The Appropriate Use of Diagnostic Services : (viii) The Investigation of Hyperlipidaemia : Why, How and for Whom ?

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INTRODUCTION

The commonest indication for plasma lipid analysis is to assess the risk of developing coronary heart disease (CHD). Together with cigarette smoking, hypertension and diabetes, lipoprotein abnormalities comprise the classical risk factors for CHD[1-3]; their detection involves a commitment to attempt to reduce cardiovascular risk by providing dietary counselling, prescribing drug therapy for certain genetic hyperlipidaemias[4] and assessing the patient's response by follow-up measurements. It also implies appropriate attention to other risk factors. Risk factor screening is only justified if this full commitment is accepted. The necessary analyses can be performed by almost all chemical pathology departments. There is a paucity of specialised lipid clinics in the UK, but some thirty centres now provide consultant opinions on investigation and management of lipoprotein disorders.

POPULATION SCREENING

One major lipoprotein disorder, heterozygous familial hypercholesterolaemia, confers about an eight-fold increase in the risk of CHD in affected men.[5] It is believed to have a prevalence of about two per 1,000 in the UK, in which case there may be 120,000 affected persons in the country or on average four per general practitioner. Only a small proportion of these are diagnosed, particularly at an early age when treatment is likely to have maximum benefit; drug prescribing data suggest that some 4,000 are receiving optimal therapy. In relation to this disease alone there is therefore a compelling argument for a suitable mode of screening to find individuals with this source of potentially treatable high cardiovascular risk. The last word has yet to be said on how best to perform such screening; and the subject has been further confused by the entirely false notion that screening is a competing alternative to the necessary strategy of reducing *population* risk by public education and other measures directed to diet and other aspects of health-related behaviour. This strategy has been advocated in the report to the DHSS Committee on Medical Aspects of Food Policy[6] and in other reviews.[7-9] It seeks to reduce risk by lowering the average concentration of plasma cholesterol in the entire community. It is the only practicable means of improving the health of a population in which more than half the adults have plasma cholesterol levels above the optimal range[10] as defined on the basis of epidemiological and other data by the bulk of authoritative opinion.[2, 9, 11] In a current survey of CHD risk factor prevalence,[12] 23% of British men and women aged 25–59 had serum cholesterol levels exceeding 6.5 mmol/l, an unequivocally high value; no less than 64% had undesirable levels, i.e. exceeding 5.2 mmol/l.

The limitation of a population strategy is that persons at particularly high risk will be little benefited by the extent of change in dietary and other habits likely to be brought about by health education alone; they require individualised care, often including drug therapy, regular follow-up and ongoing support to maintain motivation and compliance. Both the population strategy and the high risk strategy are therefore necessary, and each is likely to complement the other.

To identify persons at high risk due to major disorders of lipid metabolism poses no problem at the laboratory level, but involves certain difficulties:

(i) the distribution of plasma cholesterol levels in the UK is such that the number of persons exceeding any reasonable cut off point is large;

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(ii) the relationship between plasma cholesterol level and relative risk being continuous, selection of a cut off point to define hypercholesterolaemia is arbitrary, unless it were set so low that most UK adults would thereby be assigned to the hyperlipidaemic group;

(iii) the lower the cut off point, the larger becomes the number who would require individualised care and follow-up, imposing a logistically impracticable load on clinical and chemical pathology services; the higher the cut off point, the smaller the potential benefit to the community, for Rose[13] has demonstrated that a "high risk strategy... cannot influence that large proportion of deaths occurring among the many people with slightly raised [relative] risk";

(iv) asymptomatic persons identified as being at high risk by a screening procedure may require sustained efforts by their doctors to educate them in the need to modify dietary and other health habits.

