

Oxysterols

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Oxysterols

- ✦ Oxysterols are 27-carbon products of cholesterol oxidation which have been shown to possess many potent and diverse biological activities in vitro, several of which may implicate them in the initiation and/or development of atherosclerosis.
- ✦ Various oxysterols have been detected in appreciable quantities in human tissue and fluids, including human plasma, atherogenic lipoproteins and atherosclerotic plaque.

Oxysterols

- ✦ Oxysterols are oxygenated derivatives of cholesterol and noncholesterol (plant) sterols.
- ✦ Enzymatic and nonenzymatic oxygenation of cholesterol results in a number of circulating and cellular derivatives which can have a variety of activities.
 - Sphingolipid metabolism
 - Platelet aggregation
 - Apoptosis
 - Protein prenylation
 - Bile acid oxysterol precursors
- ✦ Oxidized sterols in the diet are absorbed by the intestine and incorporated into chylomicrons and they increase atherosclerosis (have been identified in the arterial wall)

Nomenclature of Common Oxysterols

Abbreviation	Common name(s)	Origin
✦ Cholestenone	Cholestenone	E
✦ α -EPOX	Cholesterol α -epoxide	N
✦ β -EPOX	Cholesterol β -epoxide	N
✦ α -TRIOL		N
✦ 4aOH	4 α -Hydroxycholesterol	N
✦ 4 β OH	4 β -Hydroxycholesterol	N
✦ 6 β OH	6 β -Hydroxycholesterol	N
✦ 7 α OH	7 α -Hydroxycholesterol	E/N
✦ 7 β OH	7 β -Hydroxycholesterol	N
✦ 7 α OOH	7 α -Hydroperoxy-cholesterol	N
✦ 7 β OOH	7 β -Hydroperoxy-cholesterol	N
✦ 7K	7-Ketocholesterol, 7-oxocholesterol	N
✦ 7 Kdiene		N
✦ 24OH	24-Hydroxycholesterol	E
✦ 25OH	25-Hydroxycholesterol	E:N
✦ 27OH	26-Hydroxycholesterol, 27-Hydroxycholesterol	E

Oxysterols

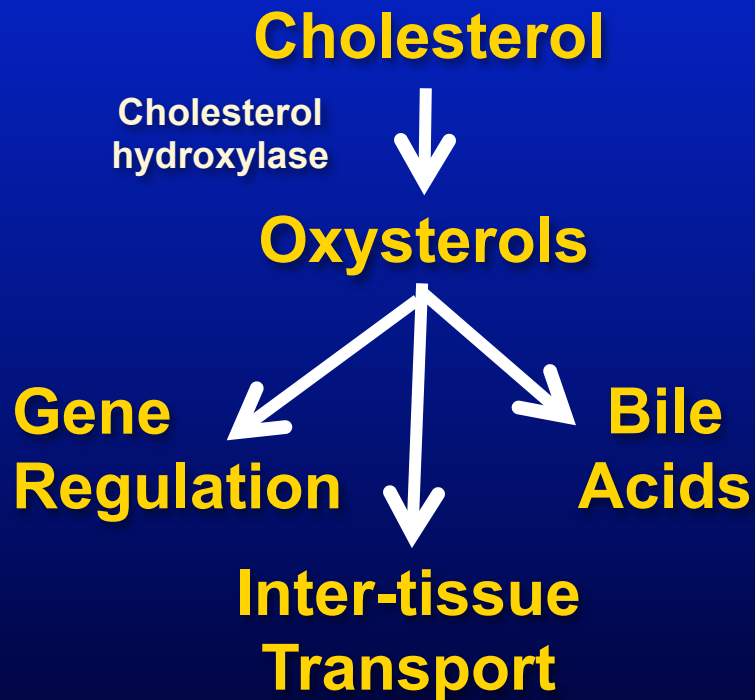
- ✦ Dietary sources of oxysterols are cholesterol-rich foods (dairy, egg, meat products), especially those products which are heated in air during processing or are stored for lengthy periods.
- ✦ But oxysterols at ppm levels are more usually encountered in cholesterol-rich foods (e.g.. The most commonly detected oxysterols in foods are the major products of cholesterol autoxidation: 7K, 7aOH, 7bOH, a-EPOX, and b-EPOX.

