Treatment for Lipid Disorders

Physician’s Pocket Treatment Guide
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Elevated LDL Cholesterol

**LIPID DISORDER**

LDL is one of the classes of lipoproteins that transports cholesterol to tissues and organs. Lowering LDL-C is a primary focus of the NCEP-ATP III and 2013 ACC/AHA ASCVD Risk and Treatment Guidelines. Elevated LDL-C is an independent risk factor for CVD and associated with a 1.6x increased risk in CVD events.

**CONTRIBUTING FACTORS**

- Genetic predisposition
- High consumption of saturated fats
- Overweight or obesity
- Sedentary lifestyle
- Illness: Nephrotic syndrome, hypothyroidism, cystic fibrosis
- Drugs: Androgens, progestins, thiazide diuretics, cyclosporines, tacrolimus, sertraline absorption inhibitors

**TREATMENT CONSIDERATIONS**

- Cardio-protective diet
- Restricted saturated fat
- Fat weight loss
- Statins
- Nicotinic acid
- Bile acid sequestrants
LIPID DISORDER

HDL is the major class of lipoproteins that facilitates cholesterol transport from cells, plasma cholesterol esterification, cholesterol transfer to other lipoproteins, and cholesterol transfer to the liver for excretion (reverse cholesterol transport). Low HDL-C is a secondary focus of NCEP-ATP III guidelines. Low HDL-C is independently associated with a 1.7x to 2.4x increased CVD risk.

CONTRIBUTING FACTORS

- Genetic predisposition
- High triglycerides
- High consumption of simple carbohydrates
- Overweight or obesity
- Sedentary lifestyle
- Insulin resistance/diabetes mellitus
- Smoking
- Illness: Liver, kidney, and thyroid disease
- Drugs: Non-selective beta blockers, androgens, progestins, isotrentinoins

TREATMENT CONSIDERATIONS

- Cardio-protective diet
- Fat weight loss
- Regular aerobic exercise
- Smoking cessation
- Correct insulin resistance
- Control diabetes mellitus
- Nicotinic acid
- Fibrates
- Thiazolidinediones
- Omega-3 fish oil
- Some statins
Elevated Triglycerides

**LIPID DISORDER**

A triglyceride is an ester derived from glycerol and three fatty acids. The major lipid in chylomicrons, VLDLs, and IDLs. Hypertriglyceridemia may increase CVD risk. Elevated triglycerides are a secondary focus of NCEP-ATP III guidelines. Elevated triglycerides are a component of the metabolic syndrome and are associated with a 1.7x to 4.0x increased CVD risk.

**CONTRIBUTING FACTORS**

- Genetic predisposition
- High consumption of simple carbohydrates and saturated fats
- Overweight or obesity
- Sedentary lifestyle
- Insulin resistance/diabetes mellitus/metabolic syndrome
- Illness: Hypothyroidism, renal failure, excess alcohol intake
- Pregnancy and lactation
- Smoking
- Drugs: Androgens, estrogens, beta blockers, thiazide diuretics, glucocorticosteroids, cyclosporines, protease inhibitors, tacrolimus, sertraline, isotretinoin, valproate

**TREATMENT CONSIDERATIONS**

- Regular aerobic exercise
- Fat weight loss
- Avoid high glycemic foods
- Low simple carbohydrate and saturated fat diet
- Avoid alcohol consumption
- Fibrates
- Nicotinic acid
- Omega-3 fish oil
- Thiazolidinediones (pioglitazone but NOT rosiglitazone)
- Some statins
- Treat levels >500 mg/dL to help prevent acute pancreatitis
## LIPOPROTEIN LDL PARTICLE NUMBER DISORDER

Ion mobility measures the number of particles in each of the eight LDL subclasses. These eight subclasses comprise the LDL particle number. An elevated total LDL particle number is associated with a 1.4x increased CVD risk.

