Dyslipidemia Non-pharmacologic Treatment. An Integrative and Evidenced Based Review

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The Endothelium Maintains Vascular Health

Dilatation
Growth Inhibition
Antithrombotic
Anti-inflammatory
Antioxidant

Constriction
Growth promotion
Prothrombotic
Proinflammatory
Pro-oxidant
The Role of Nutraceutical Supplements in the Treatment of Dyslipidemia
1. Intolerable adverse effects of anti-lipid drugs
2. Contraindications or allergic response to drugs
3. Perceptions of adverse effects of drugs
4. Personal preference for natural / alternative therapies
SPECTRUM OF NATURAL THERAPIES FOR DYSLIPIDEMIA

- **Nutrition**: Foods and “Designer Food” Substances
- **Nutraceuticals**: Vitamins, Antioxidants and Minerals
- **Herbs**
34 patients with dyslipidemia treated with three diets for one month each in random order

- Control Diet: very low saturated fat
- Diet 2: control diet plus lovastatin 20 mg
- Diet 3 (Portfolio): plant sterols, soy foods, almonds, viscous fibers, okra, eggplant
PORTFOLIO DIET RESULTS

- Control Diet: reduced LDL 8.5%
- Diet 2: reduced LDL 33.3% and TG 11%
- Portfolio Diet: reduced LDL 29.6% and TG 9.3%
Niacin Clinical Trials and CHD

- Coronary Drug Project reduced CHD
- HATS reduced CV events and coronary atheroma
- ARBITOR 2 has ns trend to reduce carotid IMT and increased HDL 7 mg% on 1000 mg/d with statin
- ARBITOR 3 had regression of carotid IMT and increased HDL 9 mg % (23%) at 12-24 months on 1000 mg/d with statin
Niacin Clinical Trials and CHD

- Oxford Niaspan Study: MRI showed regression of carotid plaque and increased HDL 23% in 12 months on 2000 mg/d with statin
- FATS, CLAS I, CLAS II, AFRS: Reduced progression of coronary atherosclerosis with colestipol
- Niacin with statin is superior to ezetimibe with statin to induce regression of Carotid IMT.
- AIM-HIGH: Statin with Niacin: No CVD reduction ?? Flawed study design
Preventing Niacin Flushing

- Start low dose and titrate slowly: 100 mg every week
- Take with food
- Take with apple, apple pectin, apple sauce
- Avoid alcohol
- Never interrupt treatment
- Take with baby aspirin
POLICOSANOL
(SACCHARUM OFFICINARUM)

- Sugar cane wax extract of 8 aliphatic alcohols: octacosanol (60%), triacontanol and hexacosanol plus five others (minor)
Policosanol Multicenter Trial
JAMA 2006;259: 2262
J Clinical Lipidology 2010;4:248

- 12 week DBPC trial in 143 subjects with dyslipidemia
- 5 groups with 10, 20, 40, 80 mg vs. placebo
- No change in LDL, TC, TG or HDL in any dose group vs placebo.
- Not recommended at this time
CHINESE RED YEAST RICE (MONASCUS PURPUREUS)

- **Lipid Effects**: “Statin Like” at 2400 mg at night
  - Reduce LDL ~ 22%
  - Reduce TC ~ 17%
  - Reduce TG ~ 12%
  - HDL - No change

- **Monacoline** are active ingredients, which inhibit cholesterol synthesis via HMG-CoA reductase (also omega 3 FA, MUFA, lovastatin hydroxy acid, isoflavones, isoflavone glycosides and plant sterols)
Multicenter: Study of RYR nutraceutical drink

J of Clinical Lipidology 2012;6: 150-158

- 59 subjects, DBPC for 8 weeks
- Niacin, phytosterol esters, l carnitine, vitamin C, CoQ 10 with or without 600 mg of RYR
- In the RYR supplement lipids improved:
  - TC fell 14%
  - LDL fell 17.8 %
• 5000 Chinese patients with previous MI received Xuezhikang, an extract of RYR at 600 mg for 4.5 years vs placebo
• Primary end point of MI and death
• LDL decreased 17.6% lower with RYR p< 0.001 and HDL 4.2% higher p<0.001
• 10.4 % frequency of primary end point in placebo vs. 5.7% in RYR. P<0.001 , a RR reduction of 45% and absolute reduction of 4.7%
• CV mortality decreased 30%  p<0.005
• Total mortality decreased 33%  p<0.0003
• No change in CVA
PLANT STEROLS

- Plant Sterols: B-sitosterol, campesterol and stigmasterol (4-desmethyl sterols of the cholestane series). Stanols (saturated).

