심혈관질환의 기능의학적 접근 및 치료

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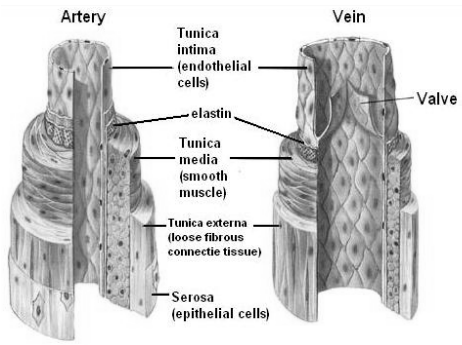
아주의대 가정의학과

Contents

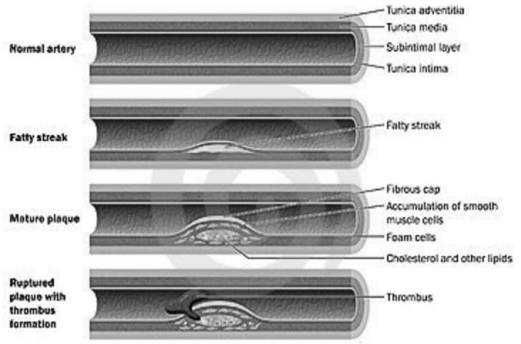
- Pathophysiology of atherosclerosis and vascular calcification
- Traditional Approach of ASCVD
- New options from Function medicine

Pathophysiology of atherosclerosis and vascular calcification

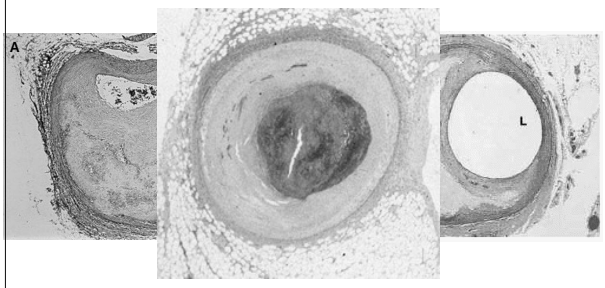
Anatomy of Blood vessels



Gross development of atherosclerosis



Which is more dangerous?

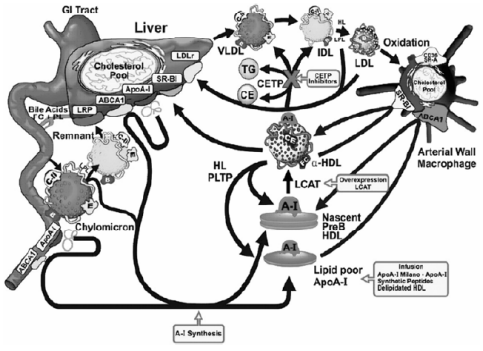


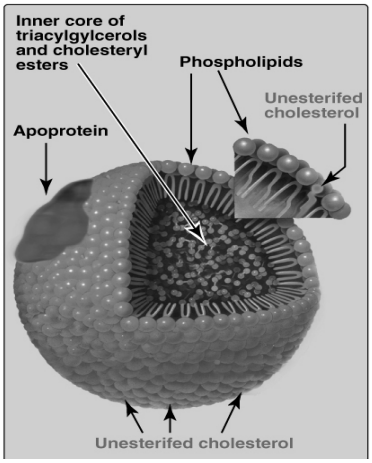
Lipoprotein Metabolism

Functions of Cholesterol in Body

- Membrane fluidity
- Synthesis of steroidal hormones
- Synthesis of vitamins – D, E
- Synthesis of Bile acid

