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11. TREATMENT OF LIPID DISORDERS IN CARDIOVASCULAR PATIENTS

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11.1 Introduction

We can measure a variety of appropriate lipids in the blood stream of patients and we know the accuracy and precision with which we can do this. But it would be a waste of time and effort and money if we merely chased more accurate and more precise assays, if the results of these assays did not also benefit the patients from whom the samples had been taken. The aim of this lecture is to show that identifying those at risk of cardiovascular disease by means of good analytical methodology does indicate a variety of treatments that can be offered to the patients and that that treatment does benefit their cardiovascular risk. There are long-term studies that show that this is true on a statistical basis and these results will be referred to. But the emphasis of the lecture is to show the help that has been given to individual patients because of the hard work that has been done in clinical chemistry laboratories

11.2 Hypertriglyceridemia and CHD risk

There is some evidence for a role of triglyceride in the development of CHD:

- fasting serum TG concentration is an independent risk factor in epidemiologic studies
- direct role of TG-rich lipoproteins in atherogenesis
- association with other abnormalities of lipid and carbohydrate metabolism
- association with hypercoagulability

TG elevation is generally associated with increased risk for CHD on univariate analysis. Is the relation causal? Or is the TG elevation simply a marker for CHD risk through its associations with such conditions as type II diabetes mellitus, low HDI-C, and obesity? The TG-CHD relation tends to weaken or disappear on multivariate analysis.

There are also a number of associated abnormalities that could play a role in making triglyceride a cardio-vascular risk factor. These are listed in Table 2.

Table 1. Clinical Benefits of Cholesterol Reduction (1)

A recent meta-analysis of 38 trials demonstrated that for every 10% reduction in TC $\,$

- CHD mortality decreased by 15% (P<0.001)
- total mortality decreased by 11% (P<0.001)

Decreases were similar for all treatment modalities Cholesterol reduction did not increase non-CHD mortality

Frequent Causes of 2° Hypertriglyceridemia:

- Diabetes mellitus
- Nephrotic syndrome
- Chronic renal failure
- Estrogen replacement therapy
- Excessive alcohol intake
- Medications

Table 2. Hypertriglyceridemia and CHD risk: associated abnormalities

Accumulation of chylomicron remnants Accumulation of VLDL remnants Generation of small, dense LDL-C Association with low HDL-C Increased coagulability plasminogen activator inhibitor (PAI-1) factor VIIc activation of prothrombin to thrombin

11.3 Initial investigations of the patient

The first stage in dealing with an individual patient is to assess the degree of cardiovascular risk of that particular patient.

Perhaps I should first of all try to modify some widely held views. On the one hand, although we can quite easily calculate a normal range of sodium or potassium, there is no such thing as a normal range for cholesterol. The sodium or potassium normal ranges are calculated statistically from the general healthy population. But in Western Europe and the United States a calculation of the upper limit of the total cholesterol normal range by such statistical methods shows that the $95^{\rm th}$ percentile is sometimes quite a high level, one which is generally agreed to be unhealthy.

On the other hand, it is not helpful to identify a particular cholesterol level below which the risk is acceptable and above which the risk is increased. Thus, a cholesterol level which, in a young adult who exercises well, has no family history, and has a good HDL concentration, may be perfectly acceptable for that individual, at least for the time being, but might be dangerous in an older patient with a strong family history, and previous cardiovascular prob-lems who lives a sedentary life and who has a very low HDL cholesterol level. The former patient may require treatment in due course, but it is to no-one's benefit to jump in immediately and proffer lifelong treatment with hypolipidaemic drugs. It is therefore necessary to assess every individual patient and to ask questions about their family history of cardiovascular disease, their personal cardiovascular history, to find out what their blood pressure is, whether they smoke (and how much), are they overweight, do they drink excess alcohol, do they have an unhealthy diet, and to look in detail at various aspects of their lipid profile and their lifestyle.

