Therapy of Dyslipidemias

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Therapy of Dyslipidemias

- **Hypercholesterolemia, elevated low-density lipoprotein (LDL), low high-density lipoprotein (HDL) and elevated lipoprotein(a) Lp(a) are linked to increased risk for coronary heart disease, peripheral vascular disease, and cerebrovascular disease (both morbidity and mortality).**
- **Hypertriglyceridemia is associated with the development of acute pancreatitis. VLDL also increase the risk of vascular diseases.**

Therapy of Dyslipidemias

- **Initial therapy of lipoprotein disorder is life-style modification:**

1. **Restricted intake of total and saturated fat and cholesterol**
2. **Modest increase in unsaturated fat intake (specially mono-unsaturated fat)**
3. **Regular exercise**
4. **Smoking cessation**
5. **Weight reduction.**

Therapy of Dyslipidemias

- A Statin is the drugs of choice for patients with hypercholesterolemia.
- Patients NOT responding to statin monotherapy may be treated with combination therapy for hypercholesterolemia, but should be monitored closely because of an increased risk of adverse effects and drug interactions.

Therapy of Dyslipidemias

- **Hypertriglyceridemia usually responds well to niacin, and fibrates (gemfibrozil, fenofibrate).**
- **Low HDL-C needs life-style modifications such as smoking cessation, and exercise; and drug therapy with niacin and fibrates which can significantly increase HDL-cholesterol.**

Therapy of Dyslipidemias

- **Lp(a) is formed from LDL and apolipoprotein (a).**
- **It is homologous with plasminogen but is NOT activated by tissue plasminogen activator.**
- **Lp(a) may be found in atherosclerotic plaques and may contribute to coronary disease by inhibiting thrombolysis.**

Therapy of Dyslipidemias

- **It can be secondarily elevated in patients with severe nephrosis and some inflammatory states.**
- **Lp(a) is associated with about six times the atherogenic risk of LDL**
- **Its level is variable (0 - 2000 nM/L).**
- **Niacin reduces levels of Lp(a) in many patients.**

Therapy of Dyslipidemias

- **Hypertriglyceridemia is also associated with increased cardiovascular risk.**
- **VLDL carries about 10 - 15% of serum cholesterol and most fasting triglycerides.**
- **VLDL cholesterol is atherogenic.**
- **It is a risk factor for developing acute pancreatitis.**
- **Chylomicrons are triglyceride-rich particles formed from dietary fat solubilized by bile salts.**

Secondary Causes of Lipoprotein Abnormalities

A. **Hypercholesterolemia:**

1) **Hypothyroidism.**
2) **Obstructive liver disease.**
3) **Nephrotic syndrome.**
4) **Anorexia nervosa.**
5) **Acute intermittent porphyria.**
6) **Drugs: progestins, thiazide diuretics, glucocorticoids, β-blockers, isotretinoin, protease inhibitors, cyclosporine, sirolimus, mirtazapine.**

Secondary Causes of Lipoprotein Abnormalities

B. Hypertriglyceridemia:

1. Obesity
2. Diabetes mellitus
3. Lipodystrophy
4. Glycogen storage disease
5. Ileal bypass surgery
6. Sepsis
7. Nephrotic syndrome
8. Chronic renal disease
9. Pregnancy
10. Acute hepatitis
11. Systemic lupus erythematous
12. Monoclonal gammopathy: multiple myeloma, lymphoma.

Secondary Causes of Lipoprotein Abnormalities

13. Drugs: Alcohol, estrogens, isotretinoin, thiazides, β-blockers, glucocorticoids, **bile-acid binding resins**, asparaginase, interferons, azole antifungals, bexarotene, mirtazapine, anabolic steroids, sirolimus.

C. Low HDL:

- Malnutrition, **obesity**, sedentary life-style.
- **Drugs:** non-ISA β-blockers, anabolic steroids, isotretinoin, progestins.

