COMMONWEALTH OF AUSTRALIA

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Drug regulation of serum lipids

Foundations of Biomedical Science
MEDS90001

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References
• Katzung, Basic & Clinical Pharmacology Ch 35
• Australian Medicines Handbook
Objectives

• explain the types of dyslipidaemias
• appreciate the rationale for instituting non-pharmacological approaches as well as lipid lowering and other agents to improve prognosis
• describe the mechanisms of action of drugs used to lower blood lipids
• demonstrate an understanding of the adverse effects of drugs used to alter blood lipids
Dyslipidaemia

- 1950s and 60s
  - recognition that high blood cholesterol correlated with increased risk of IHD
- dyslipidaemia = abnormal lipid profile
  - can lead to atherosclerosis, increased risk of MI, stroke
  - hypercholesterolaemia
    - high risk > 7.5 mmol/L total cholesterol, treatment target < 4 mmol/L
  - hypertriglyceridaemia
  - mixed hyperlipidaemia

http://www.web-books.com/eLibrary/Medicine/Cardiovascular/Images/Athero.gif
Serum lipid levels

• “normal” total cholesterol levels not necessarily healthy

<table>
<thead>
<tr>
<th></th>
<th>Normal fasting levels</th>
<th>Target levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/l</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Total Cholesterol:</td>
<td>0.0 - 5.5</td>
<td>&lt; 4.0</td>
</tr>
<tr>
<td>Triglyceride:</td>
<td>0.5 - 2.0</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>HDL Cholesterol:</td>
<td>0.9 - 2.2</td>
<td>&gt; 1.0</td>
</tr>
<tr>
<td>LDL Cholesterol:</td>
<td>0.0 - 3.4</td>
<td>&lt; 2.5</td>
</tr>
<tr>
<td>Chol/HDL Ratio:</td>
<td>0.0 - 5.0</td>
<td></td>
</tr>
</tbody>
</table>

(Medical Journal of Australia, 2001)
Treatment for dyslipidaemia

- establish fasting plasma lipid profile for diagnosis
- consider cardiovascular status and risk factors
- treat secondary causes
  - obesity, diabetes, hypothyroidism
- manage modifiable risk factors
  - stop smoking
  - avoid alcohol
  - weight reduction
  - increase exercise
  - these can all reduce risk of cardiovascular events independently of lipid lowering
- modify diet
Targets for hypercholesterolaemia

• Diet
  – reduce *saturated* and *trans* fat intake
  – introduce
    • Mediterranean diet – reduces risk, not LDL (bad) cholesterol
    • plant sterol esters – reduce LDL cholesterol
    • fish oils – reduce triglycerides, increase HDL (good) cholesterol
  – lifestyle/diet intervention for people at low risk

• Synthesis, transport and uptake
  – Drug targets for intervention for people at > moderate risk
Sources of cholesterol

- cholesterol derived from
  - diet (in animal fat, eggs - absorbed via intestine)
  - no Recommended Daily Allowance (RDA) set
  - de novo synthesis (primarily in liver) adequate

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acetyl-CoA → acetoacetyl-CoA → 3-hydroxy-3-methylglutaryl-CoA
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HMG-CoA reductase
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Rate-limiting step
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HOOC–CH2–C–(CH2)2–OH

mevalonic acid
```

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CH3

squalene
```

```
cholesterol
```

Fate of cholesterol

- stored in liver for export in VLDL (very low density lipoproteins)
- converted to bile acids, stored in gall bladder to emulsify fat
- used for steroid hormones and vitamin D synthesis
- used for membrane synthesis
Cholesterol transport

- transported in plasma lipoproteins:
  - Chylomicrons
  - Very low density lipoproteins (VLDL)
  - Intermediate density lipoproteins (IDL)
  - Low density lipoproteins (LDL = “bad” cholesterol)
  - High lipoproteins (HDL = “good” cholesterol)

- complex metabolism (see Fig 35.1 Katzung)
Cholesterol transport and metabolism
Cholesterol transport

• transported in plasma lipoproteins:
  – Chylomicrons
  – Very low density lipoproteins (VLDL)
  – Intermediate density lipoproteins (IDL)
  – Low density lipoproteins (LDL = “bad” cholesterol)
  – High lipoproteins (HDL = “good” cholesterol)

• complex metabolism (see Fig 35.1 Katzung, Fig 1 Toth)

• lipoproteins that contain apolipoprotein (apo) B-100 can transport lipids into artery walls = “bad”
  – LDL, IDL, VLDL

• HDL can retrieve cholesterol from artery wall = “good”

• “normal” total cholesterol levels not necessarily healthy
Discovery of statins as HMG-CoA reductase inhibitors

Kuroda and Endo (Tokyo Noko University), 1970s
• reasoned that microbes would synthesise sterol synthesis inhibitors to combat other microbes that require sterols for growth
• screened 6,000 microbial strains
• discovered mevastatin (from \textit{Penicillium citrinum})

\textit{Endo} (1992) \textit{J Lipid Res} 33: 1569-1582

Merck, late 1970s
• isolated lovastatin (from \textit{Aspergillus terreus})

Statins approved for clinical use the late 1980s
Treatment of hypercholesterolaemia with statins

Lova, atorva, fluva, prava, simvastatin

- decrease mevalonic acid and therefore cholesterol synthesis
  - compensatory increase in hepatic LDL receptors
  - increased clearance of LDL (with bound cholesterol) from blood
  - decreased plasma total cholesterol and LDL (and TGs to lesser extent)
  - increased plasma HDL
Statin effect on LDL cholesterol

Figure 1. Statin effect on LDL cholesterol [F] [44]

F Derived from a meta-analysis of short-term trials. Height of bar indicates the point estimate for the dose.