From_these factors an overall cardiovascular risk can be calculated and those with a high cardiovascular risk can be treated without delay, but those without such a risk need not be immediately treated despite having a cholesterol level which is above a certain value.

Secondly, it is important to ascertain whether the hyperlipidaemia is a primary condition or secondary to some other medical condition. In particular, hypothyroidism, diabetes or alcoholism can cause increases in blood lipids levels which, if looked at on their own would suggest that treatment should be immediately instituted. However, it is preferable to treat the hypothyroidism, the diabetes, or even the alcoholism, to see if the cardiovascular risk associated with the lipid profile improved significantly when these treatments are instituted.

Finally, every patient must be treated as an individual and the whole of his or her cardiovascular risk profile must be assessed, together with that of any other primary cause of the hyperlipidaemia.

In those with a high cardiovascular risk it is usually essential to start treating with hypolipidaemic drug treatment as soon as possible but in those whose cardiovascular risk is less serious, it is often helpful to try and change the patient's lifestyle to something which is more healthy and which change will itself improve the lipid profile and cardiovascular risk. Thus, a patient with a very high cholesterol will require drug treatment without delay, whether or not there are other factors that increase the cardiovascular risk. But if the cholesterol is only mildly raised, then time can be taken to attempt lifestyles changes before considering seriously the need for hypolipidaemic drug treatment. Such lifestyle changes include changes in diet, increase in exercise, weight loss and cessation of smoking. Perhaps it should also be pointed out that many patients dislike the idea of having to take drugs that are absorbed into their blood system and have specific effects on their liver, particularly if, as in the case of hypolipidaemic drugs, these have to be taken virtually for the rest of their life.

Examples of successful lifestyle changes are given in the following tables.

Male aged 58 years — mildly raised cholesterol and triglycerides. Followed advice on diet, exercise and weight loss

testdate	cholesterol	triglycerides
01/11/2000	5.6	2.2
12/12/2000	4.0	1.8
14/01/2002	4.1	1.6

Female aged 28 – family history of raised cholesterol; did not want long-term drug therapy; followed advice on diet, exercise and weight loss

testdate	cholesterol	triglycerides	HDL-C	LDL-C
06/02/2001	9.5	0.8	1.9	7.3
18/06/2001	6.1	0.6		
25/09/2001	5.9	0.7	1.3	4.3
14/02/2002	6.2	0.7	1.3	4.6

11.4 DrugTreatment

There are three major types of drug treatment that have been shown to be effective (2).

1.4.1 Bile-acid binding Resins

These resins are taken orally with food and pass through the gastrointestinal tract without being absorbed into the blood stream. Some patients see this as an advantage. During its passage through the small intestine the Resin is able to absorb bile acids that are secreted by the bile duct into the duodenum. Approximately 20-30 g. of bile acids per day are secreted into the duodenum and then reabsorbed further down the small intestine. If these bile acids are unable to be re-absorbed because they are bound to resins, then up to 30g per day of bile acids (and hence cholesterol) are lost to the body. Also the bile acids are unable to perform their normal function of binding with the lipid products in the food, allowing the fats to be absorbed in the form of forming micelles. The enterohepatic circulation of bile acids is therefore broken, cholesterol and triglycerides in the diet are absorbed much less readily. Additionally, because bile acids are not reabsorbed and returned to the liver, more cholesterol must be metabolized into bile acids within the liver in order to maintain the secretion of bile acids into the duodenum. These activities combine to cause a mild to moderate reduction in the blood cholesterol level. Unfortunately their use is often accompanied by gastrointestinal side-effects and they are rather difficult to take on a regular three-times-a-day basis. Their use has therefore declined somewhat in recent years. An example is given in the following table.