- Lipids:
  - TC decreased 8%
  - LDL decreased 10%
  - HDL and TG - no change

- Anti-inflammatory: reduce CRP, IL6, TNF alpha, PLA 2 and fibrinogen
SOY

- 38 studies using 31 – 47 grams soy protein / day dose related and proportional to initial cholesterol levels
  - ↓TC 2- 9.3%
  - ↓ LDL 4-12.9%
  - ↑ HDL 0- 2.4%
  - ↑ TG 0- 10.5%
- Micellar lipid content and absorption decreased
- Fiber, isoflavones, phytoestrogens improve lipid profile
- Best reduction in dyslipidemic vs. normal
- Most reduction with enriched isoflavones
- Reduce HMG-COA reductase, SREBP, increase LDL receptors, and increases the antioxidant enzymatic activity of catalase and SOD.

(Am J Clin Nutr 1998; 68:1385S)
Am J Clin Nutr  2007; 85:1148
Arch. Int Med 2007;167:1060
J of Clinical Lipidology 2010;4:248
Atherosclerosis 2008;200:13
Nutrition Research 2011;31:922
GREEN TEA (EGCG)

- Catechins, especially EGCG, improve lipid profile, interfere with micellar solubilization of cholesterol in GI tract and reduce absorption
- Reduce FA synthase gene
- Inhibit HMG COA Reductase
- Increase mitochondrial energy expenditure
- Reduce oxidation of LDL and increase PON 1, paraoxonase, which protects lipoproteins from oxidation, upregulate the LDL receptor
- Decreases APO-B lipoprotein secretion from cells
- Improves FMD

Mol Nutr Food Res 2006; 50: 211
J Am Coll Nutr 2005:24: 342
J Nutr Biochem 2005 ;16: 144
J of Nutritional Biochemistry 2009:20: 816
Am J Clin Nutr 2011;93:506
GREEN TEA (EGCG)

- Mimics insulin action by activating similar pathways and increases PI3K to regulate gluconeogenesis. Reduces body fat
- In a rats study: TC reduced 37% (p < 0.05) Non HDL cholesterol reduced 25% (p < 0.05)
- Human Study: EGCG green tea extract at 224-674 mg per day or 60 oz green tea per day reduced LDL 13% and decreased postprandial TG by 15 to 29% and decreased remnant particles
- Reduce CHD and CVD
- Dose: 500 mg BID of EGCG or 60 to 100 oz of green tea/day


Mol Nutr Food Res 2006; 50: 211
J Am Coll Nutr 2005:24: 342
J Nutr Biochem 2005 ;16: 144
J of Nutritional Biochemistry 2009:20: 816
Am J Clin Nutr 2011;93:506
Br J Nutr 2011;7:1
J Am Coll Nutr 2008;27:209
EGCG stimulates NF-E2 related factor and heme-oxygenase -1 via caveolin – 1 displacement

J of Nutritional Biochemistry 2012;23:163-168

- EGCG activates Nrf2 and increased HO-1 expression and cellular production of bilirubin and decreased inflammation and improved oxidative defense.
- Displaces caveolin-1, increases nitric oxide and reduces endothelial inflammation.
MARINE OMEGA 3 FATTY ACIDS

- **RCCT**: Reduce CVD, CHD, MI, CVA
  - **DART**: 29% reduction in mortality in 2 years in 2,033 men post MI with fatty fish or fish oil supplements
  - **GISSI**: Prevenzione Trial – 11,324 patients for 3.5 years given EPA / DHA had 20% decrease in total mortality, 30% decrease in CV deaths and 45% decrease in sudden death
  - **Kuopio Heart Study in Finland**: Men with the highest quintile of omega 3 FA intake had 44% decrease in fatal or nonfatal CHD compared to lowest quantile (p = 0.014)
  - Reduces CHD progression and CABG occlusion
Japan EPA Lipid Intervention Study (JELIS trial)

