging population. A normal coagulation pathway represents a balance between thrombosis and hemorrhage. This thrombo–hemorrhagic balance is

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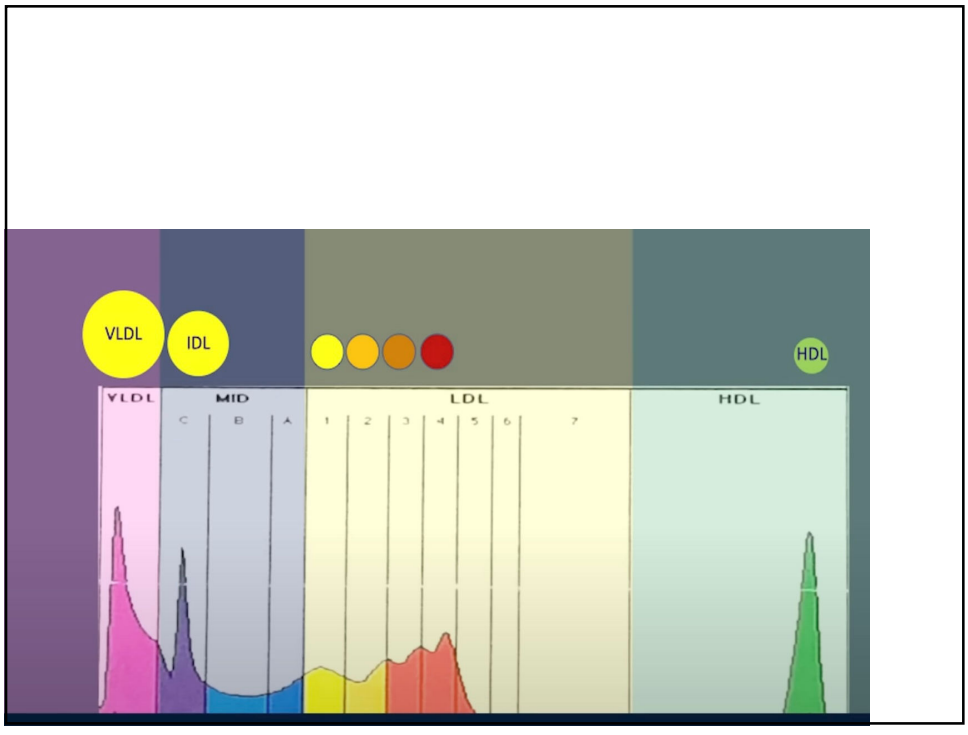

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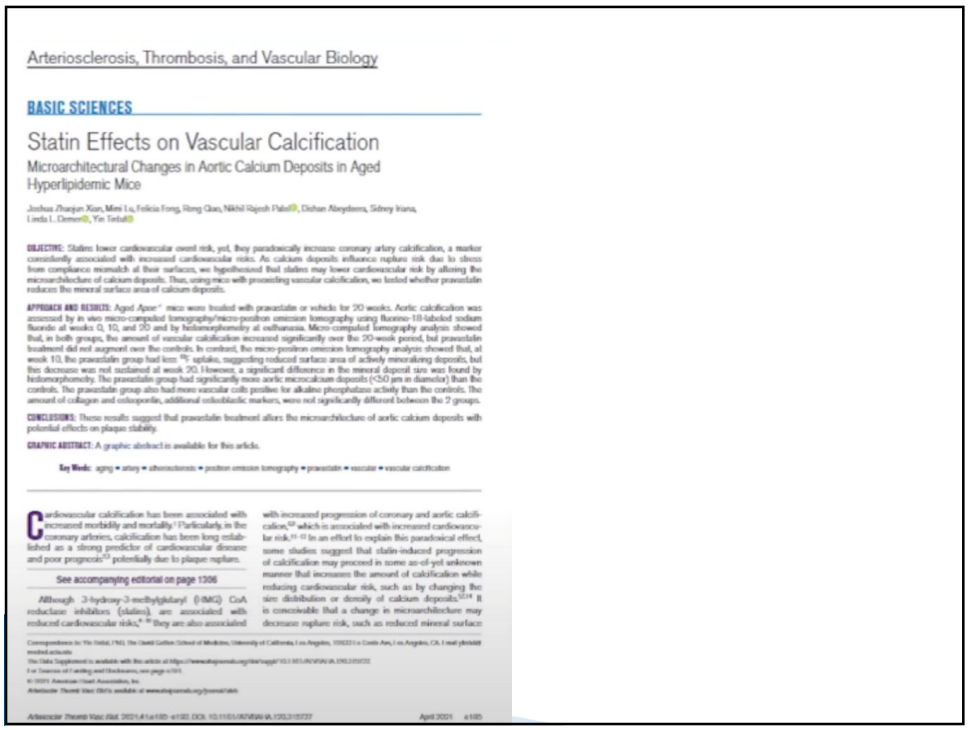