Lipoprotein Metabolism
- overview -



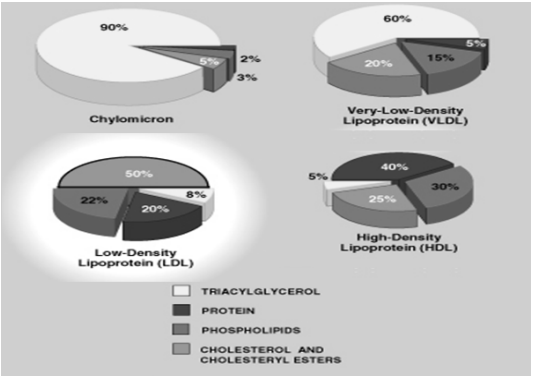


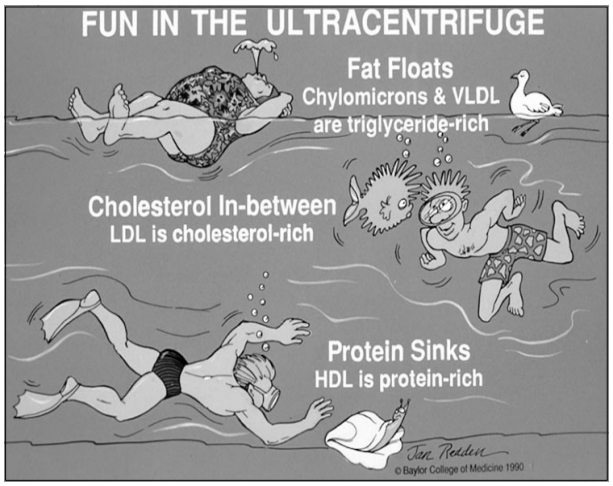
Structure of a Lipoprotein

Functions of a Apoprotein

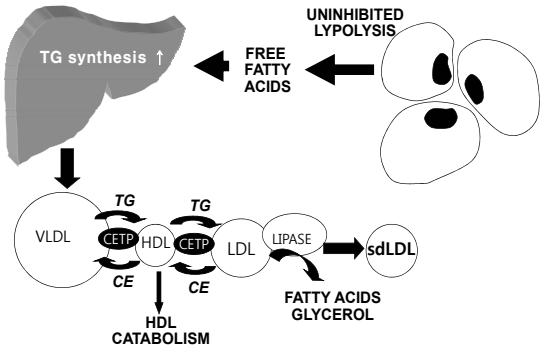
1. **Structural proteins**
2. **Activators**
3. **Recognition sites**

Composition of Lipoproteins





Dyslipidemia of Metabolic Syndrome



Intervention points 1

- Free Fatty Acid reduction
  - Calorie Restriction
  - Avoid fatty meal and CHO rich diet
  - High Fiber diet
  - Moderate exercise for at least 20 Min
- Endothelial dysfunction correction
  - L-arginine

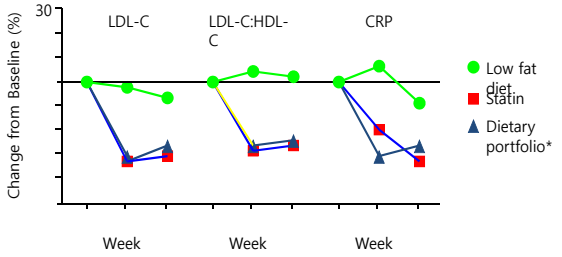
Dietary Adjuncts: Efficacy at Reducing LDL-C

Therapy	Dose (g/day)	Effect
Dietary soluble fiber	2-8	↓ LDL-C 5-10%
Soy protein	20-30	↓ LDL-C 5-7%
Stanol esters	1.5-4	↓ LDL-C 10-15%

Jones PJ. *Curr Atheroscler Rep* 1999;1:230-235
Lichtenstein AH. *Curr Atheroscler Rep* 1999;1:210-214
Rambjor GS et al. *Lipids* 1996;31:S45-S49
Ripsin CM et al. *JAMA* 1992;267:3317-3325

Diet Evidence: Effect on Lipid Parameters and CRP

46 dyslipidemic patients randomized to a low fat diet, a low fat diet and lovastatin (20 mg), or a dietary portfolio* for 4 weeks

