CASE 6

Short case number: 3.2.6
Category: Cardiovascular
Discipline: Medicine
Setting: General Practice
Topic: Hyperlipidaemia – congenital hyperlipidaemia, pharmacological and dietary management [SDL]

Case

Sven Graham, aged 28 years presents for a check up. His brother recently died from an acute myocardial infarction aged 30 years. His advises that his father also died at 32 from a heart attack. On examination Sven has normal blood pressure. You order some investigations and these confirm a diagnosis of severe hypercholesterolaemia and hypertriglyceridaemia.

Questions

1. Outline how cholesterol and triglycerides are synthesised, taken into cells and transported.
2. List the common causes for high cholesterol. Given Sven's presentation, what congenital causes of hypercholesterolaemia and hypertriglyceridaemia need to be considered?
3. What is the role of LDL and of HDL as markers of cardiovascular risk and why?
4. Using a table, summarise the mechanism of action of each of the following drugs - bile acid sequestrants, nicotinic acid derivatives, HMGCoA reductase inhibitors, fibrates.
5. How would you manage Sven?
6. Outlines the principles of dietary management and list 4 examples of foods that are low in cholesterol.

Suggested reading:

- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014. Chapter 18.

Advanced Reading

- Ford I. Murray H. Packard CJ. Shepherd J. Macfarlane PW. Cobbe SM. West of Scotland Coronary Prevention Study Group. Long-term follow-up of the West of Scotland Coronary Prevention Study. New England Journal of Medicine. 357(15):1477-86, 2007 Oct 11. http://www.nejm.org/doi/full/10.1056/NEJMoa065994

ANSWERS

1. **Outline how cholesterol and triglycerides are synthesised, taken into cells and transported.**
   Cholesterol is exported to the peripheral tissues in LDL and VLDL. About 70 percent of the cholesterol molecules in LDL are esterified with a fatty acid (for example, palmitate) on the OH group. Cells take up cholesterol from the LDL by means of LDL receptors in the outer cell membrane.

   The pathway for uptake involves several steps, including the following:

   1. The assembly of the receptor-LDL complexes into a coated pit on the cell surface.
   2. The pit folds into a spherical endosome which is a small vesicle of cell membrane with receptor-LDL complexes on the inside.
   3. The endosome fuses with a lysosome containing a large number of degradative enzymes and a low pH on the inside.
   4. The receptors separate from the endosome-lysosome and return to the cell surface.
   5. The cholesterol esters are hydrolysed to free cholesterol.
   6. The free cholesterol inhibits the synthesis and/or causes the degradation of HMG-CoA reductase and of LDL receptor. This last step ensures that more cholesterol will not be taken up or made than is needed.
   7. Cholesterol is re-esterified with a fatty acid for storage inside the cell.

   A close connection exists between the regulation of cholesterol biosynthesis and uptake. When HMG-CoA reductase is inhibited, the cell responds by synthesizing more LDL receptors to ensure the uptake of cholesterol from the serum. When cholesterol is present in a high enough concentration in the cell, LDL receptors are not exported to the cell surface i.e. down regulation. The capability of LDL receptors to *remove* LDL cholesterol from the circulation can rationalise these clinical observations. If little cholesterol is available in the diet, the cells of the peripheral tissues respond by up-regulating the number of LDL receptors on the cell surface. The higher concentration of receptors means that more of the cholesterol will be removed from the circulatory system. Because the inappropriate deposition of cholesterol is a major contributor to blocked arteries, if the cholesterol is removed from the circulation, less risk of blockage exists. On the other hand, if a large amount of cholesterol exists in the diet, and the cells have enough for their needs, they will synthesise fewer LDL receptors, less cholesterol will be removed from the circulatory system, and the risk of artery disease increases further.

