Cholesterol: a risk factor not to be forgotten - Cont'd

Dietary fats and cholesterol

The effects of dietary fats on serum cholesterol concentrations are now well studied. A meta-analysis of 72 studies by Clarke and colleagues showed that replacing 5% saturated fats with polyunsaturated fats produces the greatest fall in total cholesterol (0.39 mmol/L), followed by monounsaturated fats (0.26 mmol/L) and carbohydrate (0.24 mmol/L) (5). Lowering dietary cholesterol by 200 mg/day lowers cholesterol by about 0.13 mmol/L. This analysis suggests that removing 10% of energy from saturated fat in the Australian diet and decreasing dietary cholesterol could lower blood cholesterol concentrations by 14%. This would translate into a fall in heart disease mortality of about 35% in the population – a massive effect, but comparable to that achieved in Finland and Ireland.

Another meta-analysis by Mensink and Katan considered effects on HDL-cholesterol, allowing an examination of the effects of dietary changes on the total cholesterol/HDL ratio[6]. The inclusion of polyunsaturated and monounsaturated fats at the expense of carbohydrate is associated with significant falls in the total cholesterol/HDL ratio. Polyunsaturated fats are slightly superior to monounsaturated fats, which comes as a surprise to some. Trans monounsaturated fats have the most adverse affects on the ratio. This study highlights that the optimal cholesterol profile is achieved by consuming the right mix of fats, not by consuming a low fat diet. The latest advice from the National Cholesterol Education Program in the United States is that up to 35% of energy from fats is acceptable.

Plant sterols

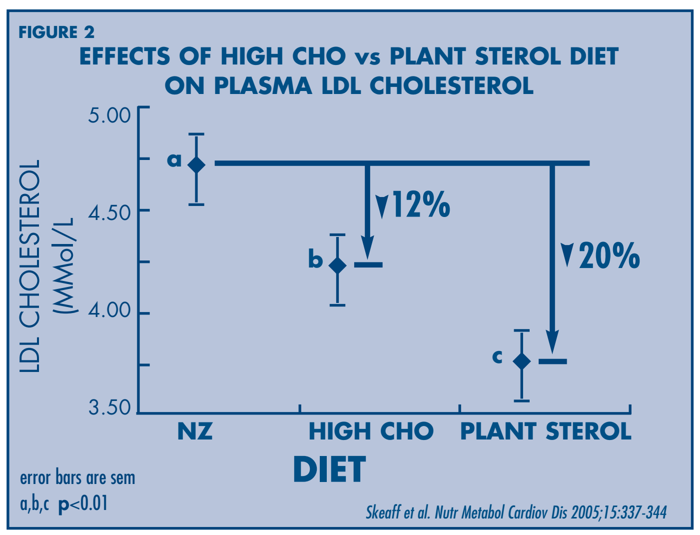
Knowledge about the effects of plant sterols on blood cholesterol is now quite extensive – over 30 studies of their effects on lipid profiles have now been conducted. A summary of these studies by Katan indicated that the consumption of 2 g/day of plant sterols lowers LDL-cholesterol by about 10% in all age groups. Most of the products currently enriched with plant sterols are margarine spreads – high fat foods – and one of the most common questions asked is whether better cholesterol levels would be achieved by simply eating as little fat as possible. Our research team at Otago University addressed this question in a study[7] comparing the effects on serum lipids of three diets:

a. a typical western (New Zealand) diet (32%E fat)

b. a plant sterol diet – a cholesterol-lowering diet including a plant sterol spread (29%E fat)

c. a high carbohydrate diet – the same diet as (b), the only change being that the plant sterol spread was replaced with an equivalent energy content from carbohydrate (25%E fat).

Figure 2 shows the effects on LDL-cholesterol when the diets were consumed over periods of 4 weeks. Compared to the typical western diet, the low fat/high carbohydrate diet lowered LDL-cholesterol by 12% and the plant sterol diet lowered LDL by 20%, the difference between the two due to the action of the plant sterols. Importantly, the low fat diet lowered HDL-cholesterol by 10% compared to a non-significant 3% fall on the plant sterol diet. As a result the total cholesterol/HDL ratio was substantially better on the plant sterol diet.



References
1. Yusuf S et al. Lancet 2004;364:937-52
2. Laatikainen T et al. Am J Epidemiol 2005;162:764-73.
3. Bennett K et al. J Epidemiol Comm Health 2006;60:322-27.
4. Australian Institute of Health and Welfare 2002. Diabetes: Australian Facts 2002. AIHW Cat No. CVD 20.
5. Clarke R et al. BMJ 1997;314:112-17.
6. Mensink RP, Katan MB. Arterioscler Thromb 1992;12:911-19.
7. Skeaff CM et al. Nutr Metabol Cardiov Dis 2005;15:337-44.