- 18,645 patients
- Randomized to statin plus 1.8 grams of EPA/DHA vs statin alone
- 19% RRR in major coronary events and non-fatal MI
- 20% RRR in Stroke

Lancet 2007;369:1090
Atherosclerosis 2008; 200: 135
Stroke 2—8;39:2952
• Dose related changes in lipids with Krill Oil
• DHA and EPA are in form of double chain phospholipid structure.
• Also contains Vitamin E, A, D and astaxanthin.
• ORAC is 48 times that of fish oil.
• TG reduced: 1.0 gram 11%, 1.5 gram 12%, 2.0 gram 27.6%, 3.0 gram 26.5%
• LDL reduced: 1.0 gram 32%, 1.5 grams 35%, 2 grams 37.42%, 3 grams 39%
• HDL increased: 1g 44%, 1.5 g 43%, 2 g 55%, 3 g 60%
Epidemiological and clinical studies indicate that higher consumption of ALA is associated with reduced risk of CVD and CHD morbidity and mortality.

- Decrease TG and increased HDL
- Decrease IR and DM
- Decrease visceral obesity
- Reduced SBP
- Reduce HS CRP
- Increase ALA concentrations with little to no change in DHA or EPA
Chia Seeds (Salvia Hispanica): ALA
J of Nutritional Biochemistry 2012;23:153

- Richest botanical source of ALA which is 60% (wt/vol).
- Major dietary component of Mayan and Aztec populations.
- In rat study: decreased IR, visceral obesity, lipids, BP, hepatic steatosis, cardiac and hepatic inflammation.
- Inhibits steryl-CoA desaturase -1
- Dose: 25 grams per day
FLAX: ALA

- **Seven Countries Study:** \( \uparrow \text{ALA} = \downarrow \text{CHD} \)
- **Lyon Diet Trial:** 50 – 70% decrease in death and CHD at 4 years
  1 – 2 grams flax seed oil 80% ALA / day
- Flax seed, flax oil, canola oil, walnuts
• **Mechanisms**
  - Anti-inflammatory
  - $\uparrow$ eNOS / NO and reduced ED and BP
  - $\downarrow$ VMSH
  - Fiber (seeds)
  - SDG (Lignan Precursor): $\downarrow$ TC via 7 $\alpha$ hydroxylase, acyl CoA cholesterol transferase
  - Phytoestrogens
Meta-Analysis: 9 trials 14-40 grams of flax seed per day
- ↓ TC and LDL: 5 – 15%
- Lower TG up to 36%
- Lower Lp(a) up to 14%
- HDL: no change

(Circulation 2001; 103:1823 and 1999; 99:779)
(Eur J Clin Nutr 1993; 47:201)
40 Grams of dietary sesame reduces LDL-C by 9% decreases TG and increases HDL.

- Increases CAT, GPx, GSH and SOD
- Increases Vit A, C and E.
- Inhibits intestinal absorption
- Increased biliary excretion
- Decreased HMG-CoA reductase activity
- Upregulates LDL receptor gene
- Upregulates Cholesterol 7-alpha hydroxylase gene expression
- Upregulates SREBP-2 genes
TOCOTRIENOLS
Current Pharm Des 2011;July 21 Epub

- Inhibit cholesterol synthesis by post-transcriptionally suppressing HMG-CoA reductase activity by two post-transcriptional actions:
  - Increased controlled degradation of reductase protein
  - Decreased efficiency of translation of HMG-CoA reductase mRNA.