Male aged 61; raised cholesterol for 5 years; initially on Questran (6 sachets); changed to Questran (4 sachets) and Lipantil micro

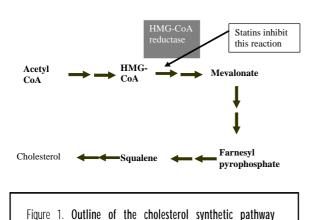
testdate	cholesterol	triglycerides	HDL-C	LDL-C
04/01/2000	5.8	1.3	1.3	3.9
05/12/2000	5.4	1.2		
05/02/2001	5.5	1.3		
25/06/2001	5.6	0.8		
15/10/2001	4.7	0.9		

1.4.2 Statins

The main activity of a statin is to inhibit the enzyme hydroxymethyl CoA reductase. This enzyme is, of course, an integral part of the cholesterol synthetic mechanism. Inhibition of its activity reduces the amount of cholesterol that can be synthesis within the liver. Statins, of which there are now quite a number of competing varieties, are therefore particularly good at reducing the level of blood cholesterol. They are also responsible for reducing the level of LDL cholesterol and triglycerides, but to a lesser extent and probably as a secondary action to the inhibition of cholesterol synthesis.

Table 3. Forms of available statins

Simvastatin (Zocor)	Atorvastatin (Lipitor)
Pravastatin (Lipostat)	Cerivastatin (Lipobay)
Fluvastatin (Lescol)	Lovastatin



An examples of treatment with statins is given in the following table.

Male 74 years old — raised cholesterol for several years, treated with Pravastatin— changed to Atorvastatin

testdate	cholesterol	triglycerides	HDL-C	LDL-C
04/02/1998	7.6	2.0	1.5	5.2
21/01/1999	4.1	1.0		
17/07/2000	5.3	1.2		
15/01/2001	4.6	1.6	1.4	2.5
24/09/2001	5.0	1.6	1.3	3.0

1.4.3 Fibrates

The mechanism of action of the fibrate drugs is not quite as clear as that of statins and resins. Nevertheless, a list of actions for which they seem to be responsible has been drawn up: -

 a) a significant lowering of plasma triglyceride levels (by 20-40%). This is mainly via the stimulation of the activity of lipoprotein lipase which is responsible for hydrolysing the trigyceride-rich Very Low Density Lipoproteins (VLDL) fraction.

- b) a modest rise in HDL-cholesterol (approx. 10%)
- c) variable change in LDL-cholesterol most fibrates cause a small (approx. 10%) fall, but at least one fibrate (Gemfibrozil) can sometimes cause a rise in LDL-cholesterol
- d) a possible inhibition of fatty-acid synthesis and increase in fatty-acid breakdown.
- e) reduction in platelet reactivity and aggregation. This action thus reduces the likelihood of platelet clumping and hence of clot formation and vessel blockage.

Work in recent years has indicated fibrates influence multiple steps in the metabolism of lipids and lipoproteins by modifying the transcription of a variety of genes through activation of the peroxisomal proliferator activated receptor (PPAR) mechanism (3, 4)).

Fibrates currently available include: -

- Fenofibrate (Lipantil)
- Ciprofibrate (Modalim)
- Bezafibrate (Bezalip)
- Gemfibrozil (Lopid)
- Clofibrate (Atromid-S)

In summary then there is good evidence to support the views that treatment of hypercholesterolaemia and hypertriglyceridaemia can cause reduction in levels of these lipids and their associated harmful lipoproteins and that such a reduction will result in a significant decrease in the cardiovascular risk of the patient. An example of treatment with a fibrate is given in the following table.

Male aged 60 - initially treated with Simvastatin only - later also put onto Lipantil micro

testdate	cholesterol	triglycerides	HDL-C	LDL-C
06/01/98	7.2			
17/12/1998	5.6			
05/03/2000	5.7	4.4		2.5
14/07/2000	5.6	1.5		
22/12/2000	5.2	2.0		
04/06/2001	5.1	1.1		
14/12/2001	5.2	1.5	1.2	3.3
09/04/2002	4.5	1.2	1.1	2.9

Recommended literature:

- Gould AL, Rossouw JE, Santanello NC, Heyse JE, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. Circulation 1998; 97: 946-52.
- Hardman KG, Limbird LE. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th edition, McGraw-Hill 1996.
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