BRITISH MEDICAL JOURNAL

LONDON, SATURDAY 27 SEPTEMBER 1986

Apoproteins: predictors of coronary heart disease?

Cholesterol and triglycerides circulate in the blood in lipoprotein particles, which also contain phospholipids and apoproteins. The risk of coronary heart disease is directly related to the amount of cholesterol circulating in low density lipoproteins[1] and may independently be inversely related to high density lipoprotein cholesterol, although this remains controversial.[2-6] Interest has now focused on whether apoprotein concentrations may be related to the risk of coronary heart disease.

Apolipoproteins are genetically determined components of lipoproteins and influence the conformation, receptor binding, and metabolism of the lipoproteins. They are classed as apo A, B, C, D, and E (with subclasses) and can now be measured by several techniques.[7-10] Lipoprotein metabolism is complex; and virtually all the apoproteins can exchange between different lipoprotein molecules. Dietary triglycerides absorbed through the gut are incorporated into chylomicrons—large particles that contain triglycerides, cholesterol, phospholipid, and apo B48, AI, AII, and AIV. In the lymphatics the chylomicrons acquire apo CI, CII, CIII,[11] and E, mainly from high density lipoproteins. Very low density lipoprotein is mainly synthesised in the liver and contains large quantities of triglyceride and apo B100, C, and E as its major apoproteins. Once in the systemic circulation chylomicrons and very low density lipoprotein particles are metabolised, mainly by lipoprotein lipase in adipose tissue and muscle. The apo CII in the particle increases the activity of this enzyme,[12] while the apo CIII inhibits uptake by the liver.[13] Thus the triglycerides of chylomicrons and very low density lipoproteins reach the sites where they are used and where they are hydrolysed. The fatty acids released are a major energy source, particularly for muscle, and are the precursors for adipose tissue triglyceride stores.

Once the bulk of the triglyceride has been removed from chylomicrons and very low density lipoprotein these particles disintegrate, leaving chylomicron remnants and low density lipoprotein. Apo A, CII, and CIII are lost and reaggregate with other molecules to form the heterogeneous group of high density lipoprotein particles. Apo AI is particularly important in high density lipoprotein particles. Chylomicron remnants, which contain apo B48 and apo E as their main apoproteins, are cleared by the liver through a receptor system more or less specific for apo E3 and apo B48.[14] The cellular uptake of the cholesterol rich low density lipoprotein is also largely mediated by a high affinity cell surface receptor.[15] This low density lipoprotein receptor present on many cells recognises apo B100 and apo E. After being taken into the cells low density lipoprotein is digested by lysosomes. Cholesterol and triglycerides are thus made available to cells, but there are many ways in which this process may be impaired.

Several clearly defined inherited apoprotein disorders result in increased morbidity. Disorders with high density lipoprotein concentrations below the 10th centile have been described and include those with absent apo AI[16] and abnormal apo As. The latter group include Tangier's disease, in which high density lipoprotein concentrations are low because of a deficiency of normal apo AI and AII. A deficiency of apo AI and of apo CIII has been described in a family with premature coronary heart disease, xanthomas, and reduced high density lipoprotein but normal total cholesterol concentrations.[17] This defect is associated with a rearrangement in the apo AI/CIII gene locus. Other polymorphisms identified in the region of the apo AI and CIII genes are associated with hypertriglyceridaemia,[18] reduced high density lipoprotein concentrations, and a high incidence of coronary heart disease.[19] The different types of disorders resulting in reduced high density lipoprotein concentrations appear to be associated with different susceptibility to coronary heart disease. The reasons are often not clear, although in Tangier's disease the reduced concentration of low density lipoprotein resulting from disordered apo A and C metabolism may explain why the risk of coronary heart disease is not high. The absence of apo CII is associated with severe hypertriglyceridaemia and chylomicronaemia[20] owing to reduced lipoprotein lipase activity, and these patients have a high risk of acute pancreatitis.

Apo E synthesis is controlled by several alleles which specify the synthesis of apo E2, E3, E4, and other forms, and possession of the different apo Es is related to a variable incidence of hyperlipidaemia.[21] People with the uncommon type III hyperlipidaemia, who have a greatly increased risk of premature atherosclerosis, nearly always have only E2/E2, which is less well recognised by the liver receptors than E3;

and very low density lipoprotein containing apo E2 is also less readily converted to low density lipoprotein.[22] This may lead to the accumulation of chylomicron remnants and very low density lipoprotein in the circulation; and apo E characterisation can help in the accurate diagnosis of this hyperlipidaemia. An additional factor does, however, appear to be necessary because 1% of the population have this genotype but few have the clinical problem. Another form of hyperlipidaemia in which abnormal apoprotein concentrations have been found is familial combined hyperlipidaemia. In this condition cholesterol, triglyceride, and apo B concentrations are high[23] and there is a high risk of coronary heart disease.