Oxysterols

- ▶ While undergoing many of the same reactions as cholesterol, such as being esterified by cells and in plasma, certain oxysterols exhibit far more potent effects than cholesterol per se
- ▶ Oxysterols perturb several aspects of cellular cholesterol homeostasis (including cholesterol biosynthesis, esterification, and efflux), impair vascular reactivity and are cytotoxic and/or induce apoptosis.
- ▶ Oxysterols appear to be concentrated in foam cells and early lesions compared to advanced lesions and are at least two orders of magnitude higher than plasma levels.
 - ▶ How much of those non-enzymic oxysterols in plaque arise from the diet and how much from free radical reactions in vivo is not known.

Oxysterols

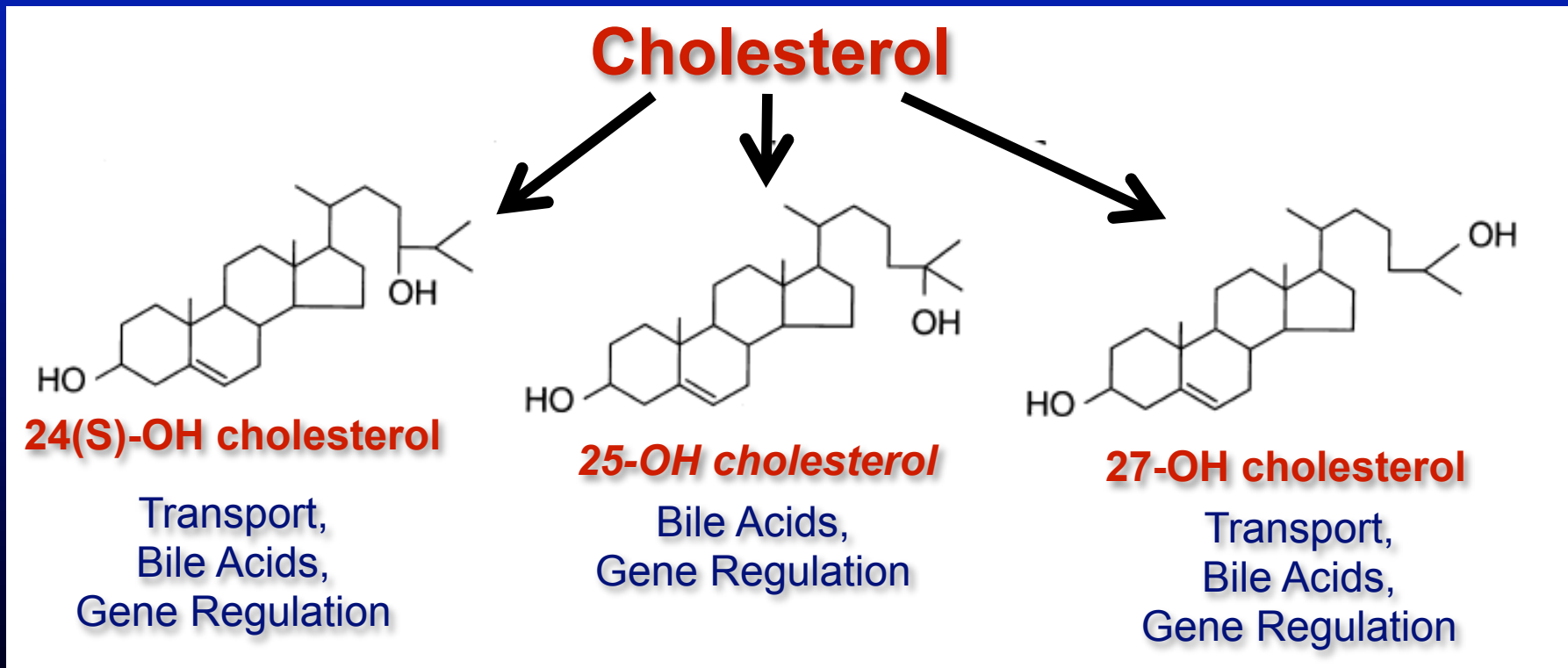
► Derivatives of cholesterol with a hydroxyl group on the side chain, which play several roles in lipid metabolism.