Arteriosclerosis, Thrombosis, and Vascular Biology

BASIC SCIENCES

Statin Effects on Vascular Calcification

Microarchitectural Changes in Aortic Calcium Deposits in Aged Hyperlipidemic Mice

Joshua Zhaojun Xian, Mimi Lu, Felicia Feng, Rong Qiao, Nikhil Rajesh Patel, Dishan Abeydeera, Sidney Irana, Linda L. Demer, Yin Tintut

OBJECTIVE: Statins lower cardiovascular overall risk, yet, they paradoxically increase coronary artery calcification, a marker consistently associated with increased cardiovascular risks. As calcium deposits influence rupture risk due to stress from compliance mismatch at their surfaces, we hypothesized that statins may lower cardiovascular risk by altering the microarchitecture of calcium deposits. Thus, using mice with promoting vascular calcification, we tested whether pravastatin reduces the mineral surface area of calcium deposits.

APPROACH AND RESULTS: Aged *Apoe*$^{-/-}$ mice were treated with pravastatin or vehicle for 20 weeks. Aortic calcification was assessed by in vivo micro-computed tomography/micro-positron emission tomography using fluorine-18-labeled sodium fluoride at weeks 0, 10, and 20 and by histomorphometry at euthanasia. Micro-computed tomography analysis showed that, in both groups, the amount of vascular calcification increased significantly over the 20-week period, but pravastatin treatment did not augment over the controls. In contrast, the micro-positron emission tomography analysis showed that, at week 10, the pravastatin group had less ^{18}F uptake, suggesting reduced surface area of actively mineralizing deposits, but this decrease was not sustained at week 20. However, a significant difference in the mineral deposit size was found by histomorphometry. The pravastatin group had significantly more aortic microcalcium deposits (<50 μm in diameter) than the controls. The pravastatin group also had more vascular cells positive for alkaline phosphatase activity than the controls. The amount of collagen and osteopontin, additional osteoblastic markers, were not significantly different between the 2 groups.

CONCLUSIONS: These results suggest that pravastatin treatment alters the microarchitecture of aortic calcium deposits with potential effects on plaque stability.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: aging ■ artery ■ atherosclerosis ■ positron emission tomography ■ pravastatin ■ vascular ■ vascular calcification

Cardiovascular calcification has been associated with increased morbidity and mortality.[1] Particularly in the coronary arteries, calcification has been long established as a strong predictor of cardiovascular disease and poor prognosis[2,3] potentially due to plaque ruptures.

See accompanying editorial on page 1306

Although 3-hydroxy-3-methylglutaryl (HMG) CoA reductase inhibitors (statins), are associated with reduced cardiovascular risks,[4–6] they are also associated with increased progression of coronary and aortic calcification,[7,8] which is associated with increased cardiovascular risk.[9–12] In an effort to explain this paradoxical effect, some studies suggest that statin-induced progression of calcification may proceed in some as-of-yet unknown manner that increases the amount of calcification while reducing cardiovascular risk, such as by changing the size distribution or density of calcium deposits.[10,13] It is conceivable that a change in microarchitecture may decrease rupture risk, such as reduced mineral surface

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For Sources of Funding and Disclosures, see page 1305.

