Atherosclerosis: Hyperlipoproteinaemia

Uptodate

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University of London Audio-Visual Centre, 1975.
Made for The British Postgraduate Medical Federation.

Black-and-white
Duration: 00:34:50:01

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<Opening titles>

<Opening film of commuters walking along crowded London streets, including men wearing bowler hats, interspersed with scenes of traffic. Brief close-up scenes in sequence of exhaust fumes; mouth smoking cigarette; sausages, egg and bacon frying in pan; callipers measuring thickness of skin fat; blood pressure gauge, rotating molecular diagram.>

<Thompson to camera>

The terms hyperlipoproteinaemia and hyperlipidaemia are often used interchangeably, however on conceptual grounds I prefer the former for reasons which I hope will become clear during the course of this programme.

Let us start by briefly reconsidering the factors involved in the pathogenesis of atheroma. This process results from the interaction of the three main factors involved in atherogenesis.

<Thompson narrates over series of diagrammatic slides>

Firstly, the arterial wall. <*Next diagram*> Secondly, the components of the blood, and thirdly, <*next diagram*> the haemodynamic forces acting within the arterial lumen.

<Thompson to camera>

During this programme, we shall focus on the role of the components on the blood, in particular the plasma lipids. There are two main lines of evidence showing the aetiological importance of blood lipids in atherogenesis. Firstly, direct evidence such as that obtained by Smith and her colleagues working in Aberdeen, who measured the cholesterol content of arteriole tissue taken at autopsy.

<Thompson narrates, using indicator, over series of diagrams and slides, interspersed with talk to camera>

These workers showed a close correlation between the amount of cholesterol in the arteriole wall and the concentration of cholesterol in serum.

<*To camera*> The second line of evidence is indirect and derived from epidemiological surveys. Studies by Slack and her colleagues, <*next diagram*> and Goldstein, and Lewis have shown that between 30 and 60% of patients with ischaemic heart disease have either a raised serum cholesterol or triglyceride or a combination of them both. Estimates of prevalence depend on whether the 95% or 90% cut-off limit was used to define hyperlipidaemia.

<*To camera*> Up to now we've talked about hyperlipidaemia, however it is now well established that lipids are not transported as such, but travel in the form of lipid-protein complexes, known as lipoproteins. Four main classes of lipoproteins have been described. <*Next image of photomicrographs*> These are the large chylomicrons which consist mainly of triglyceride which has been derived from the absorption of dietary fat. <*Indicates next image*> Very low density lipoproteins or

VLDL which are somewhat smaller but of similar composition, and which represent triglyceride which has been endogenously synthesised in the liver or small intestine. Low density lipoprotein, otherwise known as LDL, which is in fact a smaller particle than VLDL – note the scale has changed. And high density lipoprotein or HDL which is subdivided into HDL 2 and HDL 3.

<*To camera*> If one examines the lipid composition of the proteins found in fasting plasma, <*next diagram*> one can see that very low density lipoprotein or pre-β-lipoprotein consists mainly of triglyceride but also contains some cholesterol. Low density lipoprotein or β-lipoprotein contains mainly cholesterol but does have some triglyceride as well. High density lipoprotein or α-lipoprotein consists mainly of phospholipid but also contains substantial amounts of cholesterol. <*To camera*> Thus a raised serum cholesterol could result from an increase in VLDL, LDL or HDL.

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Let us now next examine the relationship between lipoproteins and atheroma. Climov and his colleagues, working in Leningrad, have done just this by taking arteriole tissue, <*next diagram*> placing it in a tissue press and squeezing it until the tissue fluid is forced out and can be collected by means of a capillary tube. They then electrophoresed and quantitated the tissue fluid lipoproteins.

<*Next slide*> They found that the amount of β and pre-β-lipoprotein in normal aortic tissue fluid was 169 mg/100ml, whereas in aortae which showed fatty streaks this increased to over 400, and in grossly atheromatous aortic tissue fluid to over 800mg/100ml.