SELECTIVE SCREENING

An alternative to population screening is selective screening, i.e. only of patients consulting their doctors, in order to identify persons at relatively high risk and to offer them effective care. This form of case finding, treatment and follow up is part of good medical practice. Even a narrow interpretation of recent controlled trials[14, 15] justifies treatment of moderately elevated plasma cholesterol levels. Risk factor assessment is targeted on persons likely to have positive findings and who may, because of characteristics implicit in the selection criteria, be motivated to comply with the treatment. Unfortunately, recent quantitative assessment of this approach suggests that its sensitivity is poorer than might be expected.[12] Nevertheless assessment of risk factor status, including lipid measurements, should certainly be carried out in the following :

(i) Persons with a family history of CHD presenting before age 60 in a first degree relative, or with a strong family history by other criteria. Inherited hyperlipidaemia is an important cause of aggregation of CHD in certain families. This criterion for screening does not identify such families as well as might be expected. A positive family history is very common, and can result from several mechanisms of which an inherited lipid disorder is only one. Conversely, a negative family history of CHD may of course be obtained from patients with a genetic hyperlipidaemia.

In the National Lipoprotein Prevalence Study, Mann, Shepherd, Winder, Rose, Guyer and I have, to date, information on 3,841 subjects aged 25–59 years randomly sampled from those attending general practice surgeries in the UK.[12] Of those with cholesterol levels > 6.5 mmol/l, a level unequivocally justifying treatment, only 43% would have been detected if the measurements had been made solely on the 36% with a positive family history.

(ii) Siblings, offspring and parents of persons with pronounced primary hyperlipidaemia. Such family studies are largely the responsibility of lipid clinic physicians. Familial hypercholesterolaemia, and familial hypertriglyceridaemia show autosomal dominant transmission; about half of the relatives of patients with familial combined hyperlipidaemia show moderate elevation of cholesterol and/or triglyceride levels.[16–18] Because of the complex mode of inheritance of Type III hyperlipo-proteinaemia, few relatives of an affected patient prove hyperlipidaemic. The usual cause of chylomicronaemia are transmitted by autosomal recessive inheritance.

(iii) The finding of xanthomas usually indicates the presence of pronounced hyperlipidaemia (rare exceptions may draw attention to other serious disorders such as cerebrotendinous xanthomatosis or myelomatosis). Common sites are the Achilles tendons and those on the dorsae of the hands, most often associated with familial hypercholesterolaemia.[4] As this condition is relatively common and is under-diagnosed a brief search for tendon xanthomas should be part of routine clinical examination; and as the lesions may be unobtrusive a high index of suspicion is necessary. 50–70% of affected adults have tendon xanthomas. Elevation of serum cholesterol is usually marked (8–14 mmol/l). Cutaneous xanthomas on the elbows or in the palmar creases usually reflect Type

III hyperlipoproteinaemia, and eruptive lesions on extensor surfaces occur in any severe hypertriglyceridaemia.[4]

(iv) Xanthelasmas (elevated orange-coloured lesions without a punctum, in the eyelids) and corneal arcus have a less consistent relation with hyperlipidaemia, but are more likely to be associated with a lipid disorder if they are detected before the age of 40 years. A thick complete arcus in younger patients is suggestive of familial hypercholesterolaemia.

(v) A personal history of CHD, peripheral vascular disease or carotid stenosis, particularly commencing before the age of 60 years. Patients with acute myocardial infarction are best studied within 24 hours of admission or three months later.[19, 20] Detection of a familial hyperlipidaemia provides an opportunity for measures directed to primary prevention in affected relatives. More information is required to clarify the effect of treating hyperlipidaemia in patients with existing cardiovascular disease. The rate of progression of established atheroma in the femoral artery is directly related to plasma levels of low density lipoprotein (LDL) cholesterol,[21] and reduction of such levels reduces the rate of progression in patients with symptomatic atherosclerosis affecting the coronary[22] and femoral arteries.[21] Coronary artery bypass grafting and peripheral vascular surgery may constitute special cases, in which the goal of risk factor reduction is to preserve graft patency.

(vi) Persons at high risk of CHD because of diabetes or hypertension.

