

Management of Hyperlipidemia— An Integrative Approach

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Integrative Medicine

The provision of health care with an attitude of mind that seeks preferentially those therapies or *therapeutic lifestyle changes* (“TLC”) that enhance one’s innate ability to recover from illness and maintain good health.

Integrative Medicine

Has no single healing paradigm or tradition and may have roots in Western, Asian, naturopathic, manual, functional, nutritional and behavioral medicine.

It is guided and informed by the evidence of scientific reasoning, systematic observation and contemporary medical research

“...what is special to modern western scientific medicine: it is one healing system among many yet it has, formally at least, in large measure broken with the traditional wisdom of the body. Herein lie its strengths and weaknesses.”

Porter, Roy: *The Greatest Benefit to Mankind—A Medical History of Humanity*; 1997; W.W. Norton, p.42

Lipid Management: First, Do No Harm

1. Assess individual risk *for the development of cardiovascular disease*
2. Consider **magnitude of benefit** (vs. harm) of any Intervention

Start with the Patient not the Lipid Profile

- Age/Gender
- HPI (Is there an illness?)
- Current Medical Problems (HTN, DM)
- Family History (Early death from CHD)
- Lifestyle/Habits (Cigs, Alcohol, Diet, Exercise)

Consider Classic Non-Lipid Risk Factors for Cardiovascular Disease

Clinical Cardiovascular Disease

Cigarette Smoking

Hypertension (BP > 140/90)

Family History of premature CHD

Diabetes mellitus

Older Age

Then look at the biomarkers

Biomarker: A measurement of a variable related to a disease that may serve as an indicator or predictor of that disease.

Biomarkers are parameters from which the presence or risk of a disease can be inferred, *rather than being a measure of the disease itself.*

Standard Lipid Biomarkers

- Total Cholesterol (TC)
- HDL Cholesterol (HDL)
- TC/HDL Ratio
- LDL Cholesterol
- Triglycerides

Additional (alternative? better?) Lipid Biomarkers

- LDL *pattern, size, density*
- LDL *particle number*
- Apolipoproteins (apoA1, apoB100)
- Lipoprotein(a)
- Lipoprotein-associated phospholipase A2

Additional (alternative? better?) Non-Lipid Biomarkers

- hsCRP
- B-type natriuretic peptide
- N-terminal pro-atrial natriuretic peptide
- Aldosterone
- Renin
- Fibrinogen
- D-dimer
- Plasminogen-activator inhibitor type 1
- Homocysteine
- Urinary albumin/creatinine ratio

Wang TJ et.al. **Multiple biomarkers for the prediction of first major cardiovascular events and deaths.** N Engl J Med 2006;355:2631-9

Recent Radical Simplification

“Lipid assessment in vascular disease can be simplified by measurement of either total and HDL cholesterol levels or **apolipoproteins** without the need to fast and without regard to triglyceride.”

The Emerging Risk Factor Collaboration.

Major lipids, apolipoproteins, and risk of vascular disease.

JAMA. November 11, 2009;302(18): 1993-2000

Current standard for assessing CVD risk: ATP III Guidelines from the NCEP

- ✓ Risk factors flow chart
- ✓ Framingham 10-year Risk of Coronary event assessment sheet

Determine: “Low, Intermediate or High” Risk

Emerging Emphasis—1.

- **Emphasis is on risk stratification for CVD not absolute lipid level**
- **Absolute CVD risk not the LDL level should be the trigger for initiating treatment**
- **Therapeutic decisions should be based on the risk the patient has for future cardiovascular events**

Ong HT **The statin studies: from targeting hypercholesterolemia to targeting the high-risk patient.** Q J Med 2005;98:599-614

Gaziano MJ and Gaziano TA **Simplifying the approach to the management of dyslipidemia.** JAMA 2009;302(18):2148-49

Highest Risk for Clinical CVD

- Known CHD—unstable (ACS)
- Known, stable CHD
- Documented coronary or non-coronary atherosclerotic disease
- Known Diabetes—especially with other coronary risk factors
- Multiple coronary risk factors

Emerging Emphasis—2.