► Oxysterols regulate the expression of genes that participate in both sterol and fat metabolism, serve as substrates for the synthesis of bile acids, and are intermediates in the transfer of sterols from the periphery to the liver.

Oxysterols

- ▶ Oxysterols in plaque are derived both non-enzymically, either from the diet and/or from in vivo oxidation, or (e.g. 25 or 27-hydroxycholesterol) are formed enzymatically during cholesterol catabolism.

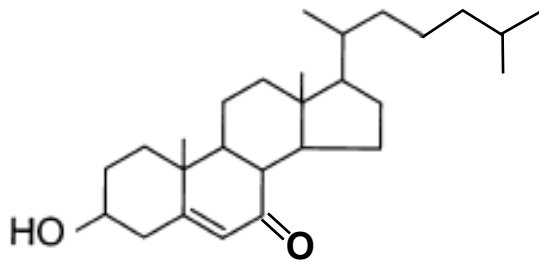


Oxysterols

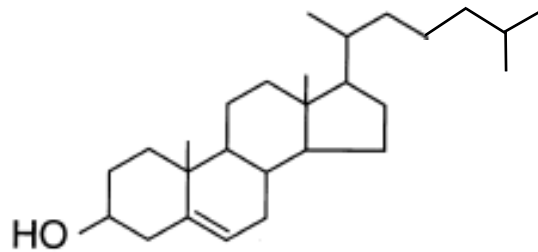
Dietary oxysterols can be absorbed and are transported in chylomicrons.

It is also possible that some oxysterols are hydrolyzed in the gut epoxides and that selective metabolism of some oxysterols may occur during absorption of dietary sterols by the intestinal epithelium.