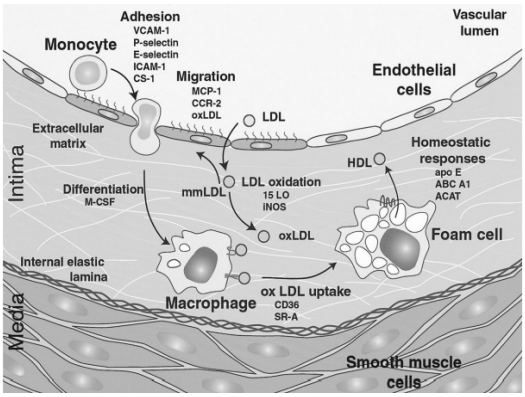


A diversified diet improves lipid parameters and CRP levels

*Enriched in plant sterols, soy protein, viscous fiber, and almonds

Jenkins DJ et al. *JAMA* 2003;290:502-10

Initiation of Atherosclerosis

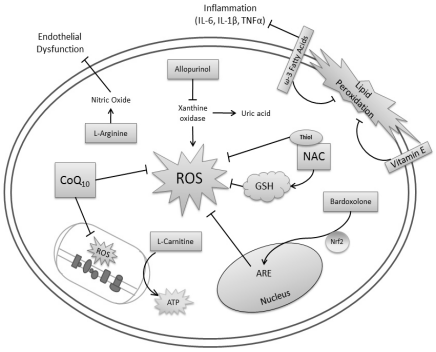


Glass and Wiztum. Cell. 2001: 104(4); 503–516

Intervention points 2

- Prevention of oxidation of LDL
  - Antioxidants
  - Avoid fatty meal and CHO rich diet
  - Chelation
  - Moderate exercise for at least 30 Min 3/week
- Reduction of inflammation
  - Treatment of Peridontal diseases and Gut dysbiosis
  - Stress regulation
  - Aspirin

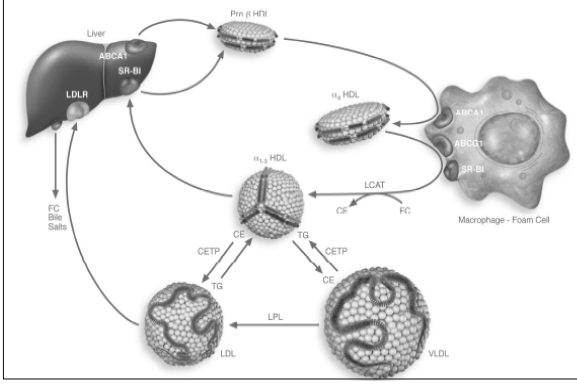
Action of antioxidants



Antioxidants prescription

- Vitamin C 500 – 1000mg
- Vitamin E 400 IU
- Vitamin A 400 IU
- Vitamin D 800 IU
- Selenium 50 μg

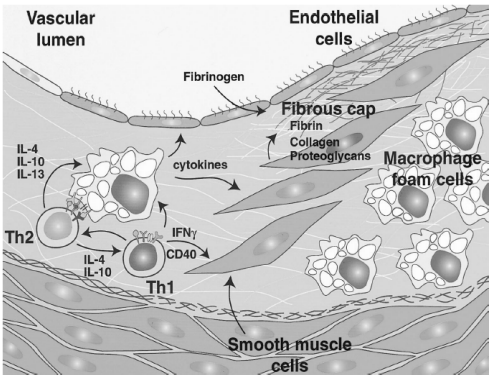
HDL metabolism



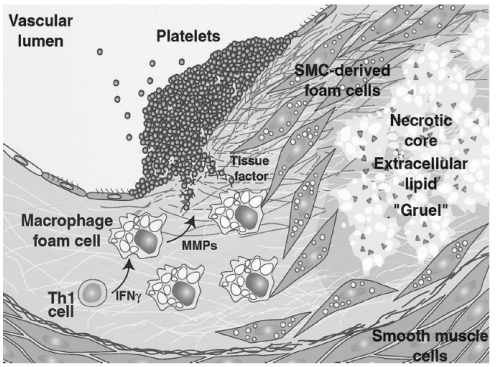
Intervention points 3

- Increase HDL and Cholesterol efflux
  - Protein
  - Niacin
  - Omega3
  - Weight reduction
  - Moderate exercise for at least 30 Min 3/week