<*To camera*> It's of interest that they found no increase in HDL even in grossly atheromatous aortic tissue fluid. It has been suggested that this phenomenon, namely the increase in β and pre-β-lipoprotein without any increase in α-lipoprotein, is due to the selective retention of pre-β and β-lipoprotein.

If one considers the structure of VLDL and HDL, one will see that <*next diagram*> both contain apoB, whereas this apoprotein is not present in HDL. <*To camera*> It has been suggested that hydrophobic and anionic interactions between apoB containing lipoproteins and certain constituents of the arteriole wall can lead to selective retention of LDL and VLDL, and that this process is accentuated in patients who have elevated amounts of these two types of lipoproteins in their plasma.

Having examined the role of lipoproteins in atherogenesis, let's now go on to look at the methods which are used to quantitate them. Five stages – there are five stages in the process of lipoprotein quantitation. <*Next slide*> Firstly, one assays the total amount of cholesterol and triglyceride in plasma taken from patients after a minimum fast of 10 to 12 hours duration. <*Next slide*> Secondly, one ultracentrifuges plasma at its own density of 1.006 into a supernatant which contains VLDL and an infranatant which contains a mixture of LDL and HDL. <*Next slide*> Thirdly, one precipitates the LDL from the density more than 1.006 fraction by the addition of either heparin-manganese chloride or dextran sulphate and calcium chloride, and then assays the cholesterol in the precipitate which represents LDL and in the supernatant which represents HDL.

<*Next slide*> Fourthly, we observe the appearance of plasma after it's been standing overnight in the refrigerator. This enables us to detect the presence of chylomicrons which float to the top like cream in a bottle of milk. And lastly, <*next slide*> we electrophorese both plasma and the density less than 1.006 fraction on either paper or, better still, agarose gel.

<*To camera*> This is just to remind you that electrophoresis of normal fasting plasma <*next diagram*> shows three bands. Firstly of β-lipoprotein or LDL, secondly pre- β-lipoprotein or VLDL, and thirdly, the most rapidly-moving of all, α-lipoprotein or HDL. If plasma had been taken after a fatty meal, then it would contain chylomicrons which would remain at the origin of an electrophoretic strip, but under normal circumstances when one is looking at plasma, one insists on a fasting sample, and therefore chylomicrons will not be found.

<*To camera*> Using methods similar to those that we have just described, Lewis and his colleagues have defined the upper limits of normal in a population of healthy Londoners. <*Next slide*> The total cholesterol should not exceed 280mg percent in males and 290 in females; the triglyceride 230 in males and 170 in females; the VLDL cholesterol 40 in males and 30 in females; and lastly the LDL cholesterol – 205 in males and 215 in females.

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<*To camera*> Let us now go on to consider the various classifications of hyperlipoproteinaemia which have been developed during the past few years. Initially, Frederickson and his colleagues described five phenotypes, but a World Health Organization committee revision increased this number to six, <*next diagram*> by subdividing type II into IIa and IIb.

Let's examine the criteria they used. The type I pattern is characterised by an increase, often gross, in plasma triglyceride, and this is entirely due to accumulation of chylomicrons. The type IIa pattern characterised by a marked increase in LDL cholesterol without any increase in plasma triglyceride. The type IIb pattern also shows an increase in LDL cholesterol, but there is also a slight but definite increase in plasma triglyceride due to the presence of excess quantities of VLDL.

The type III pattern is characterised by both an increase in triglyceride and LDL cholesterol, but the unique feature of this pattern is the presence, on electrophoresis, of the VLDL which migrates, not with the usual pre-β mobility but with β mobility. This has given rise to the term broad-β disease.

The type IV pattern is characterised by increase in plasma triglyceride without an increase in LDL cholesterol, and the hypertriglyceridaemia in the type IV pattern is due to an excess of VLDL.

The type V pattern is also characterised by an increase in plasma triglyceride without any increase in LDL cholesterol, but differs from the type IV in as much as there is an increase in both VLDL and in chylomicrons.