Metabolized by successive beta oxidation and then catalyzed by the cytochrome P450 enzymes CYP 3A4 and CYP 4F2
TOCOTRIENOLS
(continued)

Lipid Reductions
12 weeks diet + TRF$_{25}$ (p < 0.05)
(Nutr Biochem 1997; 8:290)

- ↓ TC 17%
- ↓ LDL 24%
- ↓ APO-B 15%
- ↓ PF4 14%
- ↓ TxB 31%
- ↓ Lp(a) 17%
- → HDL
- → APO A-I
- ↓ BS
PANTETHINE VS PANTOTHENIC ACID

- Pantothenic acid is the precursor to Coenzyme A
- Pantethine is the disulfide derivative of pantothenic acid and is metabolized to cystamine (SH)

PANTETHINE: 28 Clinical human trials with 646 patients
- Lowers TC 15% (up to 20.5% at 9 months)
  - Lowers LDL 20% and APO B (up to 27.6% at 9 months)
  - Increased HDL 8% and APO A-I
  - Lowers TG 33% (up to 36.5% at 9 months)
- Comparisons to fibrates showed similar reductions in lipids

- Reduces lipid deposition and fatty streak formation in aorta and coronary arteries
- Reduces intimal thickening in the aorta and coronary arteries.
- Reduces peroxidation of LDL-C
GUGULIPIDS

- Resin of mukul myrrh tree (Commiphora Mukul)
- Guggulsterones: active ingredients
- Increase hepatic LDL receptors, bile secretion and decrease cholesterol synthesis, FXR, BAR nuclear rec.
- Lipids: ↓ TC, ↓ TG, ↓ LDL, ↑ HDL (old studies)
GUGULIPIIDS
(continued)

- Dose: 50 – 75 mg guggulsterones / day divided doses
- RCCT in JAMA 103 patients for 8 weeks
  - ↑ LDL 4% – 5% (p = 0.1)
  - No change in TC, HDL, TG, VLDL
  - ↓ Lp(a)
  - ↓ HS-CRP
  Not recommended at this time

(Pharmacol Res 1990; 22:37)
(J Assoc Physicians India 1989; 37:323)
(Cardiovasc Drugs There 1994; 8:659)
(JAMA 2003; 290:765)
(Annual Rev Nutr 2003; 23:303)
Complement Ther Med 2005;13:279
Complement Ther Med 2009;17:16)
FIBER

- Mixed soluble fibers reduce TC, LDL and TG
- Average reduction in LDL is 10% in RCCT
- Reduce CVD and CHD
- Types: pectin, psyllium, B-Glucan, oat bran, guar gum, rye, glucomannan
- Alter hepatic cholesterol metabolism and synthesis by lowering hepatic cholesterol pools and shifting in bile acid synthesis and thus less for VLDL and LDL. Decreases acyl-coenzyme A cholesterol: acyltransferase activity
- Alter processing of lipoproteins in intravascular compartment by upregulating hepatic LDL receptors
- Increase catabolism of lipoproteins
- Decrease VLDL synthesis, reduce conversion of VLDL to LDL
- Reduces CETP activity
- DOSE: 30 to 50 grams per day of total fiber and at least 10 grams of soluble fiber.
GARLIC

- 13 placebo-controlled trials of 781 patients
  - Dose: 600 – 900 mg / day standardized extract
  - TC and LDL reduced 9-12% but results are varied with some studies showing no effect on any lipid

- Antihypertensive
- Fibrinolytic and anti-platelet
- Reduce oxLDL
- Decrease cholesterol absorption, inhibit HMG CoA reductase.
- Reduces coronary calcium and plaque progression in humans on statins. In DBPC trial of 23 patients over one year on aged garlic at 4 ml per day. Aged garlic CAC: 7.5+/− 9.4% vs Placebo 22.2+/−18.5%
- Active ingredients: Allicin, Ajoene, etc.

(Ann Intern Med 2000; 133:420)
(J Royal College Phys 1994; 28:39)
Arch Intern Med 2007; 167: 346-353
Life Sci 2009;85:211)
**CURCUMIN**

*J Nutritional Biochemistry* 2007;18: 113-119

- Phenolic compounds in tumeric and curry
- Induces changes in expression of genes involved in cholesterol homeostasis such as LDL-receptor mRNA, HMG CoA reductase, SREBP, cholesterol 7 alpha hydroxylase, PPAR and LXR
- Human study at 500 mg /day in 10 patients increased HDL 29% and decreased total cholesterol by 12%.