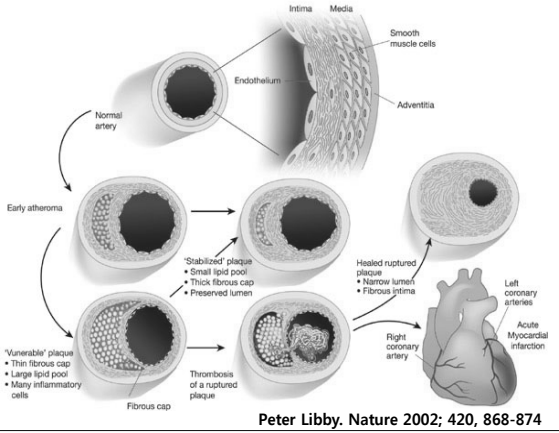
Formation of A-Plaque



Plaque rupture and Thrombosis



Natural history of Atheroma



Peter Libby. Nature 2002; 420, 868-874

Intervention Points 4

- Anti-inflammatory diet
  - Vegetarian diet
  - Fish
  - Olive oil
  - licorice
- Anticoagulants
  - Aspirin
  - Zincomin
  - Gallic
  - Onions
  - Ginger

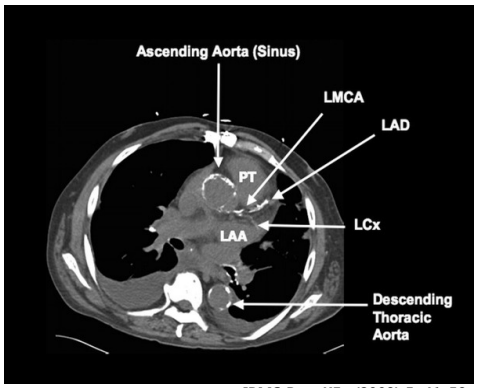
Anti-inflammatory Foods

use these in smoothies, soups and salads

alfalfa	cilantro	oregano
alfalfa grass	coconut - fresh	parsnips
almonds	cucumber	peas - fresh
almond butter	cumin seeds	pumpkin
artichokes	egg plant	red beets-fresh
asparagus	endive	red cabbage
avocado	fennel seeds	red radish
barley grass	figs	rutabaga
basil	garlic - fresh	savoy cabbage
bee pollen	ginger - fresh	sea vegetables
bell peppers	green cabbage	seaweed
black radish	horseradish root	sesame seeds
bok choy	jicama	spelt
brussels sprouts	kale	spinach
buckwheat	kamut	sprouted seeds
cabbage	leakes	squash
caraway seeds	lemon - fresh	sweet potato
carrots	lentils	tomatoes
cauliflower	lettuce	turnip
cayenne pepper	limes - fresh	wheat grass
celery	mustard greens	white radish
cherries	navy beans	yam
chives	onion	zucchini

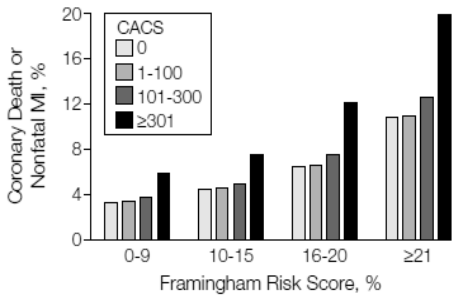
www.elementalfit.com

Calcification of arteries



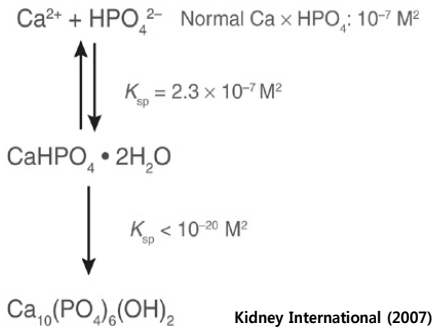
IBMS BoneKEy (2008) 5, 41–58

CVD risk and CACS
- MESA study-

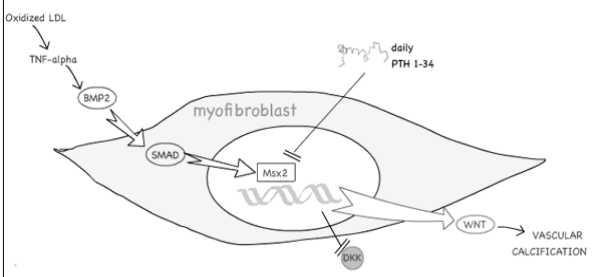


JAMA. 2004;291(2):210-215

A two-step process of ESC : formation of amorphous calcium phosphate spontaneous conversion to apatite.