<*To camera*> What's the frequency of these various types of hyperlipoproteinaemia in ischaemic heart disease? <*Next slide*> This has been examined by Hazzard and his colleague in Seattle, and Lewis and his colleagues in London. Now as you can see, patients with the type IIa pattern were fairly common, appearing between 14 to 25%, patients with the type IIb pattern slightly less common – 8 to 15%, but the most frequent form of hyperlipoproteinaemia found in these two groups of patients with ischaemic heart disease was the type IV pattern which occurred in over 30% in both series. Patients with the type III and V patterns were relatively rare.

<*To camera*> Let us now consider the clinical features of these various forms of hyperlipoproteinaemia taking each one in turn.

<*Next diagram*> The type I pattern is, as we've already said, characterised by an increase in plasma triglyceride due, almost entirely, to excess of chylomicrons as seen in plasma which has been stood overnight in the refrigerator and as observed on electrophoresis. <*To camera*> These patients often present in childhood and the presenting feature is frequently an attack of acute abdominal pain, rather similar in some of its features to acute pancreatitis. This is a rare disorder which is thought to be due to a recessive gene, and from the mechanistic point of view, it appears that there is an absence or decrease in lipoprotein lipase which prevents these patients from clearing dietary triglyceride carried in the form of chylomicrons from their plasma. Interestingly enough, it does not appear to be associated with any increased tendency to atheroma.

<*Next diagram*> The next type, type II, which as we've already said is subdivided into type IIa and IIb, is more common and much more important from the point of view of predisposition to ischaemic heart disease. It is characterised by an increase in LDL in type IIa; and if this strip was from a patient with type IIb, there would also be a slight increase in pre-β-lipoprotein.

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<*To camera*> These patients often present relatively early in life with various features associated with atheroma. These include <*next slide – close-up photograph of eyes*> an arcus, and in this particular case this man's arcus developed in his twenties. <*Next slide – x-ray*> In addition, one can find evidence of atheroma, and this shows a coronary angiogram which reveals the presence of an ostial stenosis in the right coronary artery of a relatively young patient with a type IIa pattern. <*Next slide – x-ray*> Evidence of atheroma elsewhere can be observed if one carries out an aortogram as has been done here. And, as you can see, there is a marked narrowing at the bifurcation of the aorta.

<*To camera*> In addition to evidence of atheroma, these patients may present with xanthomata. <*Next photograph – showing ankles*> This is particularly the case where the disorder is familial in origin. This patient had familial hypercholesterolaemia or familial type II hyperlipoproteinaemia and she developed these Achilles tendon xanthomata at about the age of twelve. When this disorder is inherited, <*to camera*> this often appears to be transmitted in the form of a Mendelian dominant gene, and thus one may find that a patient is heterozygous or homozygous. Homozygotes have one very striking feature, namely the presence of cutaneous xanthomata <*next photograph – showing ankles*> as can be seen in this picture of a homozygote, familial hypercholesterolaemic girl. Their prognosis is extremely poor and they frequently die from coronary atheroma before they reach the age of 30.

<*To camera*> The next type that we should examine is the type III disorder <*next diagram*> and this, although relatively rare, is extremely responsive to treatment and therefore well worth diagnosing. This is characterised by the presence of both VLDL-sized particles and chylomicrons in fasting plasma, and on electrophoresis by this broad-β band. <*To camera*> These patients frequently show multiple sites for xanthomata. Here, <*next photograph*> for example, is a patient with xanthelasma associated with a type III pattern in his plasma. <*Next photograph*> In addition, he had xanthomata, tendon xanthomata, on the backs of both hands. <*Next*

photograph> He also showed these very florid tuberous xanthomata on his elbows, and in addition <*next photograph*>, he had eruptive xanthomata on both his knees and also his buttocks<*next photograph*>. <*Next photograph*> Perhaps the most characteristic feature of this disorder, although maybe the most difficult to demonstrate, is the presence of palmar striae. I hope that perhaps with the eye of faith you will be convinced that there is a faint, abnormal discolouration in the crease of this man's palm.

