PLASMA CHOLESTEROL AND CORONARY ARTERY DISEASE: HOW BIG A HEARTACHE ?

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INTRODUCTION

Coronary atheroma is the principal cause of ischaemic heart disease. Among the factors considered to predispose to atheroma formation is raised plasma cholesterol and although it is regarded as a minor risk factor by some, others see its contribution as one of major importance. Whichever the view, the debate on plasma cholesterol and coronary heart disease (CHD) has long moved out of the exclusive domain of the scientific journal to the public arena and is reflected in the increasing frequency with which doctors are consulted by patients on the subject. The incidence of CHD in South-East Asian countries is also rising.

For the practising clinician, the problem resolves itself into deciding if the evidence incriminating plasma cholesterol as a predisposing factor is strong enough, and if it is, what prophylactic and therapeutic steps are of value in reducing the incidence of CHD. An updated and brief review of lipid metabolism and the relationship of lipids to CHD is now necessary in view of the rapid accumulation of data from recent trials and prospective studies.

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LIPID METABOLISM

Blood lipids include triglycerides, phospholipids and cholesterol which are combined in various proportions with carrier proteins to form lipoproteins in which form they are transported in the circulation. The largest and least dense of the lipoproteins are the chylomicrons which are **triglyceride-rich** and formed primarily from absorbed dietary fats. Following peripheral breakdown of the chylomicrons by lipoprotein lipase, the now cholesterol-rich remnants are rapidly taken up and degraded by the liver.

The liver (and to a lesser extent, the intestines) are responsible for the synthesis and secretion of VLDL (Very Low Density Lipoproteins) which is also **triglyceride-rich** and which is eventually converted in the periphery through various stages to LDL (Low Density Lipoproteins). LDL is **cholesterol rich** and transports 60—75% of the cholesterol in the circulation, delivering it to the tissues including the liver. Experimental evidence suggests that nearly all of plasma LDL is derived in this fashion from plasma VLDL. We now know LDL to be associated with premature atherosclerosis[1] although the actual mechanism is yet unclear.[2] Part of the plasma LDL is taken up by peripheral tissues which have specific LDL receptors, and part of it is degraded with return of the cholesterol to the plasma.

On the other hand, HDL (High Density Lipoproteins) is a relatively protein-rich and lipid-poor molecule which originates mainly from the liver and intestines. Its role seems to lie in reverse cholesterol transport i.e., it accepts unesterified cholesterol synthesised in the periphery and transports the steroid to other lipoproteins, mainly

VLDL and also back to the liver for degradation and excretion. This ability to "mop up" free cholesterol from LDL and tissues may be partly responsible for the protective effect it confers to CHD.[3,4] In short, a high HDL level is regarded from present evidence as "good" whereas a high LDL level is "bad" – this will be discussed in greater detail later.

Chylomicrons and VLDL are triglyceride-rich and are generally not considered as important as cholesterol in predisposing to premature atherosclerosis[5] although there is a divergent view that triglycerides may constitute as important an independent risk factor for CHD.[6,7] The question is still unresolved at present but further discussion falls outside the task of this review.

PRELIMINARY EVIDENCE

In the 1950's and 60's, male mortality from CHD rose steadily in the West. Epidemiological studies had shown that countries with diets high in saturated fats tend to have a higher incidence of CHD.[8] Preliminary evidence from studies of lipid patterns in small population samples not subjected to long-term follow-up also supported the link between cholesterol and CHD.[9,10] Further substantiating evidence known at that time could be summarised as follows: accumulation of cholesterol was known to be a hallmark of both experimental and human atherosclerotic lesions, and atherosclerosis could be induced in animals by raising their blood cholesterol levels. These evidence were no more than suggestive especially as there were other indirect evidence that tended to minimise the importance of cholesterol at that time.[11]

THE SEARCH FOR THE LINK

The dietary studies were prospective studies which sought to show that high cholesterol was associated with an increased risk of CHD and that lowering it by dietary means would reduce this risk. The nature of these studies entailed long-term follow-up and while they were in progress, western countries in the early 70's found themselves in a dilemma. Hard facts on a suitable diet were then not available, and there was as yet no irrefutable evidence that lowering plasma cholesterol would be of benefit; yet there was an urgent need to reduce the rising trend of CHD. It was not surprising therefore that experts on government advisory boards could not agree among themselves[12–14] and that dietary recommendations that were ultimately issued were often wooly and ambivalent (e.g. in Britain).[15]