### CONTRIBUTING FACTORS

- Genetic predisposition
- High consumption of saturated fats
- Overweight or obesity
- Sedentary lifestyle
- Illness: Nephrotic syndrome, hypothyroidism, cystic fibrosis
- Drugs: Androgens, progestins, thiazide diuretics, cyclosporines, tacrolimus, sertraline absorption inhibitors

### TREATMENT CONSIDERATIONS

- Cardio-protective diet
- Restricted saturated fat
- Fat weight loss
- Statins
- Nicotinic acid
- Bile acid sequestrants
Lipoprotein Subfraction Disorders

Ion mobility measures the number of particles in each of the eight LDL subclasses. Six of these eight subclasses are Small LDL subclass particles. These smaller particles are associated with rapid uptake into the endothelium contributing to accelerated atherosclerosis. There is a 1.3x increased CVD risk associated with the Small LDL trait and a 1.4x increased risk for the Medium LDL trait.

Contribution Factors

- Genetic predisposition
- High consumption of simple carbohydrates
- Overweight or obesity
- Sedentary lifestyle
- High triglycerides and low HDL-C
- Insulin resistance/diabetes mellitus/metabolic syndrome
- Non-selective beta blockade

Treatment Considerations

- Consider evaluation of cardio-metabolic function
- Noninvasive imaging
- Additional blood tests
- Avoid simple carbohydrate diet
- Fat weight loss
- Regular exercise
- Identify and correct insulin resistance
- Thiazolidinediones
- Control diabetes mellitus
- Nicotinic acid
- Fibrates
- Statins (minor effect)
- Omega-3 fish oil
Pattern B Phenotype/Decreased LDL Peak Size

LIPOPROTEIN SUBFRACTION DISORDERS

Pattern B is described as a predominance of Small LDL subclass particles as represented on the Ion Mobility patient result figure. Pattern B represents an atherogenic lipid profile which is associated with a 1.3x increased risk for CVD.

DECREASED LDL PEAK SIZE

Further assessment of pattern includes measurement of peak size. Average size of LDL peak subclass particles measuring less than 218 angstroms, as measured with Ion Mobility, are associated with a 1.35x increased CVD risk.

CONTRIBUTING FACTORS

- Genetic predisposition
- High consumption of simple carbohydrates
- Overweight or obesity
- Sedentary lifestyle
- High triglycerides and low HDL-C
- Insulin resistance/diabetes mellitus/metabolic syndrome
- Non-selective beta blockade

TREATMENT CONSIDERATIONS

- Consider evaluation of cardio-metabolic function
- Noninvasive imaging
- Additional blood tests
- Avoid simple carbohydrate diet
- Fat weight loss
- Regular exercise
- Identify and correct insulin resistance
- Thiazolidinediones
- Control diabetes mellitus
- Nicotinic acid
- Fibrates
- Statins (minor effect)
- Omega-3 fish oil
Decreased Large HDL

LIPOPROTEIN SUBFRACTION DISORDERS

Ion Mobility identifies five subclasses of HDL, one is identified as Large HDL. Decreased levels of the Large HDL subclass are associated with a 1.8x increased CVD risk. Large HDL particles are functionally associated with an antioxidant, paraoxanase, which may help protect the arterial wall.

CONTRIBUTING FACTORS

- Genetic predisposition
- High triglycerides
- High consumption of simple carbohydrates
- Overweight or obesity
- Sedentary lifestyle
- Insulin resistance/diabetes mellitus
- Smoking
- Illness: Liver, kidney, and thyroid disease
- Drugs: Non-selective beta blockers, androgens, progestins

TREATMENT CONSIDERATIONS

- Avoid simple dietary carbohydrates
- Fat weight loss
- Regular exercise
- Smoking cessation
- Correct insulin resistance
- Control diabetes mellitus
- Nicotinic acid
- Nicotinic acid plus statin
- Some statins
- Fibrates when triglycerides are elevated
- Omega-3
Elevated ApoB

APOLIPOPROTEIN DISORDERS
Apolipoprotein B is a chief structural protein of all non-HDL lipoproteins. The amount of ApoB is considered to correspond to the number of atherogenic particles. Elevated ApoB levels are associated with a 2.0x to 2.5x increased CVD risk.