<*To camera*> Let's now consider the last two types in the classification, namely types IV and V. It seems logical to consider these at one and the same time, in as much as they frequently interchange according to which diet an individual patient is on. <*Next diagram*> The type IV disorder is described as the presence of hypertriglyceridaemia due to VLDL present in excessive quantities, but without the presence of fasting chylomicrons, <*Next diagram*> whereas the type V disorder shows hypertriglyceridaemia which is due both to the presence of VLDL and also to chylomicrons.

<*To camera*> As we've said, these forms of hyperlipoproteinaemia particularly type IV are common and are probably of major importance in the pathogenesis of ischaemic heart disease. From the clinical point of view, patients with the type IV pattern are often obese. They may show evidence of glucose intolerance and hyperuricaemia. They, like some of the other forms of hyperlipoproteinaemia we have been discussing, will often show xanthomata, in particular will show the eruptive type of xanthomata which are so characteristic of hypertriglyceridaemia.

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Although sometimes the type IV and type V disorders may be inherited, more often they are secondary to some form of underlying disease, and for a consideration of these various secondary causes of hyperlipoproteinaemia, I should now like to hand over to my colleague, Dr Barry Lewis.

<Lewis to camera>

I would like to discuss the quite large group of hyperlipidaemias of defined aetiology, the secondary hyperlipidaemic states, of which some are very well known and others are perhaps less familiar. I was quite surprised when I first started seeing lipid patients at the Hammersmith about seven or eight years ago at the remarkable frequency of some of these secondary hyperlipidaemias. More recently, we reviewed the prevalence of them at the Hammersmith Lipid Clinic and this suggested that at least 15%, probably about 1 in 6 patients with hyperlipidaemia, had a recognisable underlying cause. They are important because they appear to bear the same relationship to ischaemic heart disease as that possessed by the primary hyperlipoproteinaemias that Gilbert Thompson has been speaking of. It may be that the secondary hyperlipoproteinaemias are fractionally less hazardous in this respect because often they are acquired during life and their duration is therefore less than the primary, often congenital, hyperlipidaemic states.

The treatment of the secondary hyperlipidaemias is, where possible, that of the underlying cause, otherwise it may be deemed necessary to treat them non-specifically by diet or by drugs or, on occasion, by plasma phoresis. The diagnosis of secondary hyperlipidaemia is for the first part clinical; it depends on the history and examination, but certain laboratory tests are of help in excluding subtler versions of secondary hyperlipidaemia. These would include liver function and renal function tests, the serum proteins, and a careful test of thyroid function such as measurement of thyroid-stimulating hormone.

Now the six patterns of serum lipoprotein that are of help in differential diagnosis of the primary hyperlipidaemias are of rather less value with the secondary states. However, some of these disorders tend to produce chiefly hypercholesterolaemia and others predominant hypertriglyceridaemia, and this is about as far as one can go with the classification. I'll start then with the secondary hypercholesterolaemias of which few are common and many are rare.

<Lewis narrates over series of slides>

Hypothyroidism is perhaps the most important and there is little proportionality between the severity of the hyperthyroidism and the magnitude of the hypercholesterolaemia, so slight hypothyroidism may produce a considerable elevation in cholesterol level. Almost as common are obstructive jaundice and nephrotic syndrome. Patients with obstructive jaundice have a curious, <*to camera*> almost unique lipoprotein in plasma which is rich in free cholesterol but poor in triglyceride, and that is why the serum pattern is usually of a pure hypercholesterolaemia.

<*Next slide*> In a nephrotic syndrome, when the disorder is relatively mild, there tends to be pure hypercholesterolaemia, but in the grosser forms of the disorder hypertriglyceridaemia becomes more prominent. <*To camera*> The mechanism appears to involve overproduction of lipoprotein, and the basis of this may well be that serum albumin normally binds free fatty acids as they circulate, but when albumin concentrations become low, free fatty acids are more weakly bound and can correspondingly escape more easily from plasma into the tissues. And the increase input of free fatty acids into the liver is likely to be the reason for overproduction of lipoprotein triglyceride.