- Once treatment initiated, **fixed LDL targets may not make sense**
- Meta-analyses of 90,000 patients in 14 primary and secondary prevention trials with statins: 20% reduction in CVD endpoints for 38 mg/dl reduction in LDL
- **Eliminate LDL targets; go for a % reduction?**
(i.e. Canadian guidelines: aim for 50%)

Gaziano MJ and Gaziano TA **Simplifying the approach to the management of dyslipidemia.** JAMA 2009;302(18):2148-49

Emerging Emphasis: Suggested Reading

1. Ong HT . **The statin studies: from targeting hypercholesterolemia to targeting the high-risk patient.** QJM 2005;98:599-614 [PMID:16006501]
2. Gaziano MJ and Gaziano TA **Simplifying the approach to the management of dyslipidemia.** JAMA 2009;302(18):2148-49
3. ALLHAT Officers and Coordinators....
Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288(23):2298-3007

“Old” and “Newer” Emphasis agreement: Isolated lipid abnormality

- Absence of other significant cardiac risk factors makes the ***overall magnitude of risk low***
- Potential benefit of an aggressive intervention also low.
- **Ideal candidate for therapeutic lifestyle changes (“TLC”) for the prevention of CHD.**

Therapeutic Lifestyle Changes ("TLC")

1. Specific dietary recommendations,
2. Use of plant stanols/sterols and soluble fiber to lower LDL cholesterol,
3. Weight reduction
4. Increased physical activity.

[Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program

(NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III).

JAMA. 2001 May 16;285(19):2486-97.]