2. **List the common causes for high cholesterol. Given Sven's presentation, what congenital causes of hypercholesterolaemia and hypertriglyceraemia need to be considered?**
   -Polygenic or non-familial hypercholesterolaemia
   -Familial hypercholesterolaemia
   -Secondary hypercholesterolaemia:
   - Hypothyroidism
   - Pregnancy
   - Cholestatic liver disease
   - Medications (diuretics, cyclosporine, corticosteroids, androgens)
   - Nephrotic syndrome
   - Anorexia nervosa
   - Porphyria
   - Hyperparathyroidism

The association of elevated lipids and cholesterol suggests that Familial Combined Hyperlipidaemia and Dysbetalipoproteinaemia need to be considered.

3. What is the role of LDL and of HDL as markers of cardiovascular risk and why?

LDL and HDL are plasma lipoproteins which are complexes of lipid and proteins. Lipoproteins carry the hydrophobic lipids. Furthermore they possess surface proteins (apoproteins) that are cofactors and ligands for lipid-processing enzymes. They are classified by size and density (defined as the ratio of lipid to protein) and are important because high levels of low-density lipoproteins (LDLs) and low levels of high-density lipoproteins (HDLs) are major risk factors for atherosclerotic heart disease.
Lipids in the blood, particularly low density lipoprotein (LDL) and very low density lipoprotein (VLDL), bind to endothelial cells and are oxidized in the subendothelium. Uptake of oxidized lipids and macrophage transformation into lipid-laden foam cells result in the typical early atherosclerotic lesions called fatty streaks. Therefore high levels of LDL increase the risk of cardiovascular disease.
Low levels of HDL are also correlated with an increased risk of heart disease. This is because HDL plays a major role in reverse cholesterol transport, by mobilizing cholesterol from the periphery to promote return to the liver.

4. Using a table, summarise the mechanism of action of each of the following drugs - bile acid sequestrants, nicotinic acid derivatives, HMGCoA reductase inhibitors, fibrates.

Medication	Action
Bile acid sequestrants: Cholestyramine Colestipol	These prevent reabsorption of bile acids, therefore increasing de novo bile acid synthesis from hepatic cholesterol. The resultant depletion of hepatic cholesterol up regulates LDL-receptor activity and reduces LDL cholesterol.
Nicotinic acid derivatives	This reduces peripheral fatty acid release with the result that cholesterol and triglycerides decline whilst HDL cholesterol increases.
HMGCoA reductase inhibitors (statins)	Statins inhibit cholesterol synthesis thereby upregulating the activity of the LDL receptor. This increases clearance of LDL and its precursor, IDL, there by leading to a second mechanism by which LDL is reduced.
Fibrates	These medications stimulate peroxisome proliferators activator receptor (PPAR)-alpha which controls the expression of the gene products that mediate the metabolism of triglycerides and HDL. As a result the synthesis of fatty acids, triglycerides and VLDL is reduced whilst that of lipoprotein lipase that catabolises TG is increased. In addition, the promoter regions of genes such as apolipoprotein A1 and the ATP binding cassette A1 are up-regulated, leading to increased cholesterol reverse transport via HDL.

5. How would you manage Sven?

Combination therapy, which includes either:
-statins plus fish oil
-statin plus nicotinc acid

-statin plus fibrate (Increase chance of rhabdomyolysis, less with Fenofibrate, higher with Gemfibrozil)

- If triglyceride is between 2 and 4 with raised cholesterol, commence with statin
- If triglyceride exceeds 4 and raised cholesterol, commence with Fibrate or/and fish oil

6. Outlines the principles of dietary management and list 4 examples of foods that are low in cholesterol

- Reduce the intake of saturated and trans-saturated fat to less than 7-10% of total energy,
- Replace sources of saturated fat and cholesterol with alternative choices of lean meat and low fat dairy, polyunsaturated spreads and low glycaemia index CHO,
- Reduce energy dense foods such as fats and soft drinks, whilst tinkering activity and exercise to achieve stable or negative energy balance,
- Increase consumption of cardio-protective and nutrient dense foods such as vegetables, unrefined CHO, fish, legumes, fruit,
- Adjust ETOH consumption, reducing the intake if necessary,
- Supplement diet with added intake of n-3-fatty acids, dietary fire and plant sterols.

Foods low in cholesterol includes fish, unprocessed grains, green vegetables and fruit.