Measurement of plasma lipids on patients identified by the six criteria listed will assist in identifying individuals who may benefit from lipid-lowering treatment. However this approach may lead to recognition of no more than a minority of persons in the population with major hyperlipidaemias. The National Prevalence Study is addressing this issue. It has recently been proposed by an expert panel convened by the US National Institutes of Health[11] that doctors be encouraged to measure serum cholesterol on all adult patients when they are first seen. Serious consideration should be given to this strategy, which would lead over a period of years to efficient identification of persons at high risk. It is likely that one consequence of the mass strategy, i.e. of public health education will be increased awareness of the significance of hypercholesterolaemia; the medical profession is likely to receive an increasing number of requests by individuals for lipid measurements. There is now a body of opinion in favour of making cholesterol measurements available as part of a full medical examination, for example when a patient is first seen, or when he or she undergoes an employment medical. If this view is generally adopted there will be a case for implementing such a policy gradually over several years, to allow parallel growth in the clinical expertise needed. Case finding of hyperlipidaemia will be fruitless until adequate skills and facilities are made available to provide appropriate management of a potentially large number of persons so identified.

INVESTIGATING LIPOPROTEIN DISORDERS

Relevant clinical information has been alluded to in part: personal and family histories of cardiovascular disease, the presence of other risk factors, examination for xanthomas and other stigmata of hyperlipidaemia, the presence of obesity and of diseases known to cause secondary hyperlipidaemia, the use of drugs (including thiazides, retinoids, oral contraceptives and anti-epileptics) that influence plasma lipids and the use of therapeutic diets.

LABORATORY STUDIES

The primary investigation for assessing coronary heart disease risk is measurement of *total serum cholesterol level.* Many believe that sharper prediction of risk is provided by measurement of total cholesterol and *high density lipoprotein (HDL) levels* in venous blood; the subject need not be fasting when the sample is obtained. Total serum cholesterol is highly correlated with levels of low density lipoprotein (LDL) cholesterol in the population, though not necessarily in hyperlipidaemic subjects. LDL cholesterol is directly related, HDL cholesterol is inversely related in some[1] but not all[23] studies, to CHD risk. The former[24] and perhaps the

latter,[25] are similarly related, though less strongly, to risk of further ischaemic events.

Many epidemiological studies indicate a progressive increase in CHD risk as the serum cholesterol exceeds 5 mmol/l.[26] Levels of cholesterol in the range 5.0–6.5 mmol/l should therefore be considered undesirable. Simple but explicit dietary counselling is recommended for such persons. The type and extent of lipid-lowering management should be graded according to baseline levels. Treatment of substantial hypercholesterolaemia (a working definition is > 6.5 mmol/l) requires more pronounced dietary change and, in many patients, drug treatment. Before treatment is instituted two baseline measurements should be obtained. Patients with levels of this magnitude should be recalled to provide a second sample for *serum cholesterol and also triglyceride* measurement in the fasted state. It should be emphasised that the reference ranges for serum cholesterol provided by some chemical pathology laboratories are potentially misleading, in that they are based on the population distribution in high risk countries, and not the optimal distribution as defined above by the relationship between cholesterol level and risk.

To avoid wide fluctuations during absorption of dietary fat the sample is usually drawn after a 12 – 14 hour overnight fast (permission to drink fat-free fluids makes the test more tolerable). In assessing CHD risk, the consensus is that knowledge of plasma triglyceride levels does not add to the information provided by cholesterol and HDL cholesterol levels.[27] However it is necessary to measure triglyceride as well as cholesterol and HDL cholesterol, as a minimum, to define the lipoprotein abnormality responsible for substantial hyperlipidaemia and to detect certain genetic disorders of lipoprotein metabolism. LDL cholesterol may be estimated from these data, provided the sample is obtained in the fasted state and the triglyceride level is > 6 mmol/l, as total cholesterol — (0.46 x total triglyceride), all in mmol/l. Reliable precipitation methods for direct measurement of LDL cholesterol are now available in kit form.