Now there are several rarer causes of secondary hypercholesterolaemia shown in the next chart <*next slide*>. Acute porphyria, acute intermittent porphyria, is one and various dysglobulinaemias are another. Idiopathic hypercalcaemia and vitamin D intoxication is an occasional cause of moderate hypercholesterolaemia, and primary carcinoma of the liver an occasional, theoretically very interesting one.

<*To camera*> The mechanism in acute porphyria is poorly understood and the same applies I think to the hypercalcaemic states. In the paraproteinaemias and in systemic lupus erythematosus, there may be an immune complex formation between the abnormal globulin and lipoprotein itself; and in other patients, it may well be that lipoprotein lipase is inhibited, perhaps by antibody binding of the necessary co-factor.

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The patients with the primary carcinoma of the liver show hypercholesterolaemia in a minority. The mechanism is fascinating and may involve the fact that the malignant cell retains its ability to synthesise cholesterol, but loses the normal feedback control of cholesterol synthesis by cholesterol itself.

There are other causes of secondary hypercholesterolaemia too, shown in the next card <*next slide*>. Exposure to certain halogenated insecticides can produce an increase in serum α-lipoprotein levels, which manifests as a mild hypercholesterolaemia of no known clinical significance, so the main point of its recognition is to justify withholding treatment.

In Turner's syndrome, there may be quite considerable hypercholesterolaemia which responds well to oestrogen replacement therapy. And in growth hormone deficiency, whether the aetiology is panhypopituitarism or selective hormone deficiency, as in ateliotic dwarfism, hypercholesterolaemia is a characteristic feature and may be quite pronounced and also tends to respond to growth hormone replacement.

<*To camera*> I'd like to turn now to the several causes of secondary hypertriglyceridaemia which, as Dr Thompson has told you, is rather prominent amongst patients with raised serum triglyceride levels. <*Next slide*> Rather more often, there is a combination of a genetic hypertriglyceridaemic state aggravated by an environmental factor such alcoholism or perhaps obesity. This chart shows the four common causes of secondary hypertriglyceridaemia, probably in decreasing order of frequency. About one third of uncontrolled diabetics have raised serum triglyceride levels which is perhaps one of conceivably multiple reasons that diabetics have a marked predisposition to ischaemic heart disease and other atherosclerotic changes. <*To camera*> The diabetic usually shows primary hypertriglyceridaemia, but occasionally massively raised levels occur and may be associated with xanthomas or acute abdominal pain.

<*Next slide*> Alcoholic hypertriglyceridaemia perhaps has not been sufficiently recognised as an extremely frequent secondary hypertriglyceridaemia <*to camera*> occurring not only in its own right, but as an aggravating mechanism in primary

hypertriglyceridaemic states. <*Next slide*> Here the mechanism appears to involve the failure of the alcohol-loaded liver to oxidise free fatty acids which have entered the liver from plasma. <*To camera*> These fatty acids are therefore available to be incorporated into triglyceride and produce the fatty liver and the overproduction of pre-β-lipoprotein which characterises this disorder.

<*Next slide*> Amongst the other causes, chronic renal disease is important and it includes not only the nephrotic syndrome in gross degree that I've already mentioned but also chronic renal failure without nephrosis. <*To camera*> Many patients with chronic renal failure, even when controlled by a dialysis programme or by renal transplantation, show hypertriglyceridaemia and the mechanism is probably multiple; it may involve the use of high doses of prednisolone, it may involve the sort of diet that chronic renal patients are often maintained on, and there may be other factors such as insulin resistance and perhaps a circulating inhibitor for lipoprotein lipase. <*Next slide*> It's fairly clear that patients with chronic renal failure die remarkably frequently, not of uraemia but of ischaemic heart disease, and this may reflect the presence of not only the lipid factor, of course, but hypertension as well. And lastly, hypothyroidism may raise the serum triglyceride level as well as cholesterol so that in lipoprotein terms the usual abnormality is the type IIb.

