

Cholesterol-lowering medication issues in inflammatory myopathies

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Drug-induced myopathies

- Necrotizing – statins, beta blockers, propofol, ETOH, heroin, cocaine, amphetamines, opioids
- Autophagocytic – chloroquine, amiodarone
- Antimicrotubular – colchicine, vincristine
- Mitochondrial – HIV medications
- Inflammatory – L-tryptophan, cimetidine, anti-epileptic drugs
- Myofibrillar – emetine, elinafide
- Steroids
- Inflammatory myopathy – L-tryptophan, D-penicillamine, Cimetidine, L-Dopa, phenytoin, lamotrigine,
- Acute quadriplegic – steroids, NMJ blockers, critical illness myopathy
- Hypokalemic – laxatives, diuretics, lithium

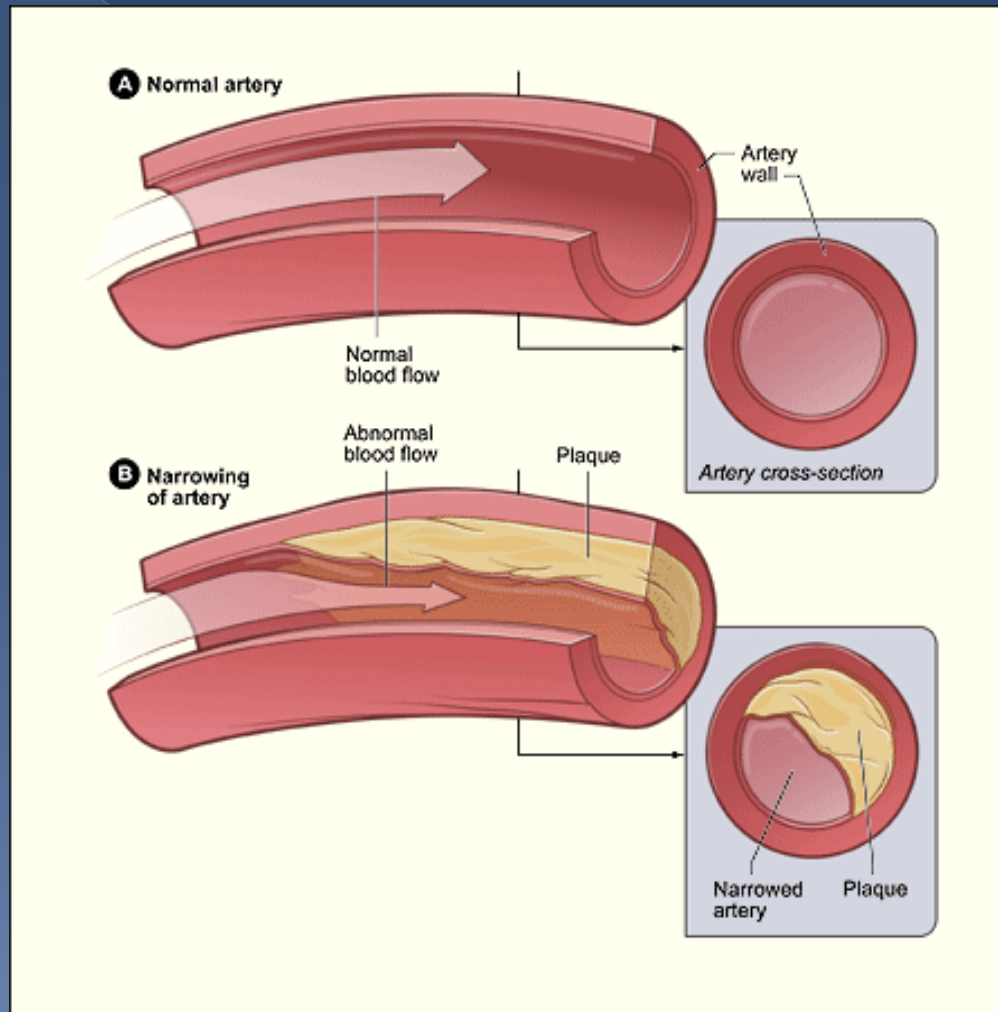
Cholesterol

- Steroid as a structure
- Best known for its association with atherosclerosis
- Biochemically is a precursor of important other steroids:
 - > Bile acids
 - > Adrenal gland hormones
 - > Sex hormones
 - > Cardiac glycosides
 - > D vitamins
- Important constituent of the brain tissue, cellular membrane and others