Considering the complex and vital role of apoproteins and the association with some specific disorders demonstrated above, it is hardly surprising that there is a general association between the concentration of some apoproteins and the incidence of coronary heart disease. Avogaro and others reported in 1979 that survivors of myocardial infarction had higher concentrations of apo B and lower concentrations of apo AI than controls.[24] Associations between high apo B and low apo AI concentrations and various manifestations of coronary heart disease have been confirmed in several other small retrospective case control studies.[25-29] In addition, marked abnormalities of apo B concentrations have been found in a few people with slightly raised total and low density lipoprotein cholesterol[30 31] and in some with raised plasma triglycerides.[32] This could help to explain the uncertain relation between hypertriglyceridaemia and coronary heart disease if, as suggested by Sniderman *et al*,[32] those with raised low density lipoprotein apo B are at higher risk.

Apo AI and apo B are the major apoproteins of high density lipoprotein and low density lipoprotein respectively, and alterations in the concentrations of these apoproteins may merely reflect changes in the concentration of the lipoproteins. An important question under investigation is whether measuring individual apoproteins provides a better indication of risk of coronary heart disease than measuring lipoproteins. Avogaro and others found that the ratios of total cholesterol to apo B and of apo AI to apo B were no better than total and high density lipoprotein cholesterol at predicting coronary heart disease below 50 but were slightly better in older people.[24] DeBacker also reported that the apo B to apo AI ratio contributed to the discrimination between survivors of myocardial infarction and controls.[29] Other studies have not shown apo AI to be better than high density lipoprotein at predicting the risk of coronary heart disease,[25] and data from the main prospective study suggested that high density lipoprotein cholesterol was more helpful.[33]

Thus it is not yet clear whether measuring individual apoproteins provides a better independent assessment of risk than the investigations available now in most laboratories. Measuring fasting triglyceride and cholesterol concentrations, together with high density lipoprotein and low density lipoprotein cholesterol in some cases, generally provides an adequate clinical assessment of risk and information on which to plan treatment. Carefully conducted case-control and cohort studies are necessary to clarify the role of apoprotein measurement in predicting risk of coronary heart disease in the population. Measurement of apoproteins has, however, increased our knowledge of lipid metabolism and might tell us more about the relation between coronary heart disease and other diseases such as diabetes. Currently apoprotein determination is useful in investigating patients with suspected type III hyperlipidaemia and families with unusual lipid problems and a high risk of coronary heart disease.

MADELEINE BALL
Lecturer in clinical biochemistry

J I MANN
Lecturer in social and community medicine and honorary consultant physician

John Radcliffe Hospital and Radcliffe Infirmary, Oxford OX2 6HE

Correspondence to: Dr Mann.