Therapy of Dyslipidemias

Desired Outcomes:

- **The ultimate goals of therapy are to reduce the risk of MI, angina, heart failure, ischemic stroke, and peripheral arterial disease, and carotid stenosis, and abdominal aortic aneurysm, ..).**

Therapy of Dyslipidemias

Nonpharmacologic Therapy:

- **Therapeutic life-style modification should be implemented in all patients prior to considering drug therapy:**

A. Reduced intakes of saturated fats, cholesterol and total fat.

Therapy of Dyslipidemias

B. The use of dietary options to reduce LDL-C:

1. **Plant phytosterols.**
2. **Increased soluble fiber intake.**
3. **Weight reduction.**
4. **Increased physical activity.**

Therapy of Dyslipidemias

- **Plant phytosterols are structurally similar to cholesterol, and compete for its intestinal absorption.**
- **They also reduce bile acid absorption, thus, cholesterol is degraded into bile acids - an LDL-lowering effect.**

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Food sources of phytosterols:

1) Cereals (oat, wheat, brown rice).
2) Legumes (peas, beans, lentils).
3) Nuts and Seeds (peanuts, almonds, sunflower seeds, pumpkin seeds, sesame seeds).
4) Fruits and vegetables (broccoli, cauliflower, apples, avocados, tomato, blueberries).

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- **Physical activity of moderate intensity 30 minutes per day for most days of the week.**
- **Patients with known CAD or at high risk should be evaluated before undertaking vigorous exercise.**
- **Restriction of alcohol drinking**
- **Weight reduction should be attempted in persons who are overweight.**

Therapy of Dyslipidemias

- **Weight control plus increased physical activity raises HDL and reduces non-HDL cholesterol.**
- **Increased intake of soluble fiber (oat bran, pectins, psyllium products) can result in useful adjunctive reductions in total and LDL cholesterol.**
- **Patients should stop smoking and have their hypertension controlled.**

Drugs Used in Hyperlipoproteinemias

- **Omega-3 fatty acids found in cold-water fish oils (eicosapentaenoic acid and docosahexaenoic acid), activate peroxisome proliferator-activated receptor-alpha (PPAR-α) and can reduce triglycerides in VLDL in some patients.**
- **May increase both HDL and LDL (modest effect).**

Drugs Used in Hyperlipoproteinemias

- **Fish oil causes also alterations in the synthesis of prostanoids → synthesis of vasodilator prostaglandins and inhibitors of platelet aggregation.**

Therapy of Dyslipidemias

Pharmacologic Therapy:

- **Many effective lipid-lowering drugs exist, but none is useful for all lipoprotein disorders.**
- **All agents are associated with adverse effects and drug-drug interactions.**

Fredrickson-Levy-Lees Classification of Hyperlipoproteinemia

Type	Lipoprotein elevated
I	Chylomicrons
IIa	LDL
IIb	LDL + VLDL
III	IDL
IV	VLDL
V	VLDL + Chylomicrons

Lipoprotein Phenotype and Recommended Drug Treatment

Lipoprotein Type	Drug of Choice	Combination Therapy
I	Not indicated	--
IIa	Statins Cholestyramine or colestipol Niacin	Niacin or bile acid resins (BAR) Statins or niacin Statins or BAR **Ezetimibe** Mipomersen, lomitapideb
IIb	Statins Fibrates Niacin	BAR or Fibrates or niacin Statins or niacin or BAR[a] Statins or Fibrates **Ezetimibe**
III	Fibrates Niacin	Statins or niacin Statins or Fibrates **Ezetimibe**
IV	Fibrates Niacin	Niacin Fibrates
V	Fibrates Niacin	Niacin Fish oils

[a]BAR are not used as first-line therapy if triglycerides are elevated at baseline since hypertriglyceridemia may be worsen with BAR alone.

[b]Mipomersen and lomitapide are used in combinations with other lipid lowering therapy, in particular, statins for patients with familial hypercholestermia (homozygotes or heterzygotes) and in patient who cannot be managed adequately with maximally tolerated statin therapy.