CONTRIBUTING FACTORS
- Genetic predisposition
- High consumption of saturated fats
- Overweight or obesity
- Sedentary lifestyle
- Illness: Nephrotic syndrome, hypothyroidism, cystic fibrosis
- Drugs: Androgens, progestins, thiazide diuretics, cyclosporines, tacrolimus, sertraline absorption inhibitors

TREATMENT CONSIDERATIONS
- Cardio-protective diet
- Restricted saturated fat
- Fat weight loss
- Statins
- Nicotinic acid
- Bile acid sequestrants
Elevated Lp(a)

**APOLIPOPROTEIN DISORDERS**
Lipoprotein(a) is a heterogeneous lipoprotein that shares many properties with low-density lipoprotein (LDL), but Lp(a) is metabolically distinct from LDL. It contains a structurally unique protein, apoprotein(a), the size of which is genetically determined and highly variable. High plasma Lp(a) concentrations are associated with a 1.5x to 5.3x increased CVD risk.

**CONTRIBUTING FACTORS**
- Genetic predisposition
- Illness: Chronic renal failure, nephrotic syndrome, hypothyroid, and diabetic nephropathy
- Androgens
- Menopausal loss of estrogen may increase Lp(a) 20-30%

**TREATMENT CONSIDERATIONS**
- Consider evaluation of cardio-metabolic function
- Noninvasive imaging
- Additional blood tests
- Nicotinic acid
- Niaspan 2,000 mg per day decreases Lp(a) -24%
- IR Niacin 3,000 mg per day decreases Lp(a) -36%
- Fibrates (limited effect)
- Consider that some statins may elevate Lp(a) in some patients
- Aggressively treat all associated atherogenic conditions
- LDL or Lp(a) apheresis in some extreme cases of resistance to Lp(a)-lowering drugs
Elevated hs-CRP

INFLAMMATORY DISORDERS

CRP is a plasma protein produced by the liver in response to systemic inflammation. The high sensitivity CRP (hs-CRP) test accurately determines CRP levels in the low range of 1-10 mg/L. Elevated hs-CRP levels correlate with the presence of the metabolic syndrome, insulin resistance, endothelial dysfunction, and impaired fibrinolysis. hs-CRP can discern the low levels of inflammation associated with a 1.5x to 2.0x increased CVD risk.

CONTRIBUTING FACTORS

• Any medical condition, lifestyle habit or drug that causes inflammation, infection, and/or tissue injury. This may include but is not limited to:
  - Insulin resistance/diabetes mellitus/metabolic syndrome
  - Obesity
  - Lifestyle: Stress, smoking, adiposity in females
  - Drugs: HRT, contraceptives

TREATMENT CONSIDERATIONS

• Consider evaluation of cardio-metabolic function
• Noninvasive imaging
• Additional blood tests
• Cardio-protective diet
• Fat weight loss
• Statins
• Statins plus ezetimibe
• Fibrates
• Nicotinic acid
Elevated Fibrinogen

**INFLAMMATORY DISORDERS**

Fibrinogen is a plasma glycoprotein that can be transformed into a fibrin clot in response to vascular or tissue injury. The combination of elevated fibrinogen with other CVD risk factors produces an additive risk and can substantially increase disease potential. There are two fibrinogen assays available; one measures clotting, the other antigen. Elevated fibrinogen is associated with inflammation and a 1.4x to 2.5x increased CVD risk.