Cholesterol

- Fractions
 - > Total
 - > Bad – LDL, VLDL, IDL
 - > Good - HDL
- Prolonged elevation of LDL, VLDL and IDL cholesterol result in atherosclerosis
- Inverse relationship between HDL levels and coronary artery disease and stroke
- HDL acts as a scavenger of cholesterol

Atherosclerosis



Sources of cholesterol

● Dietary cholesterol

- > 50% absorbed in the intestines
- > 50% excreted in the stool
- > Modification
 - Drugs decreasing absorption
 - Decrease dietary intake

● Liver biosynthesis

- > Part excreted via bile
- > Part circulates in blood to tissues
- > Modification
 - Inhibited by statins

Risk factors for stroke

Factors that cannot be changed

- **Age** - after age 55
- **Family history**
 - Increased with parent, grandparent, sister or brother with strokes
 - Genetic disorders like CADASIL (Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy), caused by a gene mutation
- **Race** - African-Americans with higher risk of death from a stroke (higher risks of high blood pressure, diabetes and obesity)
- **Sickle cell disease** - genetic disorder, African-Americans, Hispanics

Risk factors for stroke

Factors that cannot be changed

● Sex (gender)

- In most age groups, more men than women will have a stroke in a given year
- At all ages, more women than men die of stroke.
- Use of birth control pills and pregnancy pose special stroke risks for women.

● Prior stroke, TIA or heart attack

- TIAs are strong predictors of stroke.
- One or more TIAs increases the risk for stroke almost 10 times
- Heart attack increases the risk for a stroke

Risk factors for stroke

Factors that can be changed

- **High blood pressure** — leading cause of stroke
- **Tobacco**- oral contraceptives + smoking increases stroke risk
- **Diabetes mellitus** - Independent risk factor
 - Diabetics also have high blood pressure, high blood cholesterol and are overweight
- **Carotid or peripheral artery disease** — narrowed by fatty deposits
- **Atrial fibrillation**, coronary disease, heart failure, congenital defects

Risk factors for stroke

Factors that can be changed

- **High blood cholesterol** -low HDL (“good”) cholesterol - risk factor for stroke in men, not enough data for women
- **Poor diet**
 - > Saturated fat, trans fat and cholesterol raise blood cholesterol
 - > High sodium (salt) can increase blood pressure
 - > Excess calories leads to obesity
 - > Five or more servings of fruits and vegetables per day may reduce the risk of stroke
- **Physical inactivity and obesity** — increase risk of high blood pressure and cholesterol, diabetes, heart disease and stroke

Cholesterol-lowering drugs

- ◎ All can cause toxic muscle toxicity
 - > Statins (HMG-CoA reductase inhibitors)
 - Lovastatin, pravastatin, simvastatin etc.
 - > Fibric acid derivatives – branched fatty acid esters
 - Myopathy develops from 2-3 mo to 2 yrs after onset of treatment
 - Lopid (gemfibrozil), Atromid-S (clofibrate)
 - > Niacin
 - Similar mechanism as statins
 - Viatime B3, nicotinic acid
 - > Ezetimibe
 - Inhibits intestinal absorption of cholesterol
 - Zetia
 - Usually resolves within a few weeks

Statins

- Have proven efficacy in preventing heart attack and death
- Most widely prescribed drugs worldwide
- Still underused – only 50% of those who would benefit are prescribed.
- 25% taking statins stop them within 6 mo
- 60% taking statins stop them within 2 yrs
- Main reason for stopping – patient and physician fear of myopathy

Definitions

- Myalgia – muscle weakness, soreness, tenderness, cramping, aching without elevation of creatine kinase (CK)
- Myositis – elevated CK $>10x$, w/wo above symptoms, w/wo inflammation on biopsy
- Rhabdomyolysis – severe widespread destruction of muscles, elevation of CK of $>10x$ of upper limit of normal, myoglobinuria, decreased renal function or failure

Statins

- Statin myopathy – more common in real world than in clinical trials
- Trials – 1-5%
- Observation studies 9-20%
- Pooled data from 30 randomized trials:

Findings	+ Statin	Placebo
Myalgia	0.3-33%	0-33%
CK elevation	0-0.6%	0-0.5%
Myositis	0.17%	0.15%
Rhabdomyolysis	0.02%	0.014%

Statin side effects

● Muscle pain and damage

- > Mild asymptomatic increase of CK
- > Soreness, tiredness (2-7%)
- > Weakness of muscles (0.1-1%)
- > Mild discomfort to severe pain and weakness
- > Rare - life-threatening muscle breakdown, rhabdomyolysis myoglobinuria (<0.5%), severe muscle pain, liver damage, kidney failure and death
- > Resolve from several days to several months
- > Several reports – development of DM and PM with statin use – not clear relation

Statin side effects

● Liver damage

- > Increased liver enzymes
- > If mild, continue to take the drug.
- > If severe, stop the drug. May try a different statin.
- > Gemfibrozil (Lopid) and niacin (Niacor, Niaspan), increase the risk of liver problems in combination with statins
- > Liver enzymes are tested before and/or after starting a statin
- > Contact MD if you have fatigue, weakness, loss of appetite, abdominal pain, dark urine, or jaundice

Statin side effects

● Digestive problems

- > Nausea, gas, diarrhea or constipation
- > Take statin before bed or with food to reduce digestive side effects

● Rash or flushing

- > Increased risk in combination with niacin (Simcor)
- > Aspirin before statin may help when indicated

● Increased blood sugar or type 2 diabetes

- > Small risk - FDA has issued a warning on statins that

● Neurological side effects

- > Reversible memory loss or confusion

Risk factors for statin muscle toxicity - Endogenous

- Age 65 or older
- Smaller body frame
- Female gender
- Multisystem disease
 - > Kidney or liver disease
 - > Type 1 or 2 diabetes
 - > Hypothyroidism
- Metabolic muscle disease
 - > Carnitine palmitoyl transferase I deficiency
 - > Myophosphorylase deficiency (McArdle's)
 - > Myoadenylate deaminase deficiency
- Family history of muscle disease
- Personal history of muscle disease

Risk factors for statin muscle toxicity - Exogenous

- Heavy alcohol consumption
- Consuming more than 1L of grapefruit juice per day
- Heavy exercise
- Taking multiple cholesterol lowering medications
- Drugs affecting the metabolism of statins:
 - > Cyclosporine
 - > Fibrates
 - > Nicotinic acid
 - > Calcium channel blockers – verapamil, diltiazem
 - > Amiodarone
 - > Cochlincine
 - > Digoxin
 - > HIV meds
 - > Warfarin
 - > Erythromycin

Conditions that mimic statin muscle toxicity

- ETOH-related myopathy
- Arthritis
- Connective tissue disease – lupus erythematosus (LE), rheumatoid arthritis (RA), Sjogren syndrome (SS), polymyalgia rheumatica (PMR)
- Electrolyte abnormalities – low potassium and magnesium (water pills)
- Endocrine diseases – thyroid, pituitary, adrenal
- Fibromyalgia
- Guillaine-Barre syndrome
- Metabolic myopathy
- Peripheral neuropathy
- Peripheral vascular disease
- Vitamin D deficiency

Laboratory features

- Elevation of muscle enzymes in the blood
- Normal nerve conduction studies
- EMG changes in weak muscles
- Normal EMG in asymptomatic patients
- Myoglobin in urine is severe cases
- Muscle biopsy – necrosis, no inflammation

Diet changes

- Will not affect much levels if there are hereditary factors
- Increase poly- (omega-3) and monounsaturated fatty acids – sunflower, cottonseed, corn, olive and soybean oil
- Limit butterfat, beef fat and palm oil
- Limit sugars – raise blood lipids
- Limit salt –water retention, increase of blood pressure
- Increase use of whole grains, fish, vegetables, fruits, oat meal, high fiber food
- Eat more fish - highest level of omega-3 fatty acids in Mackerel, Trout, Herring, Sardines, Tuna, Salmon, Halibut
- The American Heart Association recommends at least 2 servings of fish per week
- Nuts -handful (1.5 oz) a day - almonds, hazelnuts, peanuts, pecans, pine nuts, pistachio nuts and walnuts, not salted sugar coated. Caution – high calories!!!