1 Gordon T, Kannel WB, Castelli WB, Dawber TR. Lipoproteins, cardiovascular disease and death. The Framingham study. *Arch Intern Med* 1981;141:1128-31.
2 Miller NE, Forde OH, Thelle DS, Mjos OD. The Tromsø heart study. High density lipoprotein and coronary heart disease: a prospective case-control study. *Lancet* 1977;i:965-8.
3 Goldbourt U, Holtzman E, Neufeld HN. Total and high density lipoprotein cholesterol in the serum and risk of mortality: evidence of a threshold effect. *Br Med J* 1985;290:1239-43.
4 Pocock SJ, Shaper AG, Phillips AN, Walker M, Whitehead TP. High density lipoprotein cholesterol is not a major risk factor for ischaemic heart disease in British men. *Br Med J* 1986;292:515-9.
5 Peto R. High density lipoprotein cholesterol is not a major risk factor for ischaemic heart disease in British men. *Br Med J* 1986;292:1199-200.
6 Wynn V, Crook D, Godsland IF, Seed M, Shennon NM. High density lipoprotein cholesterol is not a major risk factor for ischaemic heart disease in British men. *Br Med J* 1986;292:1200.
7 Cheung MC, Albers JJ. The measurement of apolipoproteins AI and AII levels in men and women by immunoassay. *J Clin Invest* 1977;60:43-50.
8 Curry MD, Gustafson A, Alaupovic P, McConathy WJ. Electroimmunoassay, radioimmunoassay and radial immunodiffusion assay evaluated for quantification of human apolipoprotein B. *Clin Chem* 1978;24:280-6.
9 Fruchart J, Kora I, Cachera C, Clarey V, Duthilleol P, Moschetto Y. Simultaneous measurement of plasma apolipoproteins AI and B by electroimmunoassay. *Clin Chem* 1982;28:59-62.
10 Utermann G, Feossner G, Franceschiri J, Haas J, Steinmetz A. Genetic variants of group A apolipoproteins: rapid methods for screening and characterisation without ultracentrifugation. *J Biol Chem* 1982;257:501-7.
11 Hatel RJ, Kane JP, Kashyap ML. Interchange of apolipoproteins between chylomicrons and high density lipoproteins during alimentary lipaemia in man. *J Clin Invest* 1973;52:32-8.
12 Fielding CJ, Havel RJ. Lipoprotein lipase. *Arch Pathol Lab Med* 1977;101:225-9.
13 Shelburne F, Hanks J, Meyers W, Quarfordt S. Effect of apoproteins on hepatic uptake of triglyceride emulsions in the rat. *J Clin Invest* 1980;65:652-8.
14 Mahley RW, Innerarity TL, Rall SC, Weisgraber KH. Plasma lipoproteins: apolipoprotein structure and function. *J Lipid Res* 1984;25:1277-94.
15 Goldstein JL, Brown MS. Binding and degradation of low density lipoproteins by cultured human fibroblasts. *J Biol Chem* 1974;249:5153-62.
16 Schaefer EJ, Heaton WJ, Wetzel MG, Brewer HB. Plasma apolipoprotein AI absence associated with a marked reduction of high density lipoproteins and premature coronary artery disease. *Arteriosclerosis* 1982;2:16.
17 Norum RA, Lakier JB, Goldstein S, *et al*. Familial deficiency of apolipoproteins AI and CII and precocious coronary artery disease. *N Engl J Med* 1982;306:1513-9.
18 Reese A, Stocks J, Shoulders CC, Galton DJ, Baralle FE. DNA polymorphism adjacent to human apoprotein AI gene: relation to hypertriglyceridaemia. *Lancet* 1983;i:444-6.
19 Ordovas JM, Schaefer EJ, Salem D, *et al*. Apolipoprotein AI gene polymorphism associated with premature coronary artery disease and familial hypoalphalipoproteinemia. *N Engl J Med* 1986;314:671-7.
20 Breckinridge WR, Little JA, Steiner G, Chow A, Poapst M. Hypertriglyceridemia associated with deficiency of apolipoprotein CII. *N Engl J Med* 1978;298:1265-73.
21 Utermann G, Kindermann I, Kaffarnik H, Steinmetz A. Apolipoprotein E phenotypes and hyperlipidaemia. *Hum Genet* 1984;65:232-7.
22 Mahley RW, Angelin B. Type III hyperlipoproteinaemia: recent insights into the genetic defect of familial dysbetalipoproteinaemia. *Adv Intern Med* 1984;29:385-411.
23 Brunzell JD, Albers JJ, Chait A, Grundy SM, Groszek C, McDonald GB. Plasma lipoproteins in familial combined hyperlipidaemia and monogenic familial hypertriglyceridaemia. *J Lipid Res* 1983;24:147-55.
24 Avogaro P, Cazzolato G, Bittolo Bon G, Quinci GB. Are lipoproteins better discriminators than lipids for atherosclerosis? *Lancet* 1979;i:901-3.
25 Fager G, Wiklund O, Oloffson SO, Wilhelmsson C, Bondjers G. Serum apolipoprotein levels in relation to acute myocardial infarction and its risk factors. *Atherosclerosis* 1980;36:67.
26 Riesen WF, Mordasini R, Salzmann C, Theler A, Gurtner HP. Apoproteins and lipids as discriminators of severity of coronary heart disease. *Atherosclerosis* 1980;37:157.
27 Onitiri AC, Jover E. Comparative serum apolipoprotein studies in ischaemic heart disease and control subjects. *Clin Chim Acta* 1980;108:25-30.
28 Deslypere JP, DeBacker G, Roseeneu M, Vermuelen A. Lipid and apolipoprotein levels in myocardial infarction survivors. A case-control study. *Acta Cardiol (Brux)* 1981;27(suppl):95-102.
29 DeBacker G, Rosseneu M, Deslypere JP. Discriminative value of lipids and apoproteins in coronary heart disease. *Atherosclerosis* 1982;42:197-203.
30 Sniderman A, Shapiro S, Marpole D, *et al*. Association of coronary atherosclerosis with hyperapobetalipoproteinemia (increased protein but normal cholesterol levels in human plasma low density B lipoproteins). *Proc Natl Acad Sci USA* 1980;77:604-8.
31 Connor WE, Teng B, Sniderman AD. Hyperapobetalipoproteinaemia in two families with xanthomas and phytosterolaemia. *Lancet* 1981;i:466-70.
32 Sniderman AD, Wolfson C, Teng B, Franklin FA, *et al*. Association of hyperapobetalipoproteinemia with endogenous hypertriglyceridemia and atherosclerosis. *Ann Intern Med* 1982;97:833-9.
33 Ishikawa T, Fidge N, Thelle DS, Forde OH, Miller NE. The Tromsø heart study. Serum apolipoprotein AI concentration in relation to future coronary heart disease. *Eur J Clin Invest* 1978;8:179-82.