Mediterranean Diet Pyramid

A contemporary approach to delicious, healthy eating

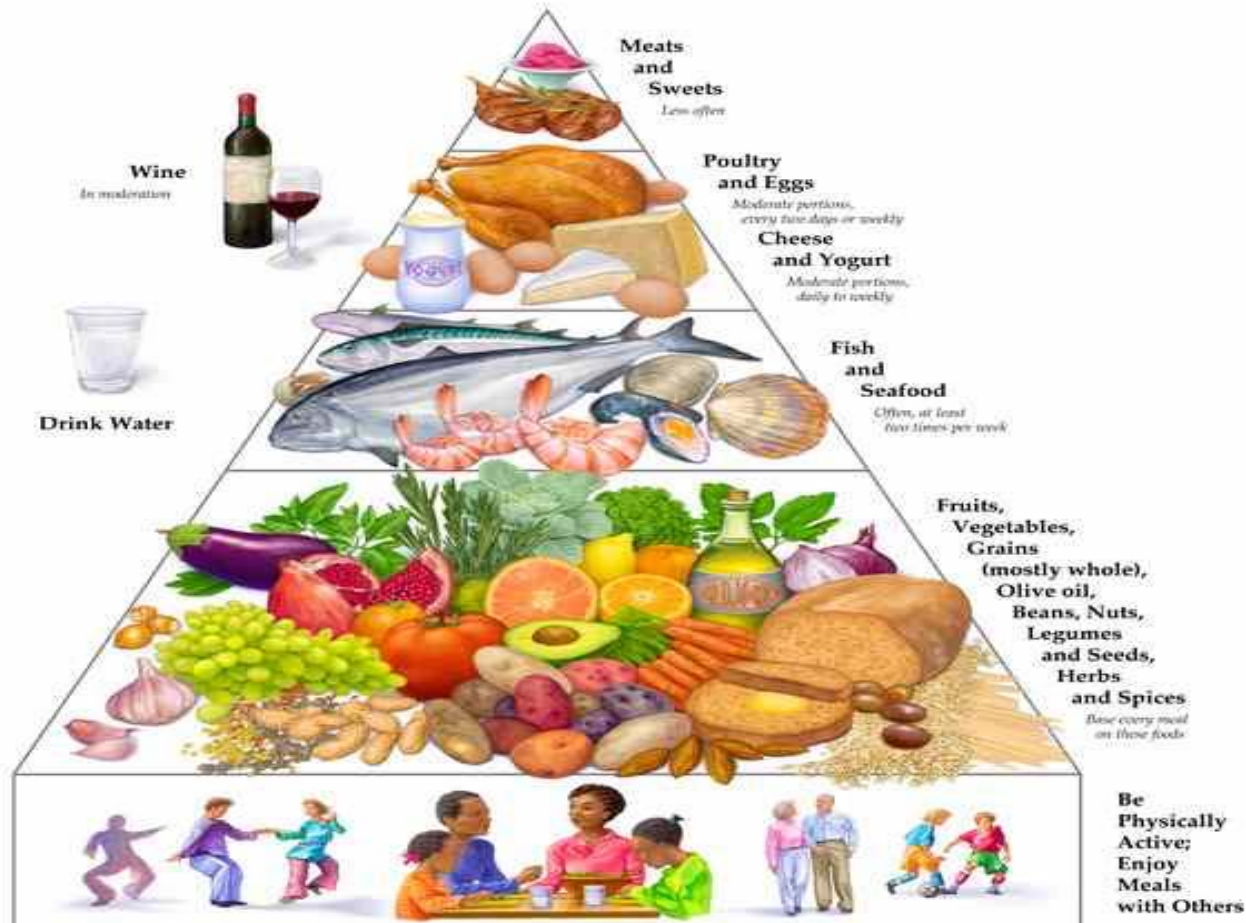


Illustration by George Middleton

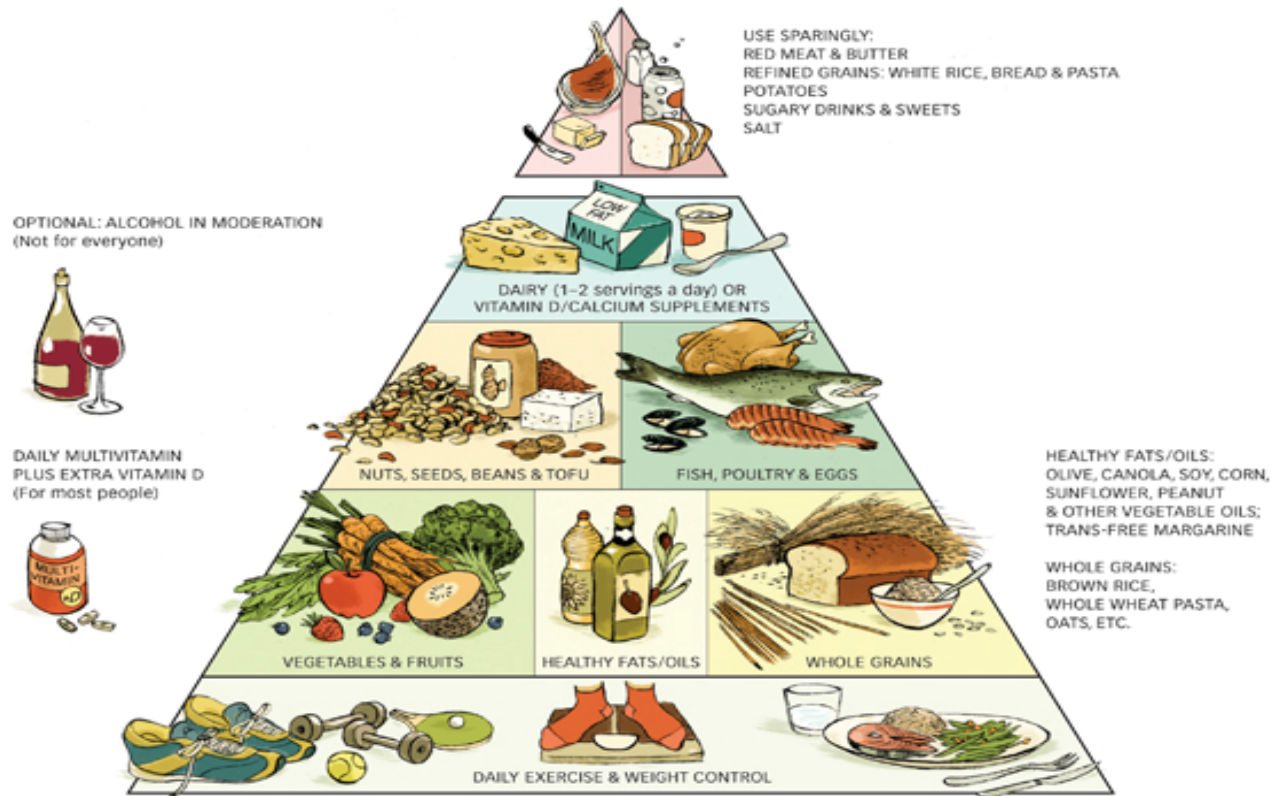
© 2009 Oldways Preservation and Exchange Trust. www.oldwayspt.org