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Arterioscler Thromb Vasc Biol is available at www.ahajournals.org/journal/atvb

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SYSTEMATIC REVIEW

A Systematic Review on the Protective Effect of *N*-Acetyl Cysteine Against Diabetes-Associated Cardiovascular Complications

Phiwayinkosi V. Dludla[1] · Stephanie C. Dias[2] · Nnini Obonye[2] · Rabia Johnson[2,3] · Johan Louw[2,3] · Bongani B. Nkambule[4]

Abstract

Introduction Heart failure is the leading cause of death in patients with diabetes. No treatment currently exists to specifically protect these patients at risk of developing cardiovascular complications. Accelerated oxidative stress-induced tissue damage due to persistent hyperglycemia is one of the major factors implicated in deteriorated cardiac function within a diabetic state. *N*-acetyl cysteine (NAC), through its enhanced capacity to endogenously synthesize glutathione, a potent antioxidant, has displayed abundant health-promoting properties and has a favorable safety profile.

Objective An increasing number of experimental studies have reported on the strong ameliorative properties of NAC. We systematically reviewed the data on the cardioprotective potential of this compound to provide an informative summary.

Methods Two independent reviewers systematically searched major databases, including PubMed, Cochrane Library, Google scholar, and Embase for available studies reporting on the ameliorative effects of NAC as a monotherapy or in combination with other therapies against diabetes-associated cardiovascular complications. We used the ARRIVE and JBI appraisal guidelines to assess the quality of individual studies included in the review. A meta-analysis could not be performed because the included studies were heterogeneous and data from randomized clinical trials were unavailable.

Results Most studies support the ameliorative potential of NAC against a number of diabetes-associated complications, including oxidative stress. We discuss future prospects, such as identification of additional molecular mechanisms implicated in diabetes-induced cardiac damage, and highlight limitations, such as insufficient studies reporting on the comparative effect of NAC with common glucose-lowering therapies. Information on the comparative analysis of NAC, in terms of dose selection, administration mode, and its effect on different cardiovascular-related markers is important for translation into clinical studies.

Conclusions NAC exhibits strong potential for the protection of the diabetic heart at risk of myocardial infarction through inhibition of oxidative stress. The effect of NAC in preventing both ischemia and non-ischemic-associated cardiac damage is also of interest. Consistency in dose selection in most studies reported remains important in dose translation for clinical relevance.

Abbreviations

AKT	Protein kinase B
AMPK	5′ AMP-activated protein kinase
Bak	Bcl-2 antagonist/killer 1

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40256-018-0275-2) contains supplementary material, which is available to authorized users.

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RED YEAST RICE

- Red yeast rice: take at bedtime – most effective. Most cholesterol metabolism happens at night.
- HDL particles are much smaller than LDL particles. There can be 4 or more ApoA-1 proteins on each HDL particle. HDL metabolism is more complicating and less understood than LDL. HDL brings cholesterol back to liver.
- apoA-1 is primarily made in liver and some in gut.
- CETP – cholesterol ester transfer protein. Takes cholesterol out of HDL. People with CETP deficiency have very high HDL-C (>100 mg/dl)
- SR-B1 receptor on liver binds HDL, removes cholesterol and sends HDL particle back out into circulation. People who lack SR-B1 have very high HDL-C, bc they can't unload cholesterol from HDL. Increases risk of CVD.

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HDL

- How to optimize HDL cholesterol: (quality over quantity)
- Exercise. Makes largest difference. More than diet and other lifestyle changes.
- Gallbladder optimization
- Olive oil. Nuts. Lycopene. EPA 1800mg
- Anthocyanin (a polyphenol: Bio Cyanidins. Red, purple and blue fruits and vegetables.
- Resveratrol. Curcumin.
- Vasodilation is dependent on presence of intact endothelium. L-Arginine shown to be precursor for synthesis of nitric oxide by vascular endothelial cells.