Pomegranate juice
Current Opinion in Lipidology 2010;21:163-4
Nutrition 2010;26:359

- Increases PON 1 in serum and binding to HDL and PON 2 in macrophages
- Anti-oxidant
- Removes oxLDL and other oxidized lipids in serum and arterial wall.
- Reduces glycosylated LDL
- Reduces carotid IMT
Citrus Bergamot

Fitoterapia November 2011;82:309
J Agric Food Chem 2010;58:10768
J Nat Prod 2009;72:1352

- 1000 mg per day lowers LDL 36%, TG 39% and increases HDL 40% in 30 days
- Active ingredients are naringin, neoeriocitrin, neohesperidin, poncerin, rutin, neodesmin, rhoifolin, melitidine and brutelidine
- Inhibits HMG COA reductase
- Reduce ROS and reduces oxLDL
- Increase cholesterol bile acid excretion
- Improves glucose and reduces weight
- Mixed high dose probiotics (billions of organisms: L. Acidophilus, Bifidobacterium, L. Deibrueckii Bulgaricus, S. Thermophilus
- In 4-8 weeks TC fell 9%, LDL 8%, TG 10%
- Precipitate bile salts, deconjugation to bile salts, incorporation of cholesterol into cell membrane and microbial assimilation of cholesterol.
Combined extractives of red yeast rice, bitter gourd, chorella, soy protein and licorice improve lipid profiles in metabolic syndrome


- 228 subjects in DBRPC trial
- Significant reductions in TC, \((p<0.001)\)
  - TG \((p<0.001)\) and LDL \((0.001)\) and DBP \((p< 0.001)\) and SBP \((p< 0.036)\) at 4 weeks.
The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials.

Clinical trials have reported lipid-lowering effects of berberine intake, but the findings have been inconsistent. The aim of this meta-analysis was to assess the safety of berberine and its effects on blood lipid profiles. A systemic review was designed, undertaken and reported in accordance with the PRISMA statement.

Eleven randomized controlled trials (including a total of 874 participants) were included in this study.

The final analysis showed that administration of berberine produced a significant reduction in total cholesterol (mean difference - 0.61 mmol/L; 95% confidence interval - 0.83 to -0.39), triglycerides (mean difference - 0.50 mmol/L; 95% confidence interval - 0.69 to -0.31), and low-density lipoprotein cholesterol (mean difference - 0.65 mmol/L; 95% confidence interval - 0.76 to -0.54) levels, with a remarkable increase in high-density lipoprotein (mean difference 0.05 mmol/L; 95% confidence interval 0.02 to 0.09).

No serious adverse effects of berberine have been reported. In conclusion, berberine may have beneficial effects in the control of blood lipid levels. However, the efficacy of berberine in treating hyperlipidemia should be further evaluated by more randomized controlled trials in a larger population of patients.
Effects of a nutraceutical combination (berberine, red yeast rice and policosanols) on lipid levels and endothelial function randomized, double-blind, placebo-controlled study

- In this single centre, randomized, double-blind, placebo-controlled study, 50 hypercholesterolemic patients (26 males and 24 females, mean age 55±7 years, total cholesterol 6.55±0.75 mmol/l, BMI 28±3.5) were randomized to 6 weeks of treatment with a daily oral dose of NC (25 patients) or placebo (25 patients).

- Evaluation of absolute changes from baseline showed significant reductions in NC versus placebo for C and LDL-C (C: −1.14±0.88 and −0.03±0.78 mmol/l, p<0.001; LDL-C: −1.06±0.75 and −0.04±0.54 mmol/l, p<0.001), and a significant improvement of FMD (3±4% and 0±3% respectively, p<0.05). After the extension phase, triglyceride levels decreased significantly from 1.57±0.77 to 1.26±0.63 mmol/l, p<0.05 and insulin sensitivity improved in a patient subgroup with insulin resistance at baseline (HOMA: from 3.3±0.4 to 2.5±1.3, p<0.05). No adverse effect was reported.
Figure 1

LDL-C (mmol/L)

