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Is a low fat diet enough to achieve serum cholesterol goals?

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or death. Determining whether or not levels of soluble adhesion molecules reflect cellular events in atherosclerotic plaques will need to await technical developments for imaging the activity of arterial inflammation directly.

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Is a low fat diet enough to achieve serum cholesterol goals?

See page 1020 for the article to which this Editorial refers

The prevalence of coronary heart disease has been shown to be correlated to the level of serum total and low density lipoprotein (LDL) cholesterol as well as inversely correlated to high density lipoprotein (HDL)^[1]. In a recent analysis of primary and secondary prevention trials, cholesterol-lowering drug studies showed a significant reduction in coronary heart disease mortality and in total mortality^[2]. It is assumed that reductions in serum LDL cholesterol level produced by dietary therapy will have similar effects^[3,4]. The overall importance of coronary heart disease in terms of morbidity, mortality and economic cost is immense in Western countries. Diet modification and dietary advice as intervention measures were perceived to be safe and effective and proved attractive to government bodies^[1]. American guidelines^[3,4] for managing patients with high serum cholesterol concentrations concur that diet is of prime importance in the management of the condition, and advocate, as initial treatment, the National Cholesterol Education Program step 1, or

general lipid-lowering diet (less than 30% total fat, less than 10% saturated fat, and less than 300 mg of cholesterol per day). The more intensive National Cholesterol Education Program step 2 diet (less than 30% total fat, less than 7% saturated fat, and less than 200 mg of cholesterol per day) is recommended if the National Cholesterol Education Program step 1 diet proves insufficient, or for the secondary prevention of coronary heart disease. Similarly, recent European recommendations^[5] advocate for secondary prevention of coronary heart disease to reduce total fat intake to 30% or less of total energy intake, the intake of saturated fat to no more than one-third of total fat intake, and the intake of cholesterol to less than 300 mg per day. There have, however, been few randomized controlled trials of intensive dietary therapy in outpatients with hypercholesterolaemia^[6] and so the efficacy of dietary therapy has not been defined. Many of the previous studies (see below) of lipid-lowering diets have been conducted in institutional settings or under metabolic-ward conditions, in which adherence to a diet can be ensured^[7]. Furthermore, the diet recommended for reducing LDL cholesterol levels

may reduce HDL cholesterol levels to a similar degree^[6,8].

In the current issue, [Aquilani and colleagues](#)^[9] use four intervention groups to investigate the efficacy of a slightly hypocaloric, very low fat diet ($\leq 20\%$ of resting energy expenditure) or the National Cholesterol Education Program step 2 diet with or without additional drug therapy (simvastatin 10 mg) to achieve the targeted serum LDL cholesterol level of $\leq 2.59 \text{ mmol} \cdot \text{l}^{-1}$ ^[4] in outpatients with coronary heart disease. One hundred and twenty-six male ex-smokers with a serum LDL cholesterol $> 3.37 \text{ mmol} \cdot \text{l}^{-1}$ were recruited for the trial. Within 6 months the serum lipid profile (total, LDL and HDL cholesterol, triglycerides) of patients on the very low fat diet alone or combined with simvastatin 10 mg daily improved significantly (total cholesterol by -13% and -26% , respectively, LDL cholesterol by -18% and -37% and HDL cholesterol by $+29\%$ in both groups). In patients with the National Cholesterol Education Program step 2 diet the lipid profile was improved only when simvastatin 10 mg daily was added and it was less improved than in the very low fat diet plus simvastatin group. None of the study participants on diet alone achieved the recommended LDL cholesterol levels of $\leq 2.59 \text{ mmol} \cdot \text{l}^{-1}$. In contrast, when associated with simvastatin 10 mg daily, the very low fat diet reduced LDL cholesterol to $\leq 2.59 \text{ mmol} \cdot \text{l}^{-1}$ in 33% of patients, the National Cholesterol Education Program step 2 diet in 3%. The majority of patients preserved their body weight.

The evidence from other trials of low fat diets

In an overview of 16 trials, [Ramsey et al.](#)^[7] observed the following: in five trials with the step 1 diet as individual intervention, the net reduction in serum cholesterol concentration ranged from 0% to 4% over 6 months to 6 years. The analysed trials were conducted in different clinical settings, including primary prevention in high-risk men or hypertensive patients and secondary prevention after myocardial infarction. In trials with population education, reductions in cholesterol concentrations ranged from 0.6% to 2.0% over 5–10 years. When population and individual dietary advice were combined, changes in cholesterol concentration ranged from a fall of 2.1% to a rise of 1.0% over 4–10 years. Diets more intensive than step 2 diet reduced serum cholesterol concentration by 13% over 5 years in selected high-risk men in the population, by 6.5–15.1% over 2–5 years in hospital outpatients, and by 12.8–15.5% over 1–4.5 years in institutionalized patients. It was concluded that the response to a step 1 diet was too small

to have any value in the clinical management of adults with serum cholesterol concentrations above $6.5 \text{ mmol} \cdot \text{l}^{-1}$. Guidelines suggesting that most people with abnormal cholesterol concentrations could be managed by diet, with few