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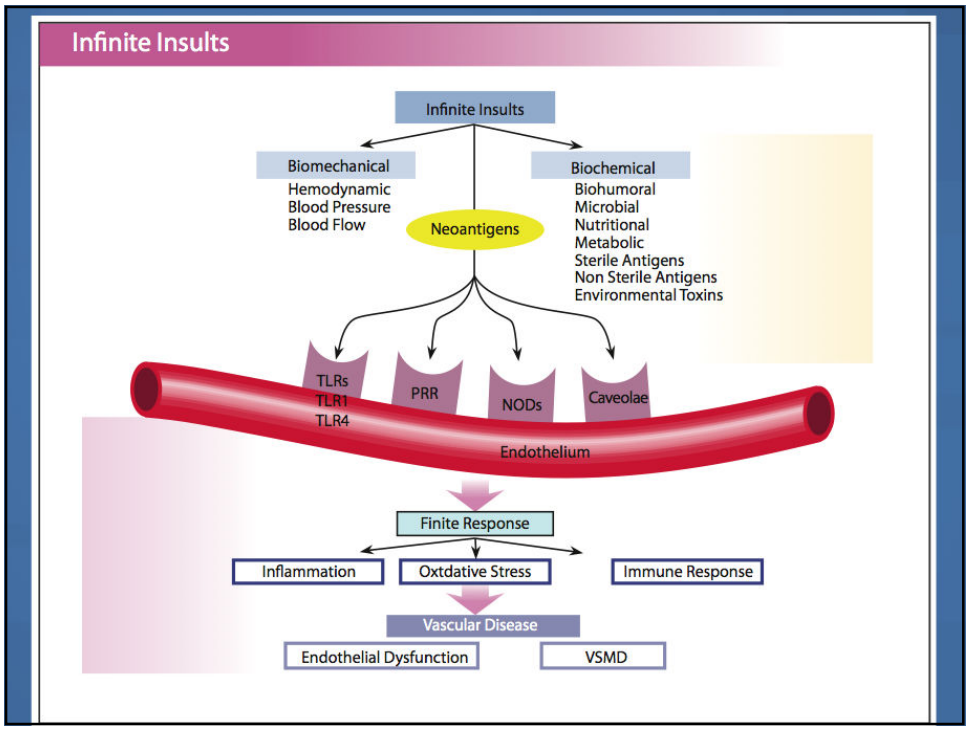
Infinite Insults
Infinite Insults
Biomechanical
Hemodynamic
Blood Pressure
Blood Flow
Neoantigens
Biochemical
Biohumoral
Microbial
Nutritional
Metabolic
Sterile Antigens
Non Sterile Antigens
Environmental Toxins
TLRs
TLR1
TLR4
PRR
NODs
Caveolae
Endothelium
Finite Response
Inflammation
Oxtdative Stress
Immune Response
Vascular Disease
Endothelial Dysfunction
VSMD

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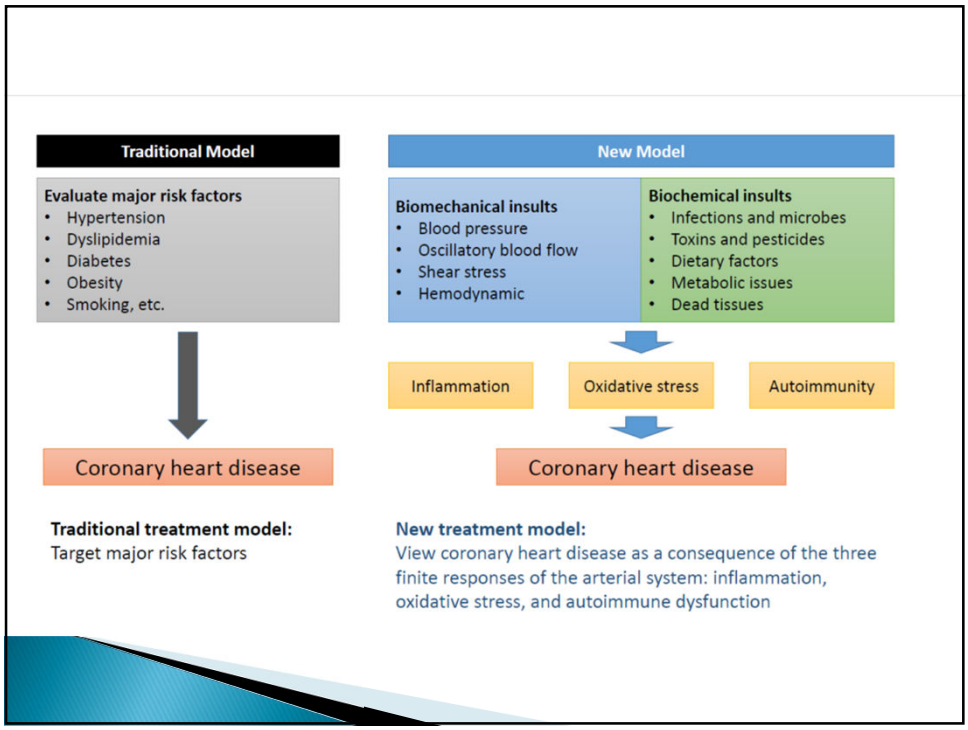
Traditional Model
Evaluate major risk factors
• Hypertension
• Dyslipidemia
• Diabetes
• Obesity
• Smoking, etc.
Coronary heart disease
Traditional treatment model:
Target major risk factors
New Model
Biomechanical insults
• Blood pressure
• Oscillatory blood flow
• Shear stress
• Hemodynamic
Biochemical insults
• Infections and microbes
• Toxins and pesticides
• Dietary factors
• Metabolic issues
• Dead tissues
Inflammation
Oxidative stress
Autoimmunity
Coronary heart disease
New treatment model:
View coronary heart disease as a consequence of the three finite responses of the arterial system: inflammation, oxidative stress, and autoimmune dysfunction