**CONTRIBUTING FACTORS**

- Genetic predisposition
- Ethnicity: Highest levels seen in South Asians, Blacks and Hispanics; lowest levels seen in Caucasians and Chinese
- Gender (females often have higher levels)
- Tobacco use
- Excess weight
- Increasing age
- Sedentary lifestyle
- Insulin resistance/diabetes mellitus
- Hypertension
- Post menopausal state
- Acute/chronic inflammation
- Drugs: Some statins, oral contraceptives, gemfibrozil

**TREATMENT CONSIDERATIONS**

- Consider evaluation of cardio-metabolic function
- Noninvasive imaging
- Additional blood tests
- Fat weight loss
- Increase physical activity
- Smoking cessation
- Nicotinic acid
- Fibrates: fenofibrate may reduce whereas gemfibrozil may elevate
- Control hypertension
- Control diabetes mellitus
Lp-PLA$_2$ is an enzyme which cleaves oxidized LDL in the vascular wall to release proinflammatory factors that initiate and fuel the formation of atherosclerotic plaque. Circulatory Lp-PLA$_2$ levels are increased when atherosclerotic plaque formation reaches an advanced stage characterized by thinning of the overlying fibrous cap and enzyme leakage into the artery lumen. Elevated Lp-PLA$_2$ levels have been associated with a 1.7x to 2.9x increased risk for CVD* and a 1.9x to 11.4x increased risk for stroke* events.

*Risk for CVD and stroke is substantially increased in patients when both Lp-PLA$_2$ and CRP are elevated.

**INFLAMMATORY DISORDERS**

**CONTRIBUTING FACTORS**
- Increasing age in both genders
- Tobacco use
- Sedentary lifestyle
- Metabolic syndrome
- Elevated blood glucose
- Hypertension
- Carotid intima-media thickness
- Periodontal disease

**TREATMENT CONSIDERATIONS**
- Consider evaluation of cardio-metabolic function
- Noninvasive imaging
- Additional blood tests
- Statins
- Fenofibrate
- Nicotinic acid
- Omega-3 fish oil supplements
- Ezetimibe
- Combination of statin with other suggested drugs results in further Lp-PLA$_2$ reduction
- Antihypertensive therapy for optimal BP control
- Diet high in Omega-3 fatty acids
Elevated NT-proBNP

HEART FAILURE

NT-proBNP is an endogenously produced neurohormone secreted from the cardiac ventricular myocytes in response to cardiac stress. As a sensitive marker for cardiac dysfunction, elevated NT-proBNP levels provide aid in diagnosis of heart failure (HF) and assessment of response to therapy, prediction of chronic HF progression (which is associated with a 1.9x to 2.9x* increased CVD risk) and incidence of CVD death or HF after ACS, which carries a 2.4x to 6.6x* increased risk for CVD.

*Risk for HF progression is substantially increased in patients when both NT-proBNP and ST2 are elevated.

CONTRIBUTING FACTORS

- Medical conditions that may be associated with myocardial stress
- Systemic hypertension
- Heart failure of any etiology
- Left or right ventricular hypertrophy
- Diastolic dysfunction
- MI
- ACS
- Cardiac arrhythmias, especially atrial fibrillation
- Cardiomyopathy
- Myocarditis, possibly endocarditis
- COPD
- Pulmonary embolism
- Sepsis
- Metabolic disease
- Diabetes mellitus
- Renal disease

TREATMENT CONSIDERATIONS

- Complete evaluation of cardio-metabolic function to exclude causes of cardiac dysfunction
- Echocardiography
- Other noninvasive imaging
- Additional blood tests
- Dependent on etiology, consider:
  - Preload medications: nitrates, diuretics
  - Rate control medications: beta blockers
  - Afterload medications: ACE inhibitors, ARBs, alpha blockers, calcium channel blockers, direct vasodilators
  - Cardiac pacing
Elevated Homocysteine

**METABOLIC DISORDERS**

Homocysteine is a metabolic by-product of methionine metabolism. Elevated homocysteine increases oxidative stress, may cause endothelial dysfunction and vascular injury, and enhances thrombogenicity. Patients with elevated homocysteine levels have a 1.5x increased risk for CVD events.

