TRIGLYCERIDES AND CORONARY ARTERY DISEASE

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INTRODUCTION
The role of hypercholesterolaemia and particularly high low-density lipoprotein (LDL) cholesterol as a contributory risk factor in the causation of coronary artery disease is now widely accepted. The adult treatment panel of the National Cholesterol Education Programme (NCEP) published its guidelines on the detection, evaluation and treatment of people with high blood cholesterol in 1988(1). These recommendations are based on epidemiological data from prospective observational studies such as the Framingham Study(2) as well as interventional studies such as the Multiple Risk Factor Intervention Trial (MRFIT)(3). Besides epidemiological data, a wealth of evidence accrued from animal, pathologic as well as clinical studies leaves little doubt that LDL cholesterol is indeed an important contributory risk factor in the pathogenesis of coronary artery disease(4), and that lowering plasma LDL cholesterol by lifestyle modification and the use of hypolipidaemic agents may lead to regression of angiographically demonstrated coronary atherosclerotic lesions(5,6).

The protective role of high-density lipoprotein (HDL) cholesterol has also been highlighted. Initial data from the Helsinki Heart Study suggested that besides reduction of LDL cholesterol, raising HDL cholesterol may confer additional benefits in reducing the number of coronary end-points(7).

The role of hypertriglyceridaemia in the causation of coronary artery disease has been more controversial(8,9). Plasma triglyceride, as measured in the routine clinical biochemistry laboratory, is a reflection of the sum total of triglyceride in several lipid subfractions such as very-low-density lipoprotein (VLDL) as well as remnant particles from the metabolism of chylomicrons and VLDL. These fractions are inextricably linked to the metabolism of cholesterol fractions and each may have a different and variable role in the pathogenesis of atherosclerosis and coronary artery disease(10). The large scale of most epidemiologic studies has meant that it is not often feasible to embark on the sophisticated methods required to measure these lipid fractions separately and plasma triglyceride has been measured instead. This fact should be borne in mind when looking at data utilizing plasma triglyceride.

TRIGLYCERIDE AS A CORONARY RISK FACTOR IN THE GENERAL POPULATION
The Framingham Study looked at potential coronary risk factors (including plasma lipids) in over 5,000 subjects free of clinical evidence of coronary artery disease at entry and thereafter monitored the incidence of coronary events in this cohort(2). Besides establishing a relationship between LDL cholesterol and coronary artery disease, incidence of coronary events was also noted to rise with increasing plasma triglyceride levels. It was initially suggested that triglyceride was a powerful predictor of coronary artery disease only in women above 50 years, but later statistical analysis showed that the relationship existed in both sexes particularly if the total cholesterol/HDL cholesterol ratio was > 3.5(11).

Several prospective Swedish studies have also demonstrated a relationship between plasma triglyceride levels and coronary artery disease(12,13). The Gothenburg study showed that non-fatal myocardial infarction, stroke as well as all-cause mortality were more frequent in initially hypertriglyceridaemic women when compared to normotriglyceridaemic women(14). The Stockholm Prospective Study, using mortality as the end-point studied, showed that amongst the lipids measured, triglyceride was an important risk factor for predicting mortality from myocardial infarction(15). Data from the Uppsala study(16) suggested that triglyceride was a more important risk factor in myocardial infarction than in angina pectoris and postulated that triglyceride may have a prothrombogenic effect. These studies have been criticised on the grounds that HDL cholesterol (measurement not available at time of initiation of study) was not entered into multivariate analysis together with triglyceride(17).

Tuning away from Western industrialised communities, a recently completed cross-sectional study of rural Chinese in China showed that amongst the lipid fractions studied, plasma triglyceride correlated significantly with coronary artery disease mortality in both sexes(18). In Singapore, the Thyroid and Heart Study documented a higher ischaemic heart disease mortality rate amongst Indians as compared to Chinese and Malay subjects; although the rates for diabetes were higher and the mean HDL cholesterol was lower, the mean serum triglyceride of the Indians was not higher than the other races(19,20).