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Cholesterol/Dyslipidemia

3 Finite Responses
Inflammation (I)
Oxidative Stress (OS)
Immune Response or Dysregulation (IRD)

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NITRIC OXIDE

- **Nitric oxide functions:**
- Inhibits activation, adhesion aggregation of platelets
- Decreased leukocyte adhesivity
- Causes vasorelaxation in smooth muscle cells
- Enhances oxygen delivery

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Triggers for endothelial cells dysfunction:

- Hypercholesterolemia
- Diabetes, metabolic syndrome
- Hypertension
- Sex hormone imbalances
- Aging
- Oxidative stress
- Proinflammatory cytokines
- Infectious agents: bacterial endotoxins (leaky gut), viruses
- Environmental toxins
- Disturbed blood flow.

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Reduce endothelial dysfunction

- NitroGreens – Green leafy veggies – high concentrations of nitrates
- Nitric oxide production is enhanced with Vitamin C and polyphenols
- Chronic inflammation:
- CoQZyme 100 – lowers IL-6
- KappArest lowers IL-6
- Preventing metabolic disease:
- Berberine
- GlucoResolve

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MEDITERRANEAN DIET

1. Lowers BP
2. Improves serum lipids: lowers total cholesterol (TC), LDL, TG, increases HDL, lowers oxLDL and Lp(a), improves LDL size and lowers LDL-P to a less atherogenic profile;
3. Improves T2DM and dysglycemia;
4. Improves oxidative defense and reduces oxidative stress: F-2 isoprostanes and 8 hydroxy guanosine;
5. Reduces inflammation: lowers hsCRP, IL-6, soluble vascular adhesion molecule, soluble intercellular adhesion molecule;
6. Reduces thrombosis and factor VII after meals;
7. Improves BNP;
8. Increases nitrates/nitrites;
9. Improves membrane fluidity;
10. Reduces MI, CHD and CVA;
11. Reduces homocysteine.

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Cholesterol

"3 Step Detox" is a System.

Although 3 STEP DETOX was not designed specifically for cardiovascular it covers all the 7 factors discussed above.

Staff can administer it… Definite start/stop

See 3 Step Detox in the manual.

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Cholesterol/Dyslipidemia

Vegetarians have the lowest cholesterol, aborigine tribes have low cholesterol…

Why?

They eat plants.. Lots of plants

Big message for me on the cholesterol topic is to eat more plants…. not grains..