Therapy of Dyslipidemias

- **Treatment of type I hyperlipoproteinemia (↑ Chylomicrons) is directed toward reduction of chylomicrons derived from dietary fat with the subsequent reduction in plasma triglycerides.**
- **Total daily fat intake should be reduced.**
- **Look for secondary causes of hypertriglyceridemia and treat them appropriately, if present.**

Therapy of Dyslipidemias

- **Type III hyperlipoproteinemia may be treated with fibric acid derivatives or niacin.**
- **Type IV hyperlipoproteinemia should be treated with fibric acid derivatives or niacin.**

Therapy of Dyslipidemias

- **Type V hyperlipoproteinemia (↑ VLDL and chylomicrons) also requires reduction of total fat intake.**
- **In addition, drug therapy (fibrates and niacin) is indicated if the response to diet alone is inadequate.**
- **Omega-3 fatty acids may be useful in lipoprotein lipase (LPL) deficiency in some patients. They upregulate the enzyme, which increase TG removal from VLDL and chylomicron.**

Niacin (Nicotinic Acid, Vitamin B_3)

Pharmacodynamics:

1. **It inhibits VLDL secretion from the liver and thus LDL production.**
2. **It raises HDL cholesterol by decreasing its catabolism (most effective agent).**
3. **It reduces the level of $LP_{(a)}$.**
4. **It reduces fibrinogen levels.**
5. **It increases tissue plasminogen activator.**

Niacin

Adverse reactions:

1. **Acanthosis nigricans, darkening of the skin in skin-folds. (external marker of insulin resistance).**
2. **Elevation of liver function tests, thus, it is contraindicated in patients with active liver disease.**

Niacin

3. **Cutaneous flushing and itching: prostaglandin-mediated and can be reduced by aspirin 325 mg given shortly before niacin ingestion.**

- **Prostaglandin D receptor subtype 1 (DP1) may mediate niacin-induced vasodilation.**
- **Laropiprant, a selective antagonist of this receptor, can be co-administred with extended-release (ER) niacin to lower flushing symptoms.**

Niacin

4. **Hyperuricemia, and hyperglycemia.**
- **Preexisting gout and diabetes may be exacerbated by niacin.**
5. **Increases risk of myopathy when given with statins.**

Fibric Acid Derivatives

- **Include phenofibate and gemfibrozil.**
- **They enhance hydrolysis of VLDL and chylomicron triglycrides in the circulation by lipoprotein lipase.**
- **A major effect is an increase in oxidation of fatty acids in liver and striated muscle. → →**

1. **Reduction of VLDL.**
3. **Elevation of HDL:**

- **They increase the production of apo-A1 and apoAII in the liver.**

Fibric Acid Derivatives

3. **Modest decrease in LDL (?! Care).**
4. **They may increase LDL in patients with hypertriglyceridemia as triglycerides are reduced.**

Fibric Acid Derivatives

Adverse effects:

1. **Gallstones due to an increase in the lithogenicity of bile.**
2. **May potentiate the effects of oral anticoagulants and the (INR) should be monitored with this combination.**
3. **Reduce platelet activity.**

