SYNOPSIS

Is high cholesterol more protective than damaging?

New perceptions about the role of cholesterol in the immune defence system have been postulated in an article in the *Quarterly Journal of Medicine*.[1] Increasing knowledge is being gained about the inflammatory response to injury of the arterial intima in the genesis of atherosclerosis. This, however, conflicts with the low density lipoprotein (LDL)-receptor hypothesis, which avers that high LDL cholesterol is the main cause of atherosclerosis. The observations which lead away from the LDL-receptor hypothesis may be explained by the idea that cholesterol is protective against infection and atherosclerosis.

Ravnskov, a Swedish independent researcher, presents evidence in the article to support the theory of the protective role of cholesterol. In his reference list, he includes 21 references dating from 1969 to 2000 which, he claims, reinforce the hypothesis.

Laboratory evidence from hypercholesterolaemic mice showed significantly lower and delayed mortality after injection with Gram-negative bacteria compared with control mice. Similarly, rats rendered hypolipidaemic had a greater increase in cytokine levels and markedly increased endotoxin-induced mortality compared with normal rats. Other effects seen in men with low total cholesterol (TC) are fewer circulating lymphocytes, total T cells, helper T cells, and CD8+ cells. In acute infections, cholesterol synthesis increases.

A meta-analysis of 129 cohort studies found an inverse relationship between TC and mortality from respiratory and gastrointestinal diseases, most of which are of infectious origin. In study after study this pattern was repeated, and confirmed an inverse relationship between TC and infections such as urinary tract, genito-urinary, musculoskeletal, skin and subcutaneous infections in men, and viral infections in women. A study of over 100 000 individuals over 15 years showed an inverse association between TC and the risk of hospitalisation from pneumonia and influenza, but not for chronic obstructive pulmonary disease or asthma. Low TC predicts impaired perioperative and long-term survival in patients with oedematous chronic heart failure, and in patients with postoperative abdominal infections.

Many clinical studies corroborate the findings mentioned above. For example, in patients who developed neutropenia and fever after chemotherapy, TC decreased by 30%, and was higher in survivors than in non-survivors. Children with inborn errors of cholesterol metabolism are prone to frequent and severe infections, which become less serious and less frequent after dietary supplementation with cholesterol.

The LDL-C receptor hypothesis argues that members of families with familial hypercholesterolaemia (FH) run a great risk of dying from coronary heart disease (CHD) at an early age. The immunoprotective effects of high cholesterol contradict the LDL-receptor hypothesis. If high TC or LDL-C were the most important cause of cardiovascular disease, it should be a risk in all populations, in all age groups. But in many populations (women, Canadian and Russian men, Maoris, patients with diabetes and patients with nephrotic syndrome) the association between TC and mortality is absent or inverse, says Ravnskov. In cohort studies of old people, high LDL-C or high TC does not predict CHD or all-cause mortality. In several of the studies the association between TC and mortality was inverse, or high TC was associated with longevity; these associations have mostly been considered as a minor aberration from the LDL-receptor hypothesis.

What of statin therapy? The fact that statin therapy lowers both total and cardiovascular mortality in high-risk individuals, is taken as evidence that cholesterol lowering is effective. However, statins are just as effective whether cholesterol is lowered by a small amount or by more than 40%. In addition, statin therapy is effective whether the initial cholesterol level is high or low. If high LDL-C were causal, the greatest effect should have been seen in patients with the highest LDL-C concentration and in patients whose LDL-C was lowered the most, but this is not the case.

The two pathways hypothesised to be involved in lesions of the arterial intima are firstly, monocytes and platelet interaction induced by hypercholesterolaemia, and secondly, direct stimulation of the endothelium by factors such as smoking, diabetes, hyperhomocysteinaemia and micro-organisms, among others. The degree to which each of these co-factors participate in atherosclerosis remains uncertain. The many observations of the lack of exposure-response and the observed inverse association between changes in cholesterol concentrations and clinical and angiographic outcome, suggest that the role, if any, of high cholesterol must be trivial.

The most likely explanation is that high cholesterol may be protective, possibly through its beneficial influence on the immune system. Ravnskov does, however, say '...there is an obvious need for more research on the role of lipids in infectious and atherosclerotic diseases'.

1. Ravnskov U. High cholesterol may protect against infections and atherosclerosis. *QJM* 2003; **96** (12):927-934.

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