Mediterranean Diet Research

- ❑ de Lorgeril M et. al. **Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease.**
Lancet 1994;343:1453-59
- Hu FB and Willett WC. **Optimal diets for prevention of coronary heart disease.**
JAMA. 2002;288:2569-2578
- ❑ Esposito K et. al. **Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial.** *Ann Intern Med.* 2009 Sep 1;151(5):306-14
- ❑ Dai J et. al. **Association between adherence to the Mediterranean diet and oxidative stress.** *Am J Clin Nutr.* 2008;88(5):1364-70
- ❑ Knoopman DS **Mediterranean diet and late-life cognitive impairment.**
JAMA, 2009; 302(6): 686-7
- ❑ Mitrou,PN et. al. **Mediterranean dietary pattern and prediction of all-cause mortality in a US population.** *Arch Intern Med.* 2007;167(22): 2461-2468

THE HEALTHY EATING PYRAMID

Department of Nutrition, Harvard School of Public Health



For more information, visit WWW.THE NUTRITION SOURCE .ORG

Basic Elements of a Good Diet

(Mediterranean Diet and the Lyon Diet Heart Study)

- ✓ Marked reduction of simple carbohydrates and animal fats
- ✓ substituting whole-grain foods, beans and nuts-- especially almonds, walnuts and hazelnuts;
- ✓ avoidance of hydrogenated oils substituting olive oil, peanut oil and canola oil;
- ✓ generous use of fruits and vegetables and the
- ✓ generous use of seafood or bean curd (tofu) as sources of protein.

Alpert JS. **What diet should we recommend to patients?** Am J Med. 2006 Sep;119(9):715-6.

Most People Need an Oil Change!

- ❑ Increased fish oils, olive oil , canola oil and the oils of certain nuts and flaxseed
- ❑ Increases the ratio of omega-3/omega-6 fatty acids.
- ❑ ***may reduce inflammation*** in a variety of tissues

Simopoulos AP. **Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases.**

Biomed Pharmacother. 2006 Nov;60(9):502-7. Review.

Diet Details: Stanols and Sterols

Plant sterols or stanols can lower LDL cholesterol by 10% in doses of 2--3 grams daily.

Benecol® spread-- 1.5 tsp. tid

Take Control™ --1 tbsp qd to bid

Cholest Off™--Capsules

Katan MB, Grundy SM et. al.

Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels.

Mayo Clin Proc. 2003 Aug;78(8):965-78. Review.

Nature Made

CHOLEST OFF

*Lowers
Cholesterol
Naturally*

COMPLETE

**Genetic
Dietary**

**Reduces
Dietary & Genetic
Cholesterol**

Clinically Proven¹
120 CAPLETS
DIETARY SUPPLEMENT
1800 mg of Natural Plant Sterols/Stanoles/Day

Diet Details: Fiber

1. Soluble Fiber (psyllium, oat , flaxseed, etc.)

- 2-3 teaspoons daily of Metamucil™ can lower LDL by 7%

[Anderson JW, et. al. **Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy. in the treatment of hypercholesterolemia.**

Am J Clin Nutr. 2000 Jun;71(6):1433-8.]