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METABOLICBIOME FUEL

- Several dietary and nutritional components have been shown to interrupt the inflammatory vascular receptors such as PRRs, NLRs and TLRs.20 These include:
- 1. Curcurmin (tumeric) blocks TLR 4, nucleotide-binding oligomerization domain (NOD) 1, and NOD 2;
- 2. Cinnamaldehyde (cinnamon) blocks TLR 4;
- 3. Sulforaphane (broccoli) blocks TLR 4;
- 4. Resveratrol (nutritional supplement, red wine, grapes) blocks TLR 1;
- 5. Epigallocatechin gallate (EGCG) (green tea) blocks TLR 1;
- 6. Luteolin (celery, green pepper, rosemary, carrots, oregano, oranges, olives) blocks TLR 1;
- 7. Quercetin (tea, apples, onion, tomatoes, capers) blocks TLR 1.

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OMEGA 3

- Omega 3 FA supplementation reduces all-cause mortality and MI in primary and secondary prevention trials, as well as many other CV outcomes. Omega 3 FAs decrease MI and CHD 18% more with concomitant use of statins, reduce stent restenosis, occlusion, plaque formation, coronary artery calcification, atherosclerosis, improve the lipid profile, lower glucose and improve insulin resistance and reduce BP.

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Cholesterol/Dyslipidemia

- Round up on wheat
- Common practice started in early 1990's
- Increases the drying process
- Increases the yield
- Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance Anthony SAMSEL and Stephanie SENEFF

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NUTRIENTS

- D-Ribose
- D-Ribose improves cardiomyopathy, systolic and diastolic CHF, acute and chronic CHD and angina, stabilizes and energizes the heart post MI and improves the postoperative ejection fraction in CABG.
- Vitamin K (Bio K Forte caps)
- K2 reduced CHD by 57% in the upper *versus* lower tertile and K2 reduced all-cause mortality by 26% in the upper *versus* lower tertile. K2 reduced aortic calcification by 52% in the upper *versus* lower tertile and reduced total mortality by 26%, but there was no association with K1
- Vitamin K2 is considered more important for vascular system health, if compared with vitamin K1.[131] The recommended dose of K2 MK7 is at least 100–150 mg per day.

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NUTRIENTS

- Carnitine
- L-carnitine reduced the all-cause mortality by 27%, ventricular arrhythmias by 65% and angina by 40% following an acute MI compared with placebo in 13 controlled trials of 3629 participants.
- Curcumin
- In a study of 121 patients, curcumin reduced MI post CABG from 30% to 13%. In addition, there was downregulation of SIRT1 (Sirtuin 1) after MI that was attenuated by curcumin pretreatment, which indicated that the activation of SIRT1 might be involved in the protective action of curcumin.

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NUTRIENTS

- Co-enzyme Q10 (CoQ Zyme 100 Plus)

- Co-enzyme Q10 (CoQ10) reduces post-MI reperfusion ventricular arrhythmias, improved LV function and total cardiac death.[137,138] In a double blind placebo controlled (DBRPC) trial of 144 subjects with acute MI, CoQ10 at 120 mg per day administered within the first 3 days of an MI resulted in significant improvements in the treated group in all parameters ($p < 0.05$):[138]
  - Angina (9.5% *versus* 25.3%);
  - Arrhythmias (9.5% *versus* 25.3%);
  - LVF improved (8.2 *versus* 22.5%);
  - Total cardiac events and death reduced at 15 *versus* 30.9% ($p < 0.02$).

- **Niacin:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4684109/

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Cholesterol/Dyslipidemia

- Gluten intolerance is a growing epidemic in the U.S. and, increasingly, worldwide.
- Celiac sprue is a more specific disorder, characterized by gluten intolerance along with autoantibodies to the protein, transglutaminase, which builds crosslinks in undigested fragments of gliadin, a major constituent of gluten (Green & Cellier, 2007).