Kidney International (2007) 71, 282–283

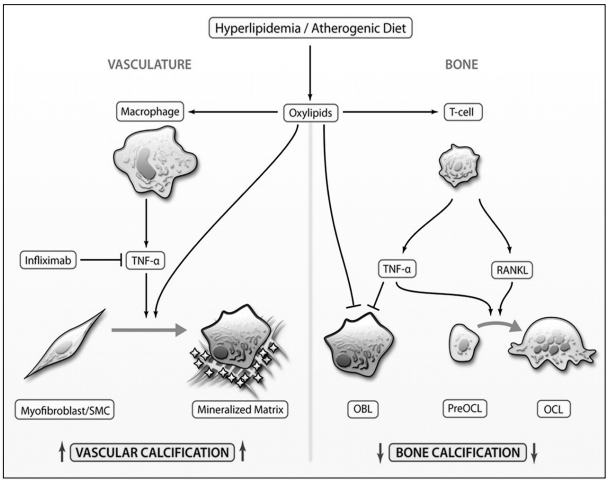


In adventitial cells of the aorta and cardiac myofibroblasts, the transcription factor Msx2 is expressed following exposure to oxidized LDL. This upregulates Wnt ligands and downregulates Dickkopf, increasing Wnt signalling which results in cardiovascular calcifications. In a mouse model, this process is inhibited by daily teriparatide (1-34 PTH) which inhibits expression of Msx2.

Shao JS, Cheng SL, Pingsterhaus JM, Charlton-Kachigian N, Loewy AP, Towler DA. Msx2 promotes cardiovascular calcification by activating paracrine Wnt signals. J Clin Invest. 2005;115(5):1210-20..

Intervention Points 5

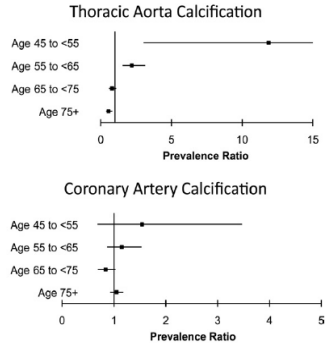
- Avoid hypercalcemia
  - Osteoporosis treatment
  - Avoid calcium supplement
- Vitamin K supplement



Intervention Points 6

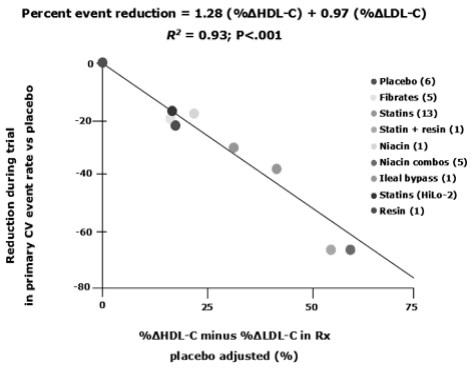
- Avoid hypercalcemia
  - Osteoporosis treatment
  - Avoid calcium supplement
    - Daily requirement less than 900mg
    - Vitamin D supplement
  - Daily PTH injection

Vascular calcification and bisphosphonate use



J Am Coll Cardiol. 2010;56(21):1752-1759

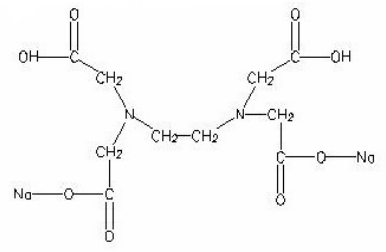
Lipid Drug Classes Effects on LDL-C and HDL-C Change Compared to Primary Clinical Trial Outcome.