2. Flaxseed

- the richest known source of alpha linolenic acid (ALA)
- may reduce LDL cholesterol, blood pressure, post-prandial blood glucose markers of inflammation.

[Bloedon LT, Szapary PO. **Flaxseed and cardiovascular risk.** Nutr Rev. 2004 Jan;62(1):18-27. Review

Diet Details: Nuts

- o Substituting a handful of: Almonds, Walnuts, Pistachio nuts.
- o Can lower LDL 8-20%

Sabate J, et. al. . **Effects of walnuts on serum lipid levels and blood pressure in normal men.**
N Engl J Med. 1993 Mar 4;328(9):603-7.

Zambon D, et. al. **Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolemic men and women. A randomized crossover trial.**
Ann Intern Med. 2000 Apr 4;132(7):538-46.

Gebauer SK et. al. **Effects of pistachios on cardiovascular disease risk factors and potential mechanisms of action: a dose-dependent study.**
Am J Clin Nutr. 2008;88(3):651-9.]

Exercise: Cardio-respiratory Fitness

- Goes beyond the measurable improvements (blood pressure, lipids, body adiposity and insulin sensitivity).
- 150 minutes a week of moderate-intensity and 75 minutes of vigorous-intensity aerobic physical activity, or an equivalent combo
- Lesser amounts of physical activity may be beneficial
Perform in bouts of at least 10 minutes and spread throughout the week.
Muscle-strengthening activities-- involve all muscle groups --twice a week --- independent and additive benefits.

Franklin BA and McCullough PA. **Cardiorespiratory fitness: an independent and additive marker of risk stratification and health outcomes.**

Mayo Clin Proc. September 2009;84(9):776-779

Rx: Exercise + Medication even for stable CHD

- Optimal medical therapy + exercise training
- (20 minutes daily with one 60 minute session per week)
- superior to PCI in event-free survival and exercise capacity.

Hambrecht R, et.al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial.

Circulation. 2004 Mar 23;109(11):1371-8.

Turning Back the Clock: Adopting a Healthy Lifestyle in Middle Age

(Dana et. al. *Am J Med* (2007) 120,598-603)

- 1. Fruits/Vegetables—5 servings/day**
- 2. Exercise—2.5 hours/week (at least walking)**
- 3. Weight Control —(BMI= 18.5—30.0)**
- 4. No Smoking**

Next 4 years:

Decreased mortality (2.5% vs. 4.2%)

Decreased cardiovascular Disease (11.7% vs. 16.5%)

Dietary Supplements and the Management of Lipid Disorders

Why not a “Statin” for every Patient?

- Statin intolerant
- Prefer non-pharma + “TLC”
- Not high enough CHD risk
- Refuse pharmaceuticals

Rx: Niacin (Nicotinic Acid)

- Raises HDL, and lowers TC, LDL, TG
- Reduced mortality in a secondary prevention study*
- Long acting preparation (*Niaspan*) can be well tolerated
- Inositolized Niacin (hexaniacinate) **does not work!**
- Can ameliorate cutaneous flushing.
- Monitoring of LFT's, uric acid and FBS initially

*Canner PL, et. al.. **Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin.** J Am Coll Cardiol. 1986 Dec;8(6):1245-55.

Rx: Red Yeast Rice

- Contains plant sterols, isoflavones and naturally occurring statins (monacolins) including lovastatin.
- Trials using a dose of 2.4 --3.6 grams daily lasting at least 6 months have shown it to be well tolerated ***even in patients who had previously been statin intolerant***
- 20-25% reductions in LDL cholesterol.

Becker DJ et. al. **Red yeast rice for dyslipidemia in statin-intolerant patients.** Ann Intern Med. 2009;150:830-839.