**CONTRIBUTING FACTORS**

- Genetic predisposition
- Deficiencies of vitamins folic acid, B6 and B12
- Illness: Renal insufficiency/failure, pernicious anemia, megaloblastic anemia, hypothyroidism, psoriasis
- Lifestyle: excess alcohol, caffeine, nicotine
- Diet low in greens, high in meats
- Drugs: Nicotinic acid (dose dependent), fenofibrates, sulfon-amides, metformin, anti-convulsants, methotrexate, theophylline, cyclosporine

**TREATMENT CONSIDERATIONS**

- Identify and treat underlying abnormality such as renal insufficiency/pernicious anemia
- Diet high in green leafy vegetables
- Traditional treatment has been folic acid, B-6 and B-12 vitamins
- Initiating treatment of elevated homocysteine continues to be controversial in reducing CVD risk versus increased risk for other conditions
Decreased Vitamin D Level

**METABOLIC DISORDERS**

Vitamin D and its metabolites are hormones and hormone precursors. A deficiency of 25-hydroxyvitamin D is associated with development of atherosclerosis and increased cardiovascular events. Decreased vitamin D level is associated with a 1.8x increased risk for cardiovascular mortality and a 1.6x to 5.0x increased risk for CVD events.

**CONTRIBUTING FACTORS**

- Elderly and newborns
- Inadequate sun exposure
  - People with more skin pigment are at higher risk for vitamin D deficiency
- Environmental factors
- Medical Conditions
  - Obesity
  - Malabsorption
  - Renal disease
  - Liver disease
- Drugs: Corticosteroids, anticonvulsants, anti-rejection medications, HIV medications

**TREATMENT CONSIDERATIONS**

- Vitamin D supplementation
- Initial loading therapy
  - 50,000 IU vitamin D$_2$ weekly for 2 months
- Maintenance therapy
  - 50,000 IU vitamin D$_2$ once or twice monthly or
  - 2,000-4,000 IU vitamin D$_3$ daily and/or appropriate sun exposure and/or high vitamin D diet (salmon, tuna fish, shiitake mushrooms)
FATTY ACID DISORDERS

Low Omega-3 fatty acid blood levels, as well as a high Omega-6 to Omega-3 fatty acid ratio, have both been associated with an increased risk of cardiovascular events. A dietary deficiency of Omega-3 FAs is associated with an 1.8x to 5x increased risk of fatal cardiovascular events.

CONTRIBUTING FACTORS

- Genetic polymorphisms in the FAD genes
- Low dietary consumption of Omega-3 fatty acids
- High dietary consumption of Omega-6 fatty acids
- Dietary deficiency of Omega-3 FAs

TREATMENT CONSIDERATIONS

- Two primary Omega-3 fatty acids are EPA and DHA. Dietary sources are:
  - Fish oil
  - Fatty fish
- ALA, one of the three major Omega-3 FAs, is found in plant-based foods. It is converted to EPA and DHA after being ingested.
Elevated Insulin

**METABOLIC DISORDERS**
Insulin is a polypeptide produced by specialized beta cells of the islets of Langerhans in the body and tail of the pancreas. Elevated fasting insulin is associated with a 3.2x increased risk for CVD events.

**CONTRIBUTING FACTORS**
- Genetic predisposition
- Advanced age
- Obesity
- Visceral adiposity
- Sedentary lifestyle
- High carbohydrate diet
- Stress
- Menopausal drop in estrogen
- Chronic inflammation with elevated inflammatory markers
- Illnesses such as:
  - Polycystic ovarian syndrome
  - Cushing’s disease
  - Hemochromatosis, insulinoma
  - Insulin resistance/diabetes
  - Diabetes mellitus/metabolic syndrome
- Elevations may be caused by postprandial blood sample or exogenous administration of insulin
- Drugs: Rifampin, progesterone, anti-retrovirals, corticosteroids

**TREATMENT CONSIDERATIONS**
- Fat restricted, cardio-protective diet
- Limit simple carbohydrates, utilize high fiber sources
- Fat weight loss
- Regular exercise
- Recommended pharmacologic methods of meeting insulin requirements or regulating insulin sensitivity
For a more comprehensive list of medications that may affect any of the assays in this publication, please refer to Goodman and Gilman’s *The Pharmacological Basis of Therapeutics* or other valued source.