Brown BG *et al.* J Clin Lipidology. (2007) 1:88-94.)

Intervention Points 7

Disodium EDTA



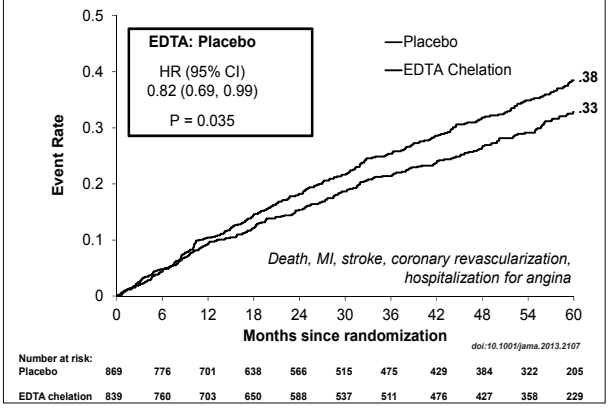
CHELATION INFUSION

- disodium EDTA, 3 grams, adjusted downward based on eGFR
- ascorbic acid, 7 grams
- magnesium chloride, 2 grams
- potassium chloride, 2 mEq
- sodium bicarbonate, 840 mg
- pantothenic acid, thiamine, pyridoxine
- procaine, 100 mg
- unfractionated heparin, 2500 U
- sterile water to 500 mL

PLACEBO INFUSION

- normal saline, 1.2% dextrose, 500 mL

TACT Primary Endpoint Results

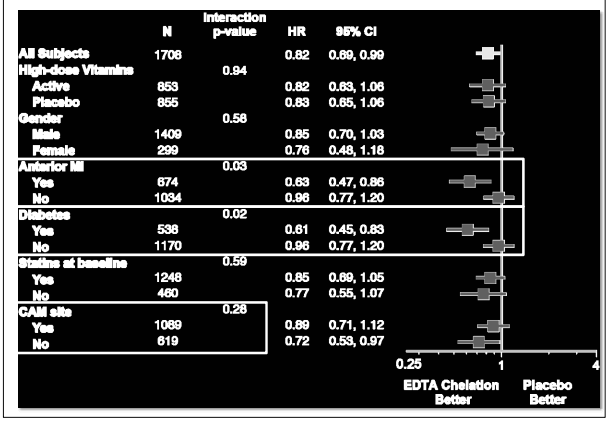


Comparison of Primary Endpoints

	EDTA Chelation (N= 839)	Placebo (N= 869)	Hazard Ratio (95% CI)	P Value
Primary Endpoint	222 (26.5%)	261 (30.0%)	0.82 (0.69,0.99)	0.035
Death	87 (10.4%)	93 (10.7%)	0.93 (0.70, 1.25)	0.642
Myocardial Infarction	52 (6.2%)	67 (7.7%)	0.77 (0.54, 1.11)	0.168
Stroke	10 (1.2%)	13 (1.5%)	0.77 (0.34, 1.76)	0.531
Coronary revascularization	130 (15.5%)	157 (18.1%)	0.81 (0.64, 1.02)	0.076
Hospitalization for angina	13 (1.5%)	18 (2.1%)	0.72 (0.35, 1.47)	0.359

doi:10.1001/jama.2013.2107

Results from Subgroup analysis



Side Effects and Safety

- 79 patients (38 EDTA, 41 placebo) discontinued infu sions due to AE or side effect
- In 611 (1.1%) instances, short infusions by at least 1 5 minutes were administered. No serious adverse e vents were reported
- 4 unexpected severe adverse events possibly or def initely related to study therapy
  - 2 placebo arm, 1 death
  - 2 chelation arm, 1 death

Take Home Message

- LDL 보다는 Small sized LDL, Oxidized LDL이 중요하다. 이를 조절하기 위한 노력이 중요하다.
- Vascular Calcification은 ASCVD의 중요한 위험인자이다.
- Chelation은 Vascular Calcification을 줄이는 좋은 Option이다.