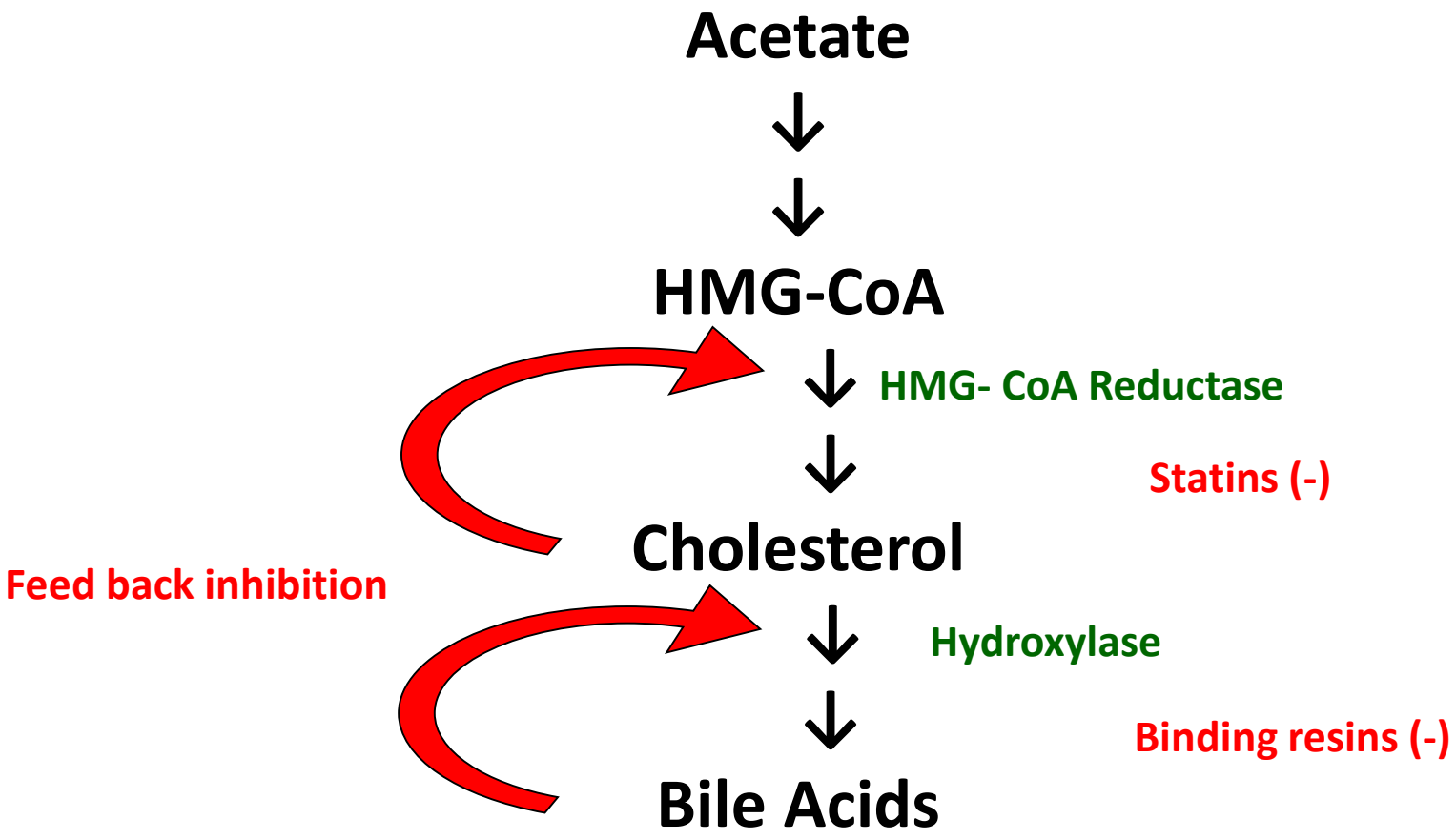
Fibric Acid Derivatives

5. **Myositis and elevations in creatine phosphokinase, especially in patients with renal insufficiency.**
6. **Elevation of serum creatinine**
7. **Elevation of liver enzymes.**

Therapy of Dyslipidemias

- **Primary hypercholesterolemia:**
- **May be treated with HMG Co-A reductase inhibitors (statins), bile acid binding resins (colestipol, cholestyramine, & colesevelam), niacin or ezetimibe.**
- **Of these, statins are the first choice.**

Cholesterol Metabolism



Statins (HMG-CoA reductase inhibitors)

- **They inhibit the rate-limiting step in cholesterol biosynthesis, the 3-hydroxy- 3- glutaryl CoA reductase.**
- **The reduced cholesterol content of hepatocytes increase LDL receptor synthesis → an increase in catabolic rate of LDL and LDL precursors (VLDL remnants) from the blood, thus reducing LDL.**

Statins (HMG-CoA reductase inhibitors)

Other actions of statins:

1) reduce oxidative stress.
2) reduce vascular inflammation.
3) stabilize atherosclerotic lesions.
4) improve the microcirculation.
5) inhibit proliferation of arterial wall smooth muscle
6) improve endothelial cell function.