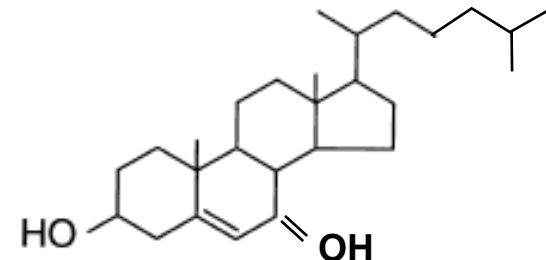
Cholesterol



7-ketocholesterol

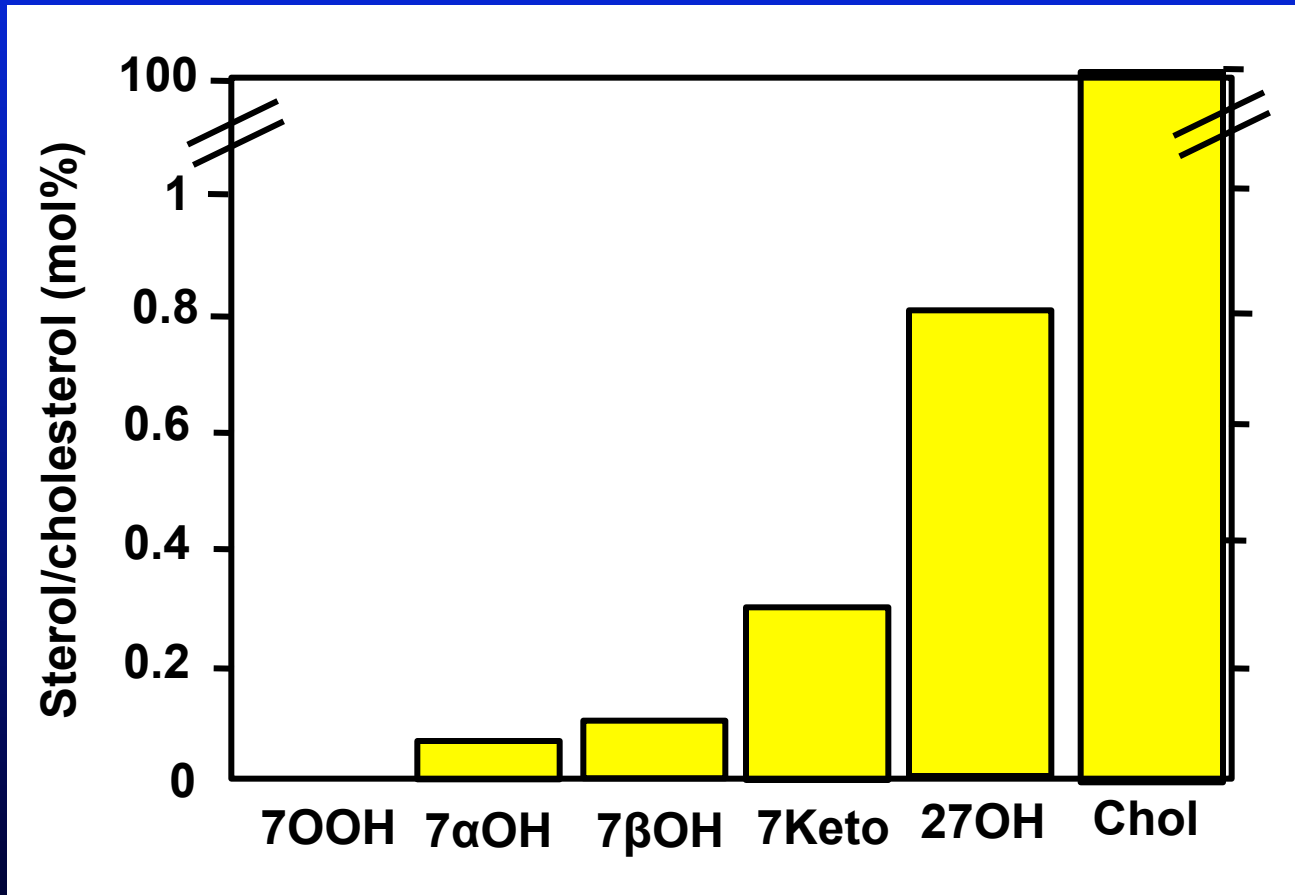


3-OH cholesterol



7-OH cholesterol

Oxysterol Levels in Human Carotid Plaque

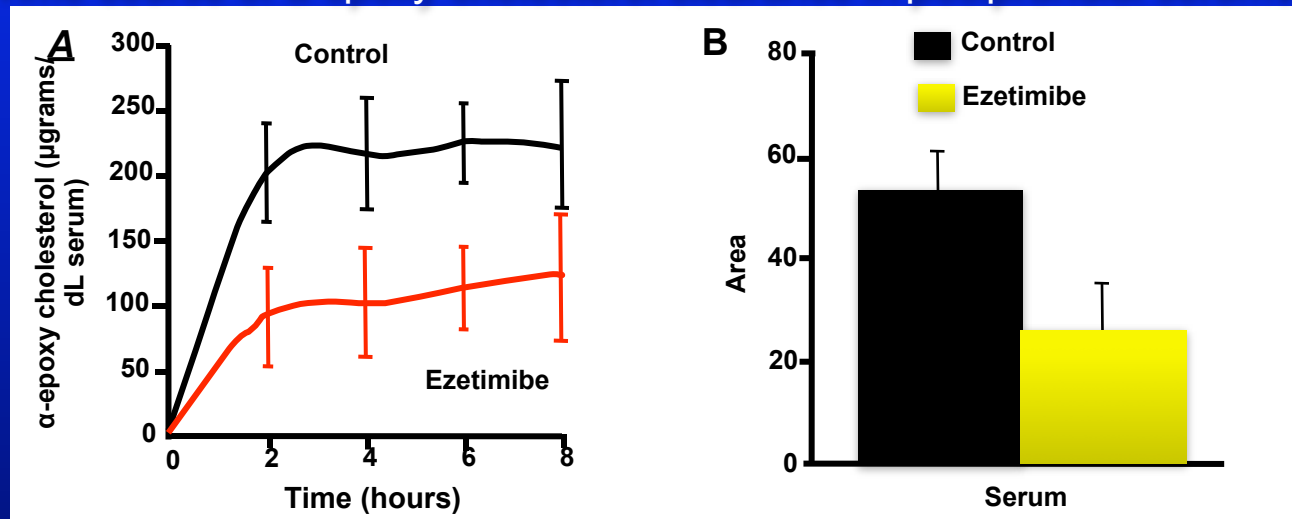


27-hydroxycholesterol & CV Effects of Estrogen

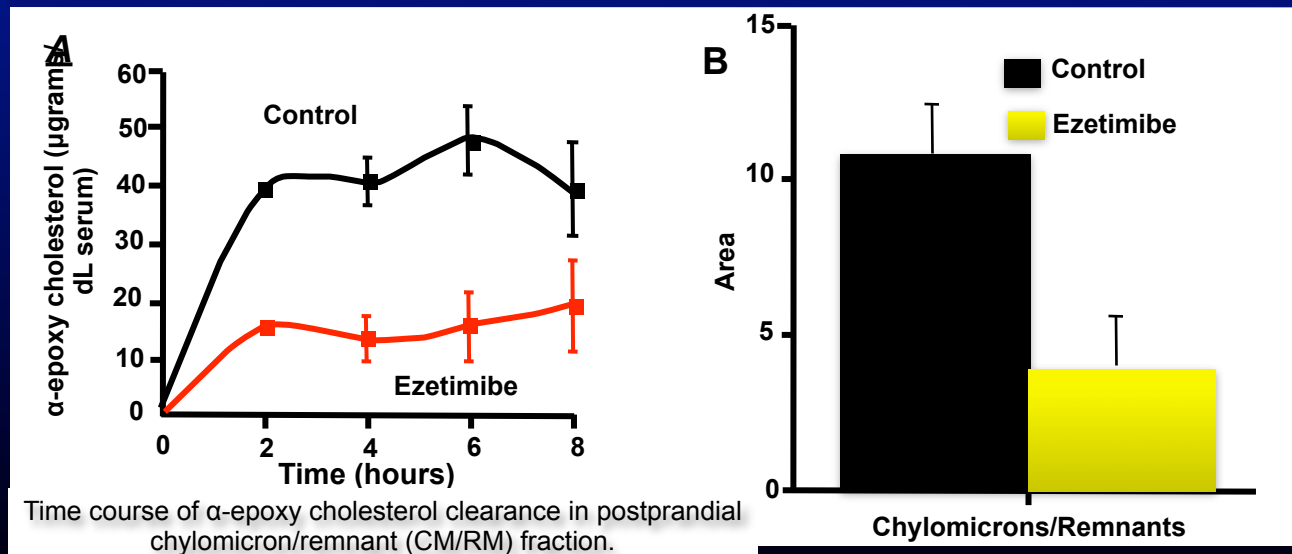
- ✦ 27-OH cholesterol is a competitive antagonist of estrogen receptor action in the vasculature, by inhibiting both transcription and non-transcription mediated estrogen-dependent production of nitric oxide by vascular cells
- ✦ 27HC functions as an endogenous SERM and is a contributing factor in the loss of estrogen protection from vasculature tissue

Ezetimibe and Oxysterols

Time course of α -epoxy cholesterol clearance in postprandial serum.



A: Subjects were administered a test meal containing α -epoxy cholesterol (400 mg). The levels of α -epoxy cholesterol in serum were determined before and after treatment with ezetimibe (10 mg/day for 30 days). B: The areas under the clearance curves were measured in arbitrary units, and the significance of the difference of areas under the curve was determined. $P = 0.010$.



Time course of α -epoxy cholesterol clearance in postprandial chylomicron/remnant (CM/RM) fraction.

A: Five control subjects were administered a test meal containing α -epoxy cholesterol. The levels of α -epoxy cholesterol in CM/RM were determined before and after treatment with ezetimibe (10 mg/day for 30 days). B: The areas under the clearance curves were measured in arbitrary units, and the significance of the difference of areas under the curve was determined. $P = 0.019$.