With these data, the clinical findings mentioned, and (where applicable) a family study, a full diagnosis can most often be made : this is a necessary goal in pronounced hyperlipidaemia. It helps establish prognosis for cardiovascular and other aspects of the natural history of the disorder, and guides optimal therapy.[4]

OTHER TESTS

If there is clinical uncertainty laboratory tests may be required to decide whether major hyperlipidaemia is secondary of hypothyroidism, alcoholism, diabetes, renal or hepatic disease.

Hypertriglyceridaemia in the fasted state is most often due to increased levels of very low density lipoprotein (VLDL); uncommonly it results from chylomicronaemia or excess of remnant particles including intermediate density lipoprotein (i.e. Type III hyperlipoproteinaemia). These can often be distinguished by the 'stored plasma test' in which the disposition of turbidity in a sample stored for 18 hours at 4° is noted;[4] in chylomicronaemia the turbidity rises to the top, leaving the subnatant clear.

Uncommonly quantitative separation of lipoproteins by ultracentrifugation is needed; this is time-consuming, costly, and available only in reference laboratories. It is helpful in the diagnosis of Type III, suspected on the basis of a cholesterol level > 8 mmol/l and triglyceride > 4 mmol/l, with or without characteristic xanthomas. In VLDL isolated by ultracentrifugation the molar ratio of cholesterol to triglyceride exceeds 0.6. There are few other purely clinical indications for ultracentrifugal analysis in investigating hyperlipidaemia. Measurement of the subclasses of HDL by this method or by differential precipitation has yet to be shown to be of value in *predicting* CHD risk, though case-control studies suggest that it is HDL_2 cholesterol rather than HDL_3 that correlates (inversely) with the extent of coronary atheroma.

Despite great research interest in apolipoproteins and their quantitative and qualitative disorders, analyses are of established clinical value in only two or three situations. In Type III, suspected on grounds mentioned above, isoelectric focusing of apolipoprotein E isoproteins will show the E2/E2 phenotype or, rarely, other variants;[28] the procedure is available in reference laboratories. In abetalipoproteinaemia and Tangier disease, apolipoprotein studies help establish the diagnoses.

In specialised lipid clinic practice other sophisticated tests include assay of lipoprotein lipase and its activator apolipoprotein C–II, lipoprotein receptor studies, the use of gene probes, and measurement of lipoprotein kinetics.

There are now few if any indications for lipoprotein electrophoresis or for nephelometry.

In hyperlipidaemic patients at high risk, gross asymptomatic coronary atherosclerosis may be present. Sudden cardiac death is a frequent occurrence in such patients. Adults with familial hypercholesterolaemia, those with Type III hyperlipoproteinaemia, and perhaps others judged to be at particular risk, without symptoms of CHD, should undergo an initial exercise stress ECG under careful supervision, and this may be repeated at intervals dictated by the physician's judgment.

BY WHOM SHOULD LIPID STUDIES BE PERFORMED ?

The pattern of referral to my lipid clinic suggests that general practitioners and occupational health services are now detecting most lipid problems so referred. Their involvement in this aspect of preventive medicine is desirable and advantageous. Many cardiologists and vascular surgeons routinely measure lipid risk factors. Other presenting features such as acute abdominal pain due to recurrent pancreatitis, xanthomas and xanthelasmas, painful swelling of the scrotum or large-joint polyarthritis[29] justify lipid measurements on selected patients.[4]

The decision to treat hyperlipidaemia is a substantial commitment, comparable to the management of diabetes of hypertension because therapy is lifelong. For most patients with mild or moderate hyperlipidaemia, the appropriate management is by diet; for those with severe or persistent hypercholesterolaemia drug therapy may be indicated. Before taking this decision the presence of hyperlipidaemia should be established in at least two baseline samples. In follow-up it is usual though not always necessary to measure both cholesterol and triglyceride, but there is no reason to repeat HDL measurements regularly unless treatment is likely to decrease this fraction. Lipid clinic patients are often seen at 6-week intervals until control is attained, and those with substantial hyperlipidaemia are then investigated annually or as required.

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