Heber D, et. al. **Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement.** Am J Clin Nutr. 1999 Feb;69(2):231-6.

Red Yeast Rice (cont.)

- 5,000 patients in China with previous MI
- Followed for an average of 4.5 years
- Significant reduction in cardiac events and cardiovascular mortality.

Lu Z et. al. **Effect of Xuezhikang, an extract from red yeast rice, on coronary events in a Chinese population with previous myocardial infarction.**

Am J Cardiol. 2008;101(12):1689-93

Role of Coenzyme Q10

- Statins significantly reduce serum CoEnzyme Q10 levels.
- No definite side effects from this depletion
- Biologic plausibility, some experimental evidence --may be a contributor to statin-associated myopathy
- Replacement may ameliorate symptoms.
- Harmless even at high doses
- Reasonable to take 100 mg. daily

Caso G et. al. **Effect of coenzyme q10 on myopathic symptoms in patients treated with statins.**

Am J Cardiol 2007 May 15;99(10): 1409-12

Marcoff L, Thompson PD. **The role of coenzymeQ10 in statin-associated myopathy: a systematic review.**

J Am Coll Cardiol. 2007 Jun 12;49(23): 2231-7

Vitamin D

Check that 25(OH) Vit D level > 32 ng/mL

Deficiency—multiple issues

Might aggravate statin myopathy

Lee, JH et. al. **Vitamin D deficiency: an important, common and easily treatable cardiovascular risk factor?**

J Am Coll Cardiol 2008;52: 1949-56

Duell PB and Connor WE. **Abstract 3701: Vitamin D deficiency is associated with myalgias in hyperlipidemic subjects taking statins.**

Circulation 2008;118:S 470

Rx: Green Tea Extract

- *Teaflavin*TM formulation of a theaflavin-enriched green tea extract.
- If successful-- 16.4% drop in LDL
- No significant side-effects
- 90 day trial

Maron DJ, et. al. **Cholesterol-lowering effect of a theaflavin-enriched green tea extract: a randomized controlled trial.**

Arch Intern Med. 2003 Jun 23;163(12):1448-53

Rx: Colsevelam

- More potent bile acid sequestrant
- Better tolerated than the older agents
- Useful in combination with other lipid-lowering agents.

Davidson MH et. al. **Colsevelam hydrochloride (cholestagel): new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects.**
Arch Intern med. 1999; 159(16): 1893-1900.

- RCT-- daily dose of 3.75 g.
- 19% drop in LDL, 8% increase in HDL; no change in TG
- Compliance with treatment very high (93%)
- No constipation

Policosanol; Guggulipid: ***No benefit***

Policosanol—

- numerous trials at a single research institute in Cuba.
- independent German study confirmed safety even at high doses
- but no benefit over placebo in lowering cholesterol.

(Berthold HK, et. al. **Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized controlled trial.**

JAMA. 2006 May 17;295(19):2262-9.

Guggulipid—a

- herbal extract from the resin of the myrrh tree dates back to 600 BC in Asia.
- considerable popularity as a cholesterol –lowering agent,
- a purported effect of its bioactive guggulsterones (25 mg. tid) but data regarding efficacy is conflicting.
- Two randomized trials showed a 12% decrease in LDL; a RCT in 2003 showed no benefit:
- Not unreasonable to do a single therapeutic trial of 1,000-2,000 mg. of a 2.5% standardized extract taken tid for 8 weeks

Szapary PO, et. al. **Guggulipid for the treatment of hypercholesterolemia: a randomized controlled trial.**

JAMA. 2003 Aug 13;290(6):765-72.