Statins -
HMG-CoA reductase inhibitors

- Indications: hypercholesterolaemia (high LDL)
  mixed hyperlipidaemia (high LDL, TGs)

- Greater benefit after 1-2 years use
- Poor compliance related to perceived lack of efficacy rather than side effects
Precautions

- avoid grapefruit juice! (common metabolic pathway increases toxicity of statins)
- drug-drug interactions due to cytochrome pathways
- statin levels are
  - increased by some antibiotics, antifungals and fibrates
  - decreased by phenytoin, barbiturates, glitazones
- mild elevation of serum aminotransferase = transaminase
  - < 2% patients
  - measure of liver function, monitor at 2-4 month intervals, reduce dose if necessary
- minor increases in creatine kinase
  - can lead to muscle pain and tenderness
Statins -
HMG CoA reductase inhibitors

• common adverse effects
  – mild GI symptoms, headache, insomnia, dizziness

• rare but serious adverse effects
  – myopathy (minimised by UQ10 treatment?)
  – rhabdomyolysis (breakdown of muscle resulting in myoglobin release into the bloodstream)
  – renal failure
  – hepatitis, liver failure

• contra-indicated in pregnancy
  – impaired fetal myelination

• withhold during infection, pre-surgery, post-trauma
Treatment of hypercholesterolaemia with bile acid sequestrants/resins

Cholestyramine, colestipol

• oral route - granular preparations, taken with liquid
• non-absorbable macromolecules
  – polymeric cationic exchange resins
• bind bile acid (cholesterol metabolites) preventing gut absorption
  – up to 10-fold increase in bile excretion
• increased demand for cholesterol for bile acid synthesis causes upregulation of hepatic LDL receptors, removal of LDL from plasma and more cholesterol metabolism
Bile acid sequestrants/resins

- Indications: hypercholesterolaemia
  mixed hyperlipidaemia

- common adverse effects
  - abdominal discomfort, bloating, constipation, flatulence

- rare adverse effects
  - increased TGs, faecal impaction, decreased absorption of fat soluble vitamins, steathorea

- decreases absorption of other drugs
  - not just anions, also drugs with neutral or cationic charge
    (including glycosides, thiazides, statins, aspirin)
  - give other drugs hours before or after resin
Ezetimibe

• specifically inhibits cholesterol absorption in the intestine by binding to a sterol transporter (Niemann-Pick C1-like 1 protein)

• does not affect absorption of bile acids, fat soluble vitamins

• lowers LDL
Ezetimibe

Possible side effects

• diarrhea, headache, tiredness
• allergic reactions, severe joint or stomach pain

• can be used alone in statin-intolerant patients, or in combination with all other lipid-lowering agents including statins (to reduce statin dose)
Treatment of hypercholesterolaemia with nicotinic acid / niacin

- Nicotinic acid = niacin = vitamin B3

- mechanism unclear
  - decrease secretion of VLDL particles from liver
  - reduces plasma LDL and triglycerides (so also for mixed hyperlipidaemia)
  - increases HDL
  - lowers potentially atherogenic lipoprotein (a)
    Lp(a) formed from LDL is found in plaques, inhibits thrombolysis
Nicotinic acid / niacin

• common adverse effects
  – vasosodilation, flushing, hypotension
  – nausea, vomiting
  – tolerance develops to flushing as gastric upsets

• rare adverse effects
  – itching
  – glucose intolerance
  – uric acid retention
  – may increase hepatic impairment

• not widely used except in combination
Treatment of hypertriglyceridaemia with fibrates

Gemfibrozil, fenofibrate

- agonists at nuclear receptors, so regulate gene expression
  - peroxisome proliferator activated receptor $\alpha$
  - increased synthesis of lipoprotein lipase (LPL)
- increase lipolysis of lipoprotein triglyceride
- moderate reduction in plasma triglycerides
- moderate increase in HDL
- variable effects on LDL
- generally used as adjunct to dietary changes for high TGs, mixed hyperlipidaemia, and second line therapy for hypercholesterolaemia
Fibrates - PPARα agonists

Precautions

• mild elevation of serum aminotransferase
  – monitor at 3 month intervals, reduce dose or discontinue if necessary

• common adverse effects
  – nausea, dry mouth, headache, rash

• rare adverse effects
  – arrhythmias
  – gallstones
  – photosensitivity
  – impotence
  – depression
Treatment of hypertriglyceridaemia with fish oils

Omega 3 fatty acids e.g. eicoapentanoic acid (EPA) docosahexanoic acid (DHA) by diet (oily fish) or capsule

• reduce triglycerides and VLDL

Plant sources such as flaxseed, canola, walnuts and their derived vegetable oils contain α-linolenic acid (ALA) which can be converted to EPA/DHA, but conversion is variable
Treatment of hypertriglyceridaemia with fish oils

Possible side effects:
• aftertaste, fishy burps
• diarrhea, abdominal discomfort
• blood thinning effect

Severe hypertriglyceridemia requires polytherapy
# Drug regulation of serum lipids

<table>
<thead>
<tr>
<th></th>
<th>↓ LDL</th>
<th>↑ LDL receptor</th>
<th>↑ HDL</th>
<th>↓ TGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>✓ ✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Bile acid resins</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>↓ Lp(a)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓ ↑</td>
<td></td>
<td>✓</td>
<td>✓ LPL</td>
</tr>
<tr>
<td>Fish oil</td>
<td>↓ VLDL</td>
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<td>✓</td>
<td>✓</td>
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</tbody>
</table>
Where do the drugs work?

Ezetimibe

Bile acid resins

Statins

Fibrates