Empower yourself

- ◉ Know your cholesterol
- ◉ Read the labels
- ◉ Find your BMI (body mass index)
- ◉ Listen to your body
- ◉ Set goals
- ◉ Go slow with changes if difficult for you
- ◉ Keep up with lifestyle changes
- ◉ Reward yourself

Lifestyle changes

- Control high blood pressure
- Control diabetes
- Quit smoking
- Eat healthy and small portions more frequently
- Decrease stress
- Small amounts of ETOH (red wine) – increase HDL
- Exercise, as tolerated – increase HDL, decrease LDL and triglycerides
- Lose weight – 5-10 lbs lower cholesterol

Alternative cholesterol-lowering supplements

Supplement	Action	Side effects/drug Interaction
Artichoke extract	Reduces total and LDL cholesterol	Gas, allergy
Barley	May reduce total and LDL cholesterol	None
Blond psyllium (in seed husk and products such as Metamucil)	May reduce total and LDL cholesterol	Gas, stomach pain, diarrhea, constipation or nausea
Fish oil (found as a liquid oil and in oil-filled capsules)	May reduce triglycerides	Fishy aftertaste, gas, nausea, vomiting or diarrhea. May interact with blood-thinners, such as warfarin
Flaxseed	May reduce triglycerides	Gas, diarrhea May interact with blood-thinners, such as aspirin, Plavix and warfarin

Alternative cholesterol-lowering supplements – cont.

Supplement	Action	Side effects/drug Interaction
Garlic extract	Reduce total and LDL cholesterol, and triglycerides	Bad breath, body odor, heartburn, gas, nausea, vomiting or diarrhea. May interact with blood-thinners, such as warfarin
Green tea extract	Lowers LDL cholesterol	Nausea, vomiting, gas or diarrhea. May interact with blood-thinners (warfarin)
Oatmeal and whole oats	Lowers total and LDL cholesterol	Gas
Sitostanol (found in oral supplements and some margarines, such as Benecol)	Lowers total and LDL cholesterol	Diarrhea
Red yeast rice	Lowers LDL cholesterol	Avoid! Contains natural form of Lovastatin!!!

What to do if statins are still needed?

- No clear recommendations
- Consider if statins are clearly needed
- Find a tolerable regimen in patients with survival benefit from statin - discuss with PCP/cardiologists if statin is definitely needed
- Prefer NOT to start statins, If LDL is borderline
- Rule out potential temporal relationship between starting the statin and the onset of the myopathy

What to do if statins are still needed? (cont.)

- Rule out history of severe myalgia, increased CPK, etc. with statin use in the past
- Myositis must be well controlled
- Instruct patients to contact MD immediately if muscle symptoms appear/worsen
- Modify immune suppressive therapy if statins are absolutely indicated
- Individualize plan
- Chose statin with a lower risk for muscle symptoms

What to do if statins are still needed? (cont.)

- Use alternate-day regimen –shown to be better tolerated and reduce cholesterol; no data on cardiovascular end-point.
- Statin holiday – a few weeks
- Coenzyme-Q10 and fish oil during statin holiday – mixed data but minimal risk.
- Try a different statin with a low risk
- Use lowest possible dose
- Avoid dehydration

Statins differ in risk for myopathy

- Higher than average overall risk
 - Lovastatin (*Mevacor*, *Altocor*, and generic) and simvastatin (*Zocor*) ~18%
- Myopathy risk - not directly proportional to cholesterol-lowering efficacy
- Low risk with
 - Atorvastatin (*Lipitor*) and ~15%
 - Both are the most effective for LDL cholesterol lowering
- Lower than average risk of myopathy
 - Pravastatin (*Pravachol*) ~ 10%
 - Fluvastatin (*Lescol*) ~5%
 - Rosuvastatin (*Crestor*) – *most hydrophilic-some data that pts may tolerate it better than other statins*

Tell your doctor about your diet or supplements!

- Vegetarians develop
 - > Vitamin B12 deficiency
 - > Carnitine deficiency
- Red yeast rice contains lovastatin
- Vitamin E can cause muscle symptoms
- Alcohol causes muscle symptoms

Acknowledgement for support!



Thank you!