Statins (HMG-CoA reductase inhibitors)

- **Some statins include lovastatin, simvastatin, atorvastatin, rosuvastatin, and others.**

Statins (HMG-CoA reductase inhibitors)

- **Combination therapy with bile acid sequestrants and statins is rational as LDL receptor numbers are increased, leading to greater degradation of LDL-C; inhibition of intracellular synthesis of cholesterol, and interruption of the enterohepatic recycling of bile acids.**
- **Combination therapy with a statin plus ezetimibe is also rational since ezetimibe inhibits cholesterol absorption through the gut.**

Statins (HMG-CoA reductase inhibitors)

Adverse effects:

1. **Elevation of serum alanine aminotransferase.**
2. **Serious muscle toxicity (myopathy), elevated serum CPK, rhabdomyolysis, myoglobinuria , renal shutdown.**
3. **Teratogenicity: contraindicated in pregnancy (and lactation).**

Statins (HMG-CoA reductase inhibitors)

Drug interactions:

- **Myopathy increases in severity if coadministered with nicotinic acid, fibrates, ketoconazole, cyclosporine, erythromycin, verapamil, cimetidine, metronidazole, amiodarone, grapefruit juice and protease inhibitors (anti HIV).**

Bile Acid Binding Resins

- **Include cholestyramine, colestipol, and colesevelam.**
- **They exchange Cl^- for the negatively charged bile acids, thus, preventing the negative feedback on the hydroxylase → enhancing of cholesterol breakdown**
- **Reduction of hepatic cholesterol increases LDL receptors which accelerates cholesterol removal from plasma → Increased uptake of LDL and IDL from plasma.**

Bile Acid Binding Resins

- **Loss of bile acids also reduces fat and cholesterol absorption from GIT.**
- **In patients with combined hyperlipidemia (hypertriglyceridemia and hypercholesterolemia), VLDL may be increased during treatment with the resins.**
- **Thus, the resins are useful only for isolated increases in LDL.**

Bile Acid Binding Resins

Adverse effects:

1. **Gastrointestinal complaints of gritty taste, constipation, bloating (epigastric fullness), nausea, flatulence, and GIT obstruction.**
- **Patients may discontinue therapy because of these adverse effects.**
2. **Impaired absorption of fat-soluble vitamins A, D, E, and K.**
3. **Hypernatremia and Hyperchloremic metabolic acidosis.**

Bile Acid Binding Resins

Drug interaction:

- **Reduced bioavailability of many drugs such as coumarin anticoagulants, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, iron, …….**
- **Drug interactions may be avoided by spacing administration by 6 hours between the bile acid resin and other drugs.**

Bile Acid Binding Resins

- **Both the statins and the resins are NOT effective in patients lacking LDL receptors (familial homozygous hypercholesterolemia).**
- **Severe forms of hypercholesterolemia may require more intensive combination therapy.**

Inhibitors of Intestinal Sterol Absorption

Ezetimibe:

- **It inhibits intestinal cholesterol absorption → reduces LDL.**
- **It may also inhibit phytosterol absorption.**
- **It is effective even in the absence of dietary cholesterol because it inhibits reabsorption of cholesterol excreted in bile.**

Inhibitors of Intestinal Sterol Absorption

- **It could be used in combination therapy in Type IIb, synergistic with statins. [unlike BARs]**
- **Plasma concentration is increased when coadministered with fibrates and reduced when given with the resins.**

Adverse effects:

- **Muscle pain and weakness**
- **Hepatitis and jaundice**
- **Pancreatitis and elevation of amylase**