0 4 8 12 16 20

weeks

Armolipid Plus Armolipid Plus

group A

group B
New Functional and Metabolic Medicine Approach to the Treatment of Dyslipidemia

- Reduce cholesterol absorption
  Plant sterols, soy, EGCG, flax seeds, sesame, garlic, fiber, ezetimibe.
New Functional and Metabolic Medicine Approach to the Treatment of Dyslipidemia

- Increase cholesterol bile excretion
  Resveratrol, citrus bergamot, fiber, probiotics, plant sterols, sesame and bile acid resin binders.
New Functional and Metabolic Medicine Approach to the Treatment of Dyslipidemia

- Decrease LDL particle number to below 900 and Apolipoprotein B to below 90 mg%
- Omega 3 fatty acids, niacin and aggressive statin use
New Functional and Metabolic Medicine Approach to the Treatment of Dyslipidemia

- Increase LDL size from small type LDL B (type 3 and 4) to large type LDL A

Niacin, omega 3 FA and plant sterols
New Clinical Treatment Approach for Dyslipidemia

- Identify and treat all secondary causes such as drugs, endocrine, metabolic and toxic problems.
- Identify and treat the metabolic and infectious endotoxemia.
  a. Chronic infections
  b. Nutritional causes
- Reduce inflammation, oxidative stress and immune dysfunction
- IBW, composition, body and visceral fat, ABCT exercise and optimal nutrition.
New Clinical Treatment Approach for Dyslipidemia

Treat beyond the lipid numbers to disrupt the atherogenic pathways. These supplements should be part of every treatment protocol for dyslipidemia to improve membrane physiology, reverse cholesterol transport and LDL modification among other effects:

- Omega 3 fatty acids
- Lycopene
- EGCG
- Resveratrol
- NAC
- Pomegranate
- Carnosine
- Curcumin
- Quercetin
Final Recommendations

- 10 servings of fruits and vegetables per day (6 veg and 4 fruit)
- 10 grams of mixed soluble fibers/day
- Gamma/delta tocotrienols 200mg/night with food.
- Pantethine: 450 mg BID
- Omega 3 FA with EPA/DHA at 3/2 ratio 2-4 grams/day
- Lycopene 20 mg per day
- Trans Resveratrol 250 mg per day
- NAC 500 mg twice per day
- Aged Garlic Kyolic standardized 600 mg twice per day
- Carnosine 500 mg twice per day
- Quercetin 500 mg twice per day
- Berberine 500 mg BID
Final Recommendations

- Niacin (nicotinic acid) 500 to 3000 mg per day as tolerated pretreated with ASA, food and applesauce.
- Red Yeast Rice 2400 to 4800 mg at night with food
- Probiotics standardized 15 billion organisms BID
- Curcumin: 500 mg twice per day
- EGCG: 500 mg BID or 60-100 oz green tea per day
- Plant Sterols: 1.6 to 3.0 grams per day
- Pomegranate Juice 8 oz per day with juice of one lemon
The Role of Nutraceutical Supplements in the Treatment of Dyslipidemia

The Mammalian Cell Mevalonate Cholesterol Pathway and PP (pyrophosphate)

- Pantethine and Sesame
  - HMG-CoA Reductase
    - Mevalonate-PP Decarboxylase
      - Squalene Synthase
        - Squalene
          - Squalene Epoxidase
            - Cholesterol
              - Farnesyl Transferase
                - Prenylated Proteins
        - Farnesyl-PP
          - All-trans Geranylgeranyl-PP
            - Ubiquinone
              - Geranylgeranyl transferase I, II
                - Tocotrienols
  - Mevalonate
    - Mevalonate-PP
      - Isopentenyl-PP
        - Geranyl-PP
          - Dimethylallyl-PP
            - Isopentenyl Adenosine
              - Dolichols
                - 2-cis Geranylgeranyl-PP
          - Geranylgeranyl transferase I, II
            - Tocotrienols
  - Acetyl-CoA
    - Acetoacetyl-CoA
      - HMG-CoA
        - Statins
          - Policosanol
            - Red Yeast Rice

The Journal of Clinical Hypertension