In some cases, however, anticholesterol diet lobbyists together with enthusiastic sectors of the lay press began advocating reduced cholesterol intake together with regular exercise, weight reduction and cessation of smoking, particularly in the United States. Recent data suggests that this "premature" policy may be paying off. There has been a steady decline in the incidence of CHD in America,[16,17] Belgium and Australia. In Britain, however, where there has been little change in life-styles and diet, the incidence of CHD has remained static.[18]

The two early major dietary studies, one of which was reported in the late 60's and the other in the late 70's were the Eight-year Veteran Administration Hospital Trial in Los Angeles[19] and the 12-year Finnish Trial in two mental institutions in Helsinki.[20]

These trials compared two diets with moderately high fat intakes (35-40% of total calories) in which the degree of saturation of the two fat mixtures varied as widely as was feasible under the test conditions. New events of myocardial infarcts were reduced in those on the high saturated fat intake; but taken as a whole, the results did not reach statistical significance. Although these pointed to a diet-heart link, the critics remained unconvinced.[14]

The results of the later Oslo Heart study in 1981 showed a much clearer benefit although it was beleagured by other confounding risk factors. Here hypercholesterolaemic men given a diet of high polyunsaturated/saturated fat ratio had decreased plasma cholesterol level and a significant reduction in mortality from CHD (-40%).[21] Unfortunately, there was also a significant concurrent reduction of cigarette-smoking in these Norwegian men which greatly weakened any conclusion that could perhaps have been drawn on the role of dietary intervention.

As later diet trials were published, the trend became increasingly for them to link CHD with the proportion of saturated fats in the total calorie intake rather than the absolute amount of saturated fats consumed. By the early 1980's, most of the diet-heart studies completed were pointing broadly in the same direction: that is with more cholesterol per 1,000 calorie intake, there was an increasingly higher risk of CHD. These were seen in the Western Electric Study[22] where a weak relationship between CHD and high saturated fat diet was established, the Honolulu Heart Study,[23] the Seventh-Day Adventist Study[24] where frequency in consumption of meat and eggs were linked to increased mortality, and more recently the 20-year Ireland-Boston Diet-Heart Study.[25]

There have been those who have pointed out that while there may be a link between the proportion of cholesterol in a diet and CHD, there is no clear link at all between the absolute amount of cholesterol consumed and CHD.[26] The reply to such arguments need not concern us here but is taken up elsewhere.[27] One of the weakness of these studies was that insufficient account was taken of the degree to which differences in life-styles, exercises and social changes rather than dietary changes were responsible for some of the differences seen in the populations studied. It however does not necessarily invalidate the main point made i.e., a high cholesterol intake predisposes to an increased risk of CHD.

Further dietary evidence comes from the Eskimos who have a high fish consumption and low incidence of CHD. Their proportionately lower intake of cholesterol is reflected in a significantly lower total plasma cholesterol and triglyceride levels and significantly higher HDL levels than in Danish controls.[28] Also partial substitution of cheese with mackerel in a European diet has also been shown to lead to a fall in plasma cholesterol level.[29] The clinical importance of this was shown in the Dutch study of males in Zutphen where a 20-year follow-up dietary study revealed an inverse relationship between fish consumption and coronary deaths within the population.[30]

Taken as a whole, therefore, the diet studies do reflect that within a given population, individuals with higher cholesterol levels have a greater chance of developing CHD, and that this is true for those with no additional risk factors as well as those with added risk due to other factors (e.g. smoking). There were also pointers that the reduction of plasma cholesterol by diet would lead to a reduction in the incidence of CHD.

LIPOPROTEINS: A MORE RIGOROUS PREDICTOR OF CHD?