TRIGLYCERIDE AS A CORONARY RISK FACTOR IN DIABETIC PATIENTS
Hypertriglyceridaemia is a common problem in patients with diabetes mellitus. Although hypertriglyceridaemia often improves with adequate control of diabetes, many patients with what is presently thought to be satisfactory diabetic control will have residual hypertriglyceridaemia. The role of hypertriglyceridaemia as a determinant of vascular disease in diabetic patients has been studied in a WHO Multinational Study(21). This study concluded that serum triglyceride appeared to be more strongly related to the prevalence of the manifestations of coronary artery disease than serum cholesterol in obese, noninsulin-dependent diabetic patients. Using multivariate analysis, the Paris Prospective Study also showed that amongst people with glucose intolerance of adult onset, serum
triglyceride was an important independent coronary risk fac-

TRIGLYCERIDE AND ASSOCIATED CONDITIONS

Recently, it has become clear that hypertriglyceridaemia does not always occur in isolation, but is often found in patients who have upper body obesity, hypertension, hyperinsulinemia, glucose intolerance as well as low HDL cholesterol230. These cluster of features is often termed Reaven's Syndrome231. It has been suggested that insulin resistance, and hence hyperinsulinemia is aetologically important232 in each of these features. Previous studies looking at the relationship between insulin and hypertriglyceridaemia have been performed in over-

weight subjects233 and studies which have looked specifically at the effect of obesity on hyperinsulinemia in hypertriglyceridaemic subjects have given conflicting re-

sults234. We have recently demonstrated that both basal se-

rum insulin as well as the insulin response during intravenous glucose challenge was increased in hypertriglyceridaemic sub-

jects independent of confounding factors such as obesity, hy-

tension and diabetes mellitus235. Many of the features of

Reaven's Syndrome are coronary risk factors and not surpris-

ingly, these people have increased coronary risk. Whether hy-

pertriglyceridaemia contributes directly to the increased coro-

nary risk is still unclear.

The metabolism of triglyceride is closely linked with that of HDL cholesterol236. As the cardioprotective role of high HDL cholesterol gains prominence, it is also becoming clear that people with low HDL cholesterol often have hypertriglyceridaemia. It has been suggested that since the me-
		

tabolism of HDL cholesterol and triglyceride are inextricably linked, it may not be appropriate to subject HDL cholesterol and triglyceride to separate statistical tests237. Thus, hypertriglyceridaemia and low HDL cholesterol may be differ-

ent facets of a 'low HDL cholesterol-high TG' syndrome (re-

miniscent of Reaven's Syndrome).

Initial reports from the Helsinki Heart Study suggested that the improvement in coronary end points amongst subjects who took gemfibrozil was attributable to a decrease in LDL cholesterol and an increase in HDL cholesterol238. A closer look at the data showed that of the lipid fractions measured, the actual magnitude of improvement, measured as percentage difference between the gemfibrozil-treated and control groups, was greatest for triglyceride rather than for LDL cholesterol or HDL cholesterol. Yet, when subjected to statistical tests, the reduc-

tion in triglyceride did not show significant association with the improvement in coronary end-points. Recently published reports based on reanalysis of the Helsinki Heart Study data revealed that in patients with serum LDL/HDL cholesterol ≥5, only those with serum triglyceride > 2.3 mmol/L appeared to be at increased coronary risk and benefitted from hypolipaemic treatment. Although some are still sceptical239, others feel that there is sufficient evidence for a consensus on the treatment of hypertriglyceridaemia240 as a coronary risk factor.

The metabolism of triglyceride and cholesterol are inextricably linked. Hypertriglyceridaemia together with a high LDL/ HDL cholesterol ratio may represent a particularly atherogenic lipid pattern. It is clear that a great deal of work remains to be done before the mysteries surrounding the metabolic milieu of hypertriglyceridaemia and its role in atherosclerosis can be unraveled. In the meantime, triglycerides should be regarded as an important coronary risk factor together with other lipid fractions241 and should certainly not be ignored!

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