<*To camera*> Now there are several rarer forms of hypertriglyceridaemia of known aetiology as well. And these are shown in the next chart <*next slide*>. About one third of patients with primary gout, inherited gout, show hypertriglyceridaemia and together with hypertension, perhaps this explains the fact that the commonest cause of death in gout is ischaemic heart disease. The association is a difficult one to explain: <*To camera*> treating the hyperuricaemia has no effect on the serum lipid concentration. Sometimes alcohol is a common aggravating factor to both the disorder of uric acid metabolism and triglyceride metabolism. Many patients with gout who have hyperlipidaemia probably merit treatment of the lipid abnormality as well as that of the hyperuricaemia.

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<*Next slide*> Next on our list are two disorders of the pituitary gland which might at first sight be apparently incompatible with each other. Patients with hypopituitarism do however frequently show moderate hypertriglyceridaemia; the mechanism is unclear. It is seen also in patients on chronic steroid therapy in whom steroid treatment is abruptly withdrawn.

<*To camera*> Hypertriglyceridaemia mechanism presumably occurs in acromegaly and may be compounded of hypothyroidism and of diabetes. Chronic liver disease <*next slide*> including cholestasis but also acute viral hepatitis and cirrhosis may produce hypertriglyceridaemia and sometimes hypercholesterolaemia. And exposure to exogenous oestrogens, of which the commonest reason is the high oestrogen form of oral contraceptives, is another cause of hypertriglyceridaemia. <*To camera*> It seems that most subjects exposed to high doses of exogenous oestrogen will show hypertriglyceridaemia, but there is a wide range in the magnitude of the response. It can become a problem in individuals with a primary hypertriglyceridaemia in whom there may be extreme aggravation by, for example, oral contraceptive medication, and the patient may develop acute pancreatitis or xanthomatosis as a first manifestation of this complication.

<*Next slide*> There are a few other causes of secondary hypertriglyceridaemia including both Cushing's syndrome in which mild hypertriglyceridaemia is the rule and Addison's disease which probably corresponds to the steroid withdrawal of hypertriglyceridaemia I mentioned a moment ago. There are also several situations which have in common an acute stress, such as the gram-negative septicaemia and also acute trauma such as burns and illnesses such as myocardial infarction which can produce hypertriglyceridaemia for a period of a few days or a week, and here the lipid abnormality is obviously an epiphenomenon. It may arise as a result of the catecholamine secretion stimulating free fatty acid mobilisation from adipose tissue with corresponding increase in lipoprotein synthesis.

<*Next slide*> Lastly, I'd like to refer to glycogen storage disease because this together with primary type I lipoproteinaemia and with the congenital nephrotic syndrome are <*to camera*> perhaps the commonest causes of hypertriglyceridaemia

in the neonate. In glycogen storage disease, there is often pronounced hypertriglyceridaemia associated with ketosis and hypoglycaemia, and the mechanism appears to involve overproduction of lipoprotein.

Although those then are the common causes of the rare secondary hyperlipidaemia, I think it is well worth a reasonably diligent search for these underlying causes, if only because the diagnosis is made more complete and because on the whole the hyperlipidaemia responds well to treatment. Now, I will return you to Dr Gilbert Thompson who is going to discuss some of the growing points in this field of primary hyperlipoproteinaemias.

<Thompson to camera>

During this programme, we've examined the pathogenetic importance of clinical features of hyperlipoproteinaemia, but have not said much about the underlying mechanisms. This is a very active area of research at the present time and is of obvious importance from the therapeutic viewpoint. For example, we need to know whether a given type of hyperlipoproteinaemia is primarily due to excessive synthesis of the lipid or the upper protein components of the lipoprotein concerned, or whether a defective catabolism is responsible. Answers to these questions are now just starting to emerge. For example, turnover studies with radioiodinated LDL suggest that reduced catabolism of LDL is a major feature of familial hypercholesterolaemia.

In vitro studies, using cultured fibroblasts, show that this defect of LDL catabolism may be due to the absence of specific LDL receptors from the surfaces of cells from affected patients. These findings have important implications from the point of view of treatment and this will be the subject of our subsequent programme.

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