Worth a therapeutic trial:

Artichoke Extract

Lycopene

Artichoke Extract

- Possible intervention to lower LDL based on some animal studies
- Human trial: Randomized controlled trial at 3 centers in Russia—1800 mg daily of artichoke dry extract for 6 weeks vs. placebo
LDL dropped 22.9% vs. placebo drop of 6.3%

Englisch W., et. al. **Efficacy of Artichoke dry extract in patients with hyperlipoproteinemia.**

Arzneim-Forsch/Drug Res. 2000;50:260-265

Bundy R, et. al. **Artichoke leaf extract (*Cynara scolymus*) reduces plasma cholesterol in otherwise healthy hypercholesterolemic adults: a randomized, double blind placebo controlled trial.**

Phytomedicine. 2008 Sep;15(9):668-75.

Lycopene

Silaste ML et. al.

Tomato juice decreases LDL cholesterol levels and increases LDL resistance to oxidation

Br J Nutr 2007;98(6):1251-8

Fuhrman B et. al.

Hypocholesterolemic effect of lycopene and beta-carotene is related to suppression of cholesterol synthesis and augmentation of LDL receptor activity in macrophages.

Biochem Biophys Res Commun. 1997;233(3):658-62

Triglycerides 1.

Before seeing a lipid specialist

Check for secondary, reversible causes:

- Alcohol
- Obesity
- High fat / refined carbohydrate diet
- Physical inactivity
- Hypothyroidism
- Diabetes mellitus—Type 2
- Meds: OCP's, ERT, Thiazides, Beta-blockers.....

Triglycerides 2.

- **Cardiac risk:** Many subgroups-- etiologies and lipoprotein patterns
(? Apo B levels to help distinguish the more benign Familial Hypertriglyceridemia from Familial Combined Hyperlipidemia), etc.....
- **Rx: Fish oils (3,000--9,000mg daily) +/- Phytosterols (2 grams/daily)**
Niacin (Nicotinic acid)
Pantethine (form of Vitamin B5)—900 mg/daily
- **Rx: Fibrates (Fenofibrate),**
Statin
Statin (Pravastatin) + Fenofibrate
Statin + Niacin (Nicotinic acid)
- Beware **Pancreatitis—if TG >1,000 mg/dl** (Unlikely below 2,000)

Brunzell JD. **Clinical practice. Hypertriglyceridemia.** N Engl J Med. 2007 Sep 6;357(10):1009-17. Review.

Micallef MA, Garg ML. **The lipid-lowering effects of phytosterols and (n-3) polyunsaturated fatty acids are synergistic and complementary in hyperlipidemic men and women.** J Nutr. 2008 Jun;138(6):1086-90.

Looking Ahead

Use of Vitamin K2

(Vitamin K1--Phylloquinone)

Vitamin K2--Menoquinones)

- subtypes MK-7, MK-8, MK-9 may affect risk of CVD
- Lack may promote vascular calcification

Gast GC et. al. **A high menaquinone intake reduces the incidence of coronary heart disease.** Nutr Metab Cardiovasc Dis. 2009 Feb 28 [Epub]

Geleijnse JM et. al. **Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study.** J Nutr. 2004;134(11): 3100-5

Look for novel biomarkers *that make a clinical difference*

- Lipid and Non-Lipid
- Measures of **Inflammation** ?
- Measures of **Oxidative stress** ?
- Undiscovered **nutritional deficiencies**?
(Vit. D, Vit. K, etc.)

**Look for imaging studies
that make a clinical difference (?)**

- EBCT variants?—(currently for coronary calcium , cardiac function)
- SPECT variants?
- Cardiac PET scan variants?

Be ready to revise thinking!

“The historian who hopes to make sense out of the development of medicine cannot simply list its discoveries in the field, adding them up as if one grew spontaneously out of the other. These conquests have been made possible only by a never-ending struggle against entrenched error, and by an unflagging recognition that the accepted methods and philosophical principles underlying basic research must be constantly revised...

Disease is as old as life, but the science of medicine is still young.”

Porter, Roy: *The Greatest Benefit to Mankind—A Medical History of Humanity*; 1997; W.W. Norton, p.42 -3

(quoting a distinguished historian of medicine, Jean Starobinski)

Thank You For Listening