Therapy of Dyslipidemias

- **Combined hyperlipoproteinemia (type IIb) may be treated with statins, niacin, or gemfibrozil combinations to lower LDL cholesterol without elevating VLDL and triglycerides.**
- **Bile acid resins monotherapy may elevate VLDL and triglycerides, and should be avoided.**
- **Fibric acid (gemfibrozil, fenofibrate) monotherapy is effective in reducing VLDL, but may increase LDL.**

Therapy of Dyslipidemias

Low HDL Cholesterol (< 40 mg/dL ???):

- **It may be a consequence of insulin resistance, physical inactivity, type 2 diabetes, cigarette smoking, very high carbohydrate intake, and certain drugs.**
- **Weight reduction, increased physical activity, and smoking cessation should be emphasized.**
- **Niacin or fibric acid derivatives are the drugs of choice.**

Therapy of Dyslipidemias

Diabetic Dyslipidemia:

- **Diabetic dyslipidemia is characterized by hypertriglyceridemia, low HDL, and minimal elevation of LDL.**
- **Most patients will require therapeutic life-style modification and drug therapy.**
- **When LDL-C is high, intensify glycemic control and add fibric acid derivatives or niacin, and intensify LDL-C-lowering therapy using statins.**

Therapy of Dyslipidemias, Special Considerations

The Elderly:

- **Older patients are more susceptible to adverse effects of lipid-lowering drugs.**
- **They are more likely to have constipation (bile acid resins), skin and eye changes (niacin), gout (niacin), gallstones (fibric acid derivatives), and bone/joint disorders (fibric acid derivatives, statins).**
- **Therapy should be started with lower doses and titrated up slowly to minimize adverse effects.**

Therapy of Dyslipidemias, Special Considerations

Pregnancy:

- **HDL may be a more important predictor of disease in women.**
- **Cholesterol and triglyceride levels rise progressively throughout pregnancy.**
- **Drug therapy is NOT instituted and it should NOT be continued during pregnancy.**
- **Dietary therapy is the mainstay of treatment, with emphasis on maintaining a nutritionally balanced diet.**
- **If their is a very high risk, a bile acid resin may be considered.**
- **Statins are Category X and are contraindicated.**
- **Ezetimibe is pregnancy Category C drug.**

Therapy of Dyslipidemias, Special Considerations

Children:

- **Drug therapy in children is NOT recommended until the age of 8 years or older.**
- **Younger children are generally managed with therapeutic life-style changes until after the age of 2 years.**
- **Statins may be safe and are effective in children.**
- **Severe forms of hypercholesterolemia (familial hypercholesterolemia) may require more aggressive treatment.**

Mipomersen

- It is an antisense oligonucleotide that specifically binds to the apolipoprotein B-100 mRNA, blocking translation of the gene product.
- The reduction in production of apo B-100 results in reduced hepatic production of the atherogenic lipoproteins VLDL, IDL, LDL, and lipoprotein(a).
- It is indicated in patients with homozygous familial hypercholesterolemia as an adjunct to diet and other lipid-lowering medications.
- It is hepatotoxic (hepatic steatosis), and its use is restricted.
- Given by SC injection.

Lomitapide

- **Lomitapide is an inhibitor of microsomal triglyceride transfer protein (MTP), which is responsible for absorbing dietary lipids and transferring triglycerides onto apolipoprotein B (apo-B) in the assembly of VLDL.**
- **Thus, transfer of lipid to apo-B is blocked, leading to apo-B destruction and inhibition of lipoprotein secretion.**
- **It also inhibits CYP3A4 and P-Glycoprotein.**
- **It is used for familial hypercholesterolemia.**

Adverse effects:

- **Elevation of serum aminotransferase.**
- **Increased hepatic fat (steatohepatitis) and hepatic fibrosis.**

Alirocumab

- **Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to LDLRs on hepatocytes → LDLR degradation, thus, elevating LDL-C blood levels.**
- **Alirocumab inhibits the binding of PCSK9 to LDLR → reduces LDL-C levels.**
- **Given by SC injection.**
- **Used as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia.**