Hitherto, plasma lipoprotein levels had received scant attention in the diet trials, many of which originated at a time when the importance of lipoproteins was overshadowed by that of the plasma lipids, especially cholesterol. However, with the recognition that plasma lipids are transported as constituents of lipoproteins it has become more meaningful to relate risk to the individual plasma lipoproteins. The Framingham study has been responsible for much of our increased understanding of the subject.[1]

The study included a total of 18,000 patients between the ages of 35 and 79 who were followed up over a period of several years. Because plasma cholesterol levels rise with age, the study found that a raised level was not necessarily a good predictor of CHD risk especially in patients above 60 years of age. In contrast, LDL levels were positively correlated with HDL even in the older age group.

What was also extremely significant was that there was a strong negative correlation between HDL levels and CHD, a fact which had been known from a separate study as early as 1951.[31] A high LDL level was associated with low CHD risk and *vice versa.* The predictive value of HDL was even greater than that of blood pressure or LDL alone and independent of either. This predictive value of HDL held true even in those above 70 years of age and served to confirm the findings of some earlier studies.[32]

However at any given level of plasma LDL or cholesterol, the CHD risk varies widely depending on the HDL level and it is therefore less accurate to predict the risk of CHD on an LDL or choles-

terol level alone. The Framingham study indicated that the LDL/HDL ratio or the Total Cholestrol/ HDL ratio provided better indicators of risk. In general, an LDL/HDL ratio of 3.5 indicates low risk whereas a ratio greater than 5 is high risk and a ratio of 9.0 is associated with a risk three times that of the general American population. Similarly, a total cholesterol/HDL ratio of 10 carries double the risk and a ratio of 20 has three times the risk.[33]

Similar findings have been obtained in the Tromso Heart study in which 6,500 men between 20 and 49 years were followed up for two years,[34] the Israeli Ischaemic Heart Disease study in which around 6,000 middle-aged men were studied for seven years[35] and the Western Collaborative Group study which followed up 2,000 men, again over a seven-year period.[5]

Metabolic studies in some hypercholesterolaemic families have lent further support to the importance of LDL cholesterol. Goldstein *et. al.*, unveiled that a single gene defect for the LDL receptor is responsible for the slower clearance of LDL from plasma in these individuals.[36] This results in higher LDL and plasma cholesterol concentrations which in turn predispose to premature atherosclerosis. Homozygotes with this disorder frequently develop myocardial infarctions in childhood in the absence of any other risk factors. This is indeed powerful evidence that raised LDL (and therefore cholesterol) levels can be the dominant and sole determining cause of atherosclerosis and CHD in some cases[37] in the absence of other risk factors.

However, as was mentioned previously, the diet studies fell short of conclusive evidence that lowering high cholesterol would confer benefit and the Framingham study was not primarily concerned with this question. It was the drug trials that provided some answers although some questions were raised in the process.

SOME ANSWERS FROM THE DRUG TRIALS

This category of trials is of interest to most clinicians because of its immediate therapeutic relevance. The largest drug trial conducted to date is the WHO Clofibrate Trial which involved populations in Budapest, Edinburgh and Prague and reported its findings in 1978.[38] Men in the top percentile of the cholesterol distribution curve were randomly assigned to a placebo of olive oil capsules or to the lipid-lowering agent, clofibrate.

Clofibrate which lowers both triglycerides and cholesterol levels was found to reduce the incidence of nonfatal myocardial infarction by approximately 20% after a period of five years. The greatest effect was seen in those with the highest coronary risk due to hypercholesterolaemia, smoking and hypertension. Total overall mortality was however greater in the treated group, mainly from noncardiovascular causes. The excess deaths became even more significant during the four-year post trial follow-up period.[39] Some investigations have attributed this phenomenon to chance as it seemed independent of the cholesterol level or the reduction in plasma cholesterol achieved, whereas others saw it as a consequence of an unknown long-term effect of the drug. Despite conflicting views, it does seem prudent to exercise caution in the use of this drug, and to prescribe it only in patients with a high risk of CHD where other lipid-lowering agents are not available or acceptable.

Early in 1984 however, the first clear evidence that reduction of plasma cholesterol and LDL cholesterol does lower the incidence of both fatal and non-fatal myocardial infarction emerged from the US Lipid Research Clinics Trial.[40,41] This is by far the most important and convincing trial to date. Over 3,800 men, aged 35-59 years belonging to the top 5% of the cholesterol distribution curve (mean plasma cholesterol concentration of 292mg/100ml) and free from coronary heart disease participated in the study. Following randomization, the treated group was given the lipid-lowering resin, cholestyramine, while the control group was given inactive silica, both on a double blind protocol. Both groups were on a relatively high polyunsaturated fat diet during the seven-to ten-year period of the trial.

An overall reduction of plasma cholesterol (−8.5%) and LDL level (−12.6%) was achieved in the treated group. There was a small increase (2.8%) in HDL levels. Fatal and non-fatal myo-

cardial infarctions were reduced by 19% in the treated group; there was also a reduction in angina and a reduction in ECG changes on stress test. A further encouraging aspect of the trial was an initial report demonstrating the regression of coronary atheroma in the treated group following decrease in their plasma cholesterol.[42] A similar observation has been made in a dietary intervention study in Leiden where a low animal fat diet prevented the progression of coronary atheroma in 18 out of 39 patients over a period of four years.[43]

Some disquiet arose when the incidence of cancers were compared in the two groups in the Lipid Research Clinics Trial. A number of the rarely seen buccal or pharyngeal tumours were present in the cholestyramine group but not in the placebo. The significance of this is unknown because interpretation is made difficult by the small numbers involved. The overall incidence of cancers was however the same in both groups and supports previous epidemiological findings that the lowering of cholesterol itself does not predispose to cancer in the long term.[44]

MANAGEMENT PRINCIPLES

What should we advise patients with a high risk lipid profile? We must bear in mind that high plasma cholesterol, LDL and low plasma HDL contributed only one of the many risk factors of CHD. Other factors are equally important and should not be neglected.

Some of these factors are irreversible, e.g. age, sex and family history and although not much can be done, they are vital factors in determining relative risks. It is on the reversible factors, e.g. blood pressure, cigarette smoking, obesity, exercise, diet and other secondary causes of hyperlipidaemia that clinicians should concentrate their advice and treatment on.

Diabetes, hypothyroidism and other secondary causes should be treated. Sometimes treatment alone will reduce the plasma cholesterol level. Obese patients should loose weight and take regular exercise. Weight reduction significantly reduces plasma cholesterol,[45] and also results in an increase in HDL level. Besides weight loss, physical activity also produces an increase in HDL level and a reduction in LDL cholesterol, although some studies indicate that it is necessary for individuals to run, swim or cycle for about half an hour four times a week to achieve this.[46]

An inverse relationship between cigarette smoking and HDL exists. All patients should stop smoking. Recent findings of the MRC mild hypertension trial suggest the effect of cessation of smoking is as important or even more important than blood pressure reduction in reducing cerebrovascular events. Blood pressure reduction in the trial benefitted only those who did not smoke.[47] There is a well-established positive correlation between high blood pressure and the incidence of myocardial infarction. In the MRC trial however, the reduction of blood pressure made no difference in the number of fatal and nonfatal coronary events in smokers although in non-smokers there was a trend towards the reduction of coronary events which just fell short of statistical significance. Thus it may be that reduction of blood pressure may yet prove to be important.

Although alcohol in moderation has been observed to increase HDL levels it cannot be recommended in view of its tendency to be abused, to raise triglyceride levels (which may be important) and to promote obesity through calorie intake.

At the end of 1984, the National Institute of Health Consensus Development Conference on cholesterol and heart disease issued dietary recommendations that plasma cholesterol level in the United States should be reduced towards that in countries where CHD was not a major health problem.[48] In the diet recommendations, total fat intake was to be reduced from the American average intake of 40% of the total calories to 30%. Not more than 10% of total calories was to be from saturated fats and dietary cholesterol intake was to be reduced from 450mg/day to 250-300mg. A similar dietary recommendation was made in Britain by the UK COMA report.[41]

It needs to be said here that there remains a minority of dissenters who hold a diminishing but valid objection that the advocation of a

national "prudent" diet such as that outlined above would only benefit high risk patients in the upper distribution of the plasma cholesterol curve. The fact is that there have been no convincing studies on women, or on populations with moderate or minimally elevated cholesterol levels which have shown that dietary modification would be of benefit to them.[50] The advisory panel in the United States however felt that such objections notwithstanding, the onus is really on the dissenters to prove that such dietary changes will not benefit most groups when an extrapolation of data from all the trials would suggest a benefit, although they do concur that further studies ought to be done.[51]

In the Asian context, dietary reduction of saturated fats would include the reduction in intake of high cholesterol foods like dried prawns, shellfish, animal entrails, eggs, and the substitution of coconut oil and animal fats with vegetable oils for cooking. Foods like soya-bean, protein and rice have been found to reduce cholesterol levels and increased dietary fibre (like gram seeds and vegetables) may also have a hypocholesterolaemic effect.[52]

Generally speaking, adherence to traditional Malaysian diets would ensure a low cholesterol consumption; however with the trend towards increasing consumption of meat and dairy products as a result of urbanisation, traditional diets are gradually being replaced. A study on urban and rural Taiwan Chinese has shown that in the average traditional Chinese diet, only 25% of the total calories is fat *(vs.* 40% in the western diet).[53] The dietary polyunsaturated/saturated (P/S) ratio is also much lower than that for the western diet and total cholesterol intake only averages 200mg/day *(vs.* 400mg/day for a western diet). A similar finding has been reported in the diet of Indian immigrants in London.[54]

So, it would seem in Malaysia, that there is probably little need for a wholescale advocation of the prudent diet as the major races already consume a diet that is in most ways similar to that advised by the Consensus Development Conference. Furthermore, if we extrapolate from the Taiwan data, then only approximately 15% or so of our population would probably fall into the moderate to high risk groups (i.e. if a plasma cholesterol above 220mg/dl is taken as the cut off point), compared with a staggering 50% of the American population.[53] In other words, although plasma cholesterol is an increasingly important health problem, it is nowhere near the magnitude of that encountered in the West.

Two points however need to be made in this context. Firstly, there should not be complacency. Unless public education is maintained, the incidence may rise steeply with increasing affluence. Secondly, there is good evidence that of the three major races in Malaysia, the Indians are much more prone to CHD[55] and this cannot be readily explained by their diet or plasma cholesterol level alone.[54] Clinicians should therefore exercise greater awareness in looking out for and treating other treatable risk factors than simply measuring plasma cholesterol in Indians.

Drugs should be used only if the above measures have been tried and have failed to reduce plasma cholesterol and LDL, especially in male patients above 50 years with a positive family history of coronary events as they are high risk patients. Amongst the newer drugs, Benzafibrate, Gemfibrozil and Benfluorex will not only reduce LDL and cholesterol levels but also raise HDL levels as well. Their long-term side effects are less well known but they might be preferred to the older clofibrate of cholestyramine. Probucol should be avoided as it tends to lower plasma HDL levels. Nicotinic acid is less popular with patients because of occasional flushing and gastric irritation.

It is entirely illogical to prescribe lipid-lowering agents to patients who refuse to loose weight, exercise, stop smoking or modify their diet. It is a well known epidemiological fact that if two risk factors are present in a patient (i.e. smoking, obesity), then the presence or absence of a third risk factor (e.g. high plasma cholesterol) may be irrelevant to the overall risk.[56] In such cases lowering plasma cholesterol by drugs may do no more than salve a clinician's conscience and enjoin both doctor and patient in a false sense of security.

CONCLUSION

Few now doubt that very high levels of plasma cholesterol predispose to CHD. There is also evidence now that moderately elevated levels do so from data from the Framingham study.

The risk of CHD in a patient however is not determined by the measurement of a single parameter alone (plasma cholesterol or lipoprotein levels). Single parameters are useful for epidemiological evaluation but are of limited value for predicting CHD risk in a particular patient. Each patient must be assessed in the light of all his known risk factors. The strongest short and long-term predictor of a myocardial infarct is not plasma cholesterol level but current evidence of coronary artery disease.

All at-risk patients should be advised to change their eating habits and lifestyles where necessary, even if such a process may be slow and tedious. It is the cheapest and probably the most effective long-term method of lowering one's plasma cholesterol. Lipid-lowering agents should in general be held in reserve unless dietary and other efforts fail to reduce plasma cholesterol, because drug therapy, once initiated, may be lifelong. Therefore we should be cautious that the "risk of correcting a risk (cholesterol) by drugs should not be greater that the uncorrected risk itself."[5 7] The long-term safety profile of the newer agents is an unknown factor, although the overall record so far as been good.

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