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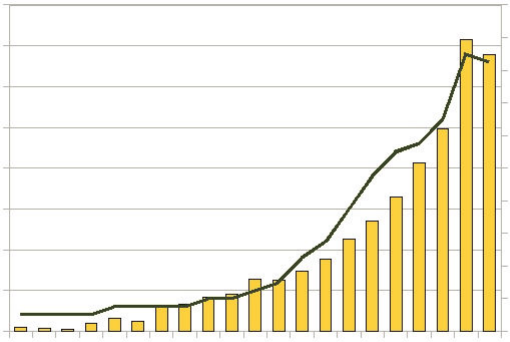
- ……..Represent …celiac incidence (hospital discharged records)
Bars…. Represent use of round up year by year 1990-2010



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Cholesterol/Dyslipidemia

Roundup lethally disrupts the all important shikimate pathway (CYP enzymes) found in liver and beneficial gut microbes which is responsible for synthesis of critical amino acids. -

Roundup significantly disrupts the functioning of beneficial bacteria in the gut which contributes to permeability of the intestinal wall and consequent expression of autoimmune disease symptoms

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Cholesterol/Dyslipidemia

CYP enzymes are critical to human biology because they detoxify the multitude of foreign chemical compounds, xenobiotics, that we are exposed to in our modern environment today.

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Cholesterol/Dyslipidemia

LDL cholesterol is only dangerous when it becomes modified i.e.

- **oxidized**
- **glycated**
- **acetylated**

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Cholesterol/Dyslipidemia

Oxidized Cholesterol and LDL

- BioProtect
- E-Mulsion 200
- Bio C Plus

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Cholesterol/Dyslipidemia

Use the Existing Cholesterol Marketing Hype

Opportunity to dig deeper and find the causes …..which will ultimately increase wellness.

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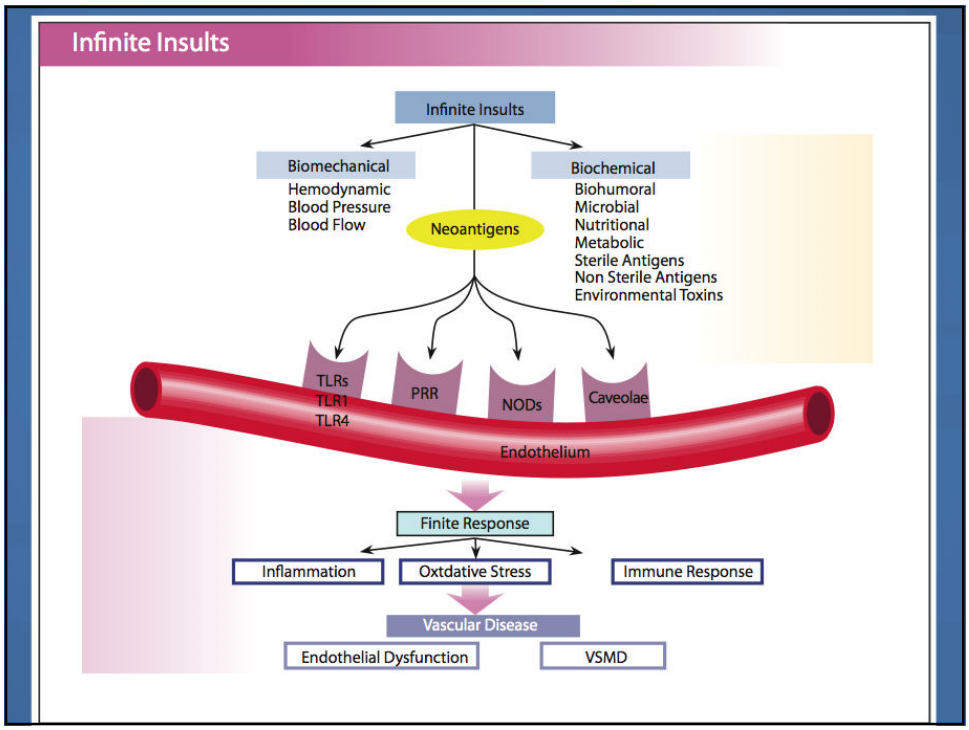
Infinite Insults
Infinite Insults
Biomechanical
Hemodynamic
Blood Pressure
Blood Flow
Neoantigens
Biochemical
Biohumoral
Microbial
Nutritional
Metabolic
Sterile Antigens
Non Sterile Antigens
Environmental Toxins
TLRs
TLR1
TLR4
PRR
NODs
Caveolae
Endothelium
Finite Response
Inflammation
Oxtdative Stress
Immune Response
Vascular Disease
Endothelial Dysfunction
VSMD

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