Key points

▲ Elevated blood cholesterol is a potent risk factor for coronary heart disease but efforts to lower the mean blood cholesterol concentration of Australian adults over the last 25 years have been unsuccessful. Achieving the right balance of fats and including 2g/day of plant sterols are effective dietary means for lowering blood cholesterol.

▲ There is currently a controversy about whether long-chain omega 3s lower cardiovascular risk but, on balance, the evidence still indicates they are protective. Advice to the general public to include regular fish meals and to people with coronary disease to take omega 3 supplements remains appropriate.

▲ Cardiovascular disease is an inflammatory condition. Weight loss and, to some extent, long-chain omega 3s and wholegrains help to reduce inflammation. Increasing or decreasing linoleic acid (omega 6) intake has no effect on inflammation. The omega 6/omega 3 ratio has major shortcomings and should not be used.

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The University of Sydney Nutrition Research Foundation

Controversies in Cardiovascular Disease

Symposium Report

Current controversies about the links between diet and coronary heart disease were explored in a symposium held by the Sydney University Nutrition Research Foundation on 14 March 2007.

Cholesterol: a risk factor not to be forgotten

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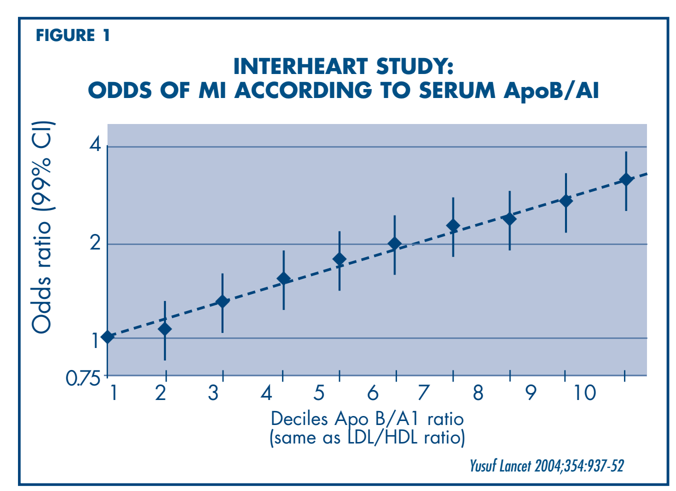
In recent years there has been a belief that a major advancement in our understanding of the causes of heart disease would unfold, perhaps through studies of antioxidants or the role of homocysteine-lowering. However, the trials of both have been very disappointing and the focus for both prevention and treatment of coronary disease has shifted back to the constellation of conventional risk factors.

Cholesterol and heart disease

The important role of elevated serum cholesterol as a risk factor for heart disease was reaffirmed by the recent INTERHEART case-control study, which compared a large number of cases and controls in 52 countries[1]. Figure 1 shows the relation of Apo B/Apo A1 to the risk of coronary heart disease in this study. The Apo B/Apo A1 ratio is equivalent to the LDL/HDL-cholesterol ratio and its relation to coronary disease is linear and strong. Those in the highest decile were at four times the risk of a myocardial infarction of those in the lowest decile and this relation held for all the regions of the world investigated. When risk factors occur in combination risk is markedly increased. The combined impact of smoking, diabetes mellitus and hypertension was a 13-fold increase in coronary risk. If a high LDL/HDL-cholesterol ratio was also present the increase in risk was 42-fold.



A number of cohort studies have assessed the associations between serum cholesterol concentrations and the risk for heart disease. The studies suggest that people with a blood cholesterol level 1 mmol/L below another group have about 40% less risk. Of course, such studies are observational – they can only predict benefits. However, the results of randomised controlled trials of cholesterol-lowering demonstrate that the actual reduction achieved corresponds almost exactly with the predictions based on the cohort studies. So there is good evidence from case-control studies, cohort studies and randomised controlled trials that altering serum cholesterol concentrations reduces individual and population risk for coronary heart disease.

Changing cholesterol in populations

A team headed by UK researcher Simon Capewell has analysed the relative contributions of treatment and prevention to the falls in rates of coronary heart disease in Finland, where rates have dropped by about 60% since the early 1980s[2]. Favourable changes in risk factors account for over half the decline in coronary mortality, with the majority (37%) attributable to falls in serum cholesterol. Similarly, falls in serum cholesterol among the Irish population have contributed about 30% of the significant fall in coronary mortality (47%) in that country since 1985[3].

In New Zealand there has been a significant 5% fall in serum cholesterol among women but not men since 1989. Five percent may not sound like much but at a population level it translates into very significant benefits. Changing the mean serum cholesterol of a population also has a profound effect on the proportion of individuals above or below certain cut-offs which may be used to decide on the prescription of medication. Unfortunately, time trends in Australia show that serum cholesterol concentrations in both men and women haven't changed since 1980[4].

Do long-chain omega 3 polyunsaturated fatty acids prevent heart disease?

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In Paleolithic times the human diet was relatively rich in long-chain omega 3 polyunsaturated fatty acids from game and/or fish and low in saturated fat. These aspects of our diet have changed considerably since the advent of civilization. In recent decades a case has steadily built that long-chain omega 3s are protective against cardiovascular disease and that intakes should be increased in the general population and, in particular, in people with the heart disease. It is somewhat surprising that there is currently a controversy on this issue and that even the safety of high intakes of omega 3s has been questioned.

The Cochrane review

The major source of this controversy is a Cochrane systematic review of 41 cohort studies and 48 randomised controlled trials assessing the effects of long-chain omega 3s on cardiovascular disease (1). This review found consumption of omega 3 was associated with a fall in total mortality of over 10% but this failed to reach significance. There were several problems with the Cochrane analysis: not all eligible trials were included; some incorrect data were used; a trial since shown to be fraudulent was included; and there was appreciable heterogeneity between trials.

Most of the criticism of the Cochrane review related to the inclusion of the so-called DART 2 trial, despite it falling outside the cut-off date for inclusion in the review. DART 2 is one of the largest and longest trials into whether fish or fish oils affect cardiovascular risk and showed no benefit (2). The design and execution of this trial have been heavily criticised for a number of reasons – some subjects were recommended fish oil tablets, while others were advised to eat fish; no measures of compliance were employed; and the trial was stopped for one year and then re-started. When DART 2 was excluded from the Cochrane analysis the fall in total mortality associated with increased omega 3 intake increased to nearly 20% and was significant.

Positive and negative trials

Some other trials of long-chain omega 3s have produced negative findings but these need to be put in perspective. Three out of four of the defibrillator trials in people with cardiomyopathy showed no benefit. But cardiomyopathy is not due to atherosclerosis. Fish oils provide protection against atherosclerosis-related sudden death and it should come as no surprise that they offer no protection to people with cardiomyopathy.

Contrast these findings with those of the GISSI-P trial [3]. This was the trial that convinced the American Heart Association to recommend 1g/day of EPA+DHA for all people with coronary heart disease. In this trial of over 11,000 subjects who had experienced a myocardial infarction, half were given fish oil supplements and half were not. After three and a half years those taking the omega 3s showed a 20% reduction in mortality. This was driven by a 53% fall in sudden death in the early months. In those with impaired left ventricular function the fall in rates of sudden death was even better.

The JELIS trial is an important study published after the cut-off for the Cochrane review which provides new evidence of the cardio-protective effects of long-chain omega 3, specifically EPA (4). It was conducted in Japan where fish is popular and the background intake of long-chain omega 3s is therefore relatively high. One would expect this would make it difficult to detect a benefit. All 18,000 subjects in the trial had hypercholesterolaemia and were taking statins. Despite low event rates in the group, a fall of nearly 20% in coronary events in those receiving EPA was observed after nearly five years of follow-up.

Mercury concerns

The debate about the cardiovascular benefits of long-chain omega 3 has been complicated by concerns about mercury levels in fish. Horror stories such as the Minamata Bay disaster in Japan, where over 900 people died and 2 million suffered health problems from eating fish high in mercury, have heightened awareness. However, the fish in Minamata Bay were contaminated by industrial waste which had been dumped in the sea over a period of over 35 years. Mercury levels in the local fish were 100 times higher than usual. This scenario is a total contrast to that of Australian fish and, in particular, salmon farmed in Tasmania which have virtually undetectable levels of mercury. A recent Harvard review concluded that the benefits of eating oily fish twice a week clearly outweighed any risks [5].

Recommendations

The Heart Foundation of Australia has recently conducted an extensive review of the role of long-chain omega 3s in the prevention of cardiovascular disease which should be published soon. In the meantime, advice to eat fish at least once a week remains appropriate for the general population. For those that have had a heart attack the use of fish oil supplements should be considered.

References
1. Hooper et al. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD003177.
2. Burr ML et al. Eur J Clin Nutr. 2003;57:193-200.
3. GISSI-Prevenzione Investigators. Lancet 354:447-455;1999.
4. Yokoyama M et al. Lancet. 2007;369:1090-8.
5. Mozaffarian D et al. JAMA. 2006;296:1885-99.

Diet, inflammation and cardiovascular disease

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Inflammation plays an integral role in several stages of cardiovascular disease. Early in the process LDL-cholesterol enters the artery wall and becomes modified. Monocytes (inflammatory cells) are then drawn from the circulation into the artery wall to ingest the modified LDL, becoming macrophages and then foam cells as atherosclerosis gets underway. Inflammation is also involved in the acute thrombotic event. Macrophages produce proteinases, which break down the fibrous cap of the atherosclerotic lesion leaving it prone to rupture. A wide variety of inflammatory mediators are produced during these processes.

C-reactive protein: an inflammatory marker

Inflammation from any source is associated with an increase in the level of C-reactive protein (CRP) in the blood. People with existing coronary disease show modest elevations in CRP and for some time this is has been accepted as a useful predictor of the risk of a future heart attack. Following a myocardial infarction this biomarker of inflammation may increase to astonishingly high levels – a 30,000 fold change – and may stay elevated for seven days or so. During this time CRP may represent about 30% of the total protein production of the liver, so it is obviously a very important inflammatory molecule. Whether CRP is simply a marker of inflammation or is actually a player in the atherosclerosis process is unclear.

Harvard researcher Paul Ridker revolutionised the field by investigating CRP levels in healthy subjects [1]. This study showed that those with the highest levels of serum CRP had three times the risk of a heart attack compared to those with the lowest levels. And there was a similar relation with stroke. More recently, Ridker showed that combining CRP with the total/HDL-cholesterol ratio greatly increased the predictability of future cardiovascular events [2].

Most of the major cardiovascular risk factors are associated with increased CRP levels and the more risk factors present, the higher the CRP. So this biomarker of inflammation appears to be a good global barometer of cardiovascular risk.

Weight loss and CRP

Correlations between obesity and elevated CRP have been observed in many studies. Even among 10-11 year old children, CRP levels may be nearly three times higher in the fattest compared to the slimmest. Weight loss lowers CRP. At CSIRO we observed a 26% fall in CRP with an 8kg weight loss in obese women [1]. Adipose tissue undoubtedly plays a significant role in CRP metabolism and the location of the body fat is important – abdominal fat having a greater effect on serum CRP than peripheral fat. Not surprisingly, people with insulin resistance have CRP levels 3-5 times higher than those without insulin resistance.
Other dietary determinants of inflammation have not been well explored. Some epidemiological evidence suggests that 'western diet' may be associated with increased CRP, and that wholegrains may be protective. Cross-sectional data from the Harvard studies suggest that high glycaemic load may be associated with a 2-3 fold increase in CRP levels. However, we have observed no carbohydrate-related changes in CRP in our intervention studies at CSIRO, involving large variations in carbohydrate intake.

Dietary fatty acids and inflammation

The role dietary fatty acids play in promoting or lowering inflammation depends on their effects on the levels of arachidonic acid (long-chain omega 6) in cell membranes. Arachidonic acid is a particularly important membrane fatty acid. Under an inflammatory stimulus it is released from the membrane and converted into prostaglandins and leukotrienes, which modulate inflammation and thrombosis.

Dietary linoleic acid (a shorter-chain omega 6) can be elongated to arachidonic acid in the body. It is often assumed that eating more linoleic acid leads to increased levels of arachidonic acid and that it is therefore pro-inflammatory. But this is not the case. The level of arachidonic acid is tightly controlled in cell membranes and feeding studies have shown that eating more or less linoleic acid has no effect on arachidonic acid levels [4], or CRP levels.

Arachidonic acid levels are very hard to shift but can be affected, to some degree, by intakes of long-chain omega 3 fatty acids. When EPA and DHA are consumed in quantity they displace arachidonic acid from the membrane, which in turn reduces inflammation. However, the effect is modest and CRP levels are largely unaffected. Large doses of long-chain omega 3s are required to achieve a significant anti-inflammatory effect. Interestingly, α–linolenic acid (a shorter chain omega 3) appears to induce some lowering of CRP, for reasons that are not clear.

Omega ratio

The omega 6/omega 3 ratio is much discussed but has major shortcomings: it does not distinguish between short and long-chain omega 3 when their actions are clearly different; the same ratio can be associated with widely different total intakes of omega 6 and omega 3 and therefore different effects; a ratio suggests there is equal benefit from reducing omega 6 as there is from increasing omega 3, which is clearly not the case. The ratio provides no information and its use is not recommended.

References
1. Ridker PM et al. N Eng J Med 1997;336:973-79.
2. Ridker PM et al. N Engl J Med 2000;342:836-43.
3. Heilbronn LK et al. Arterioscler Thromb Vasc Biol 2001;21:968-70.
4. Adam O et al. Ann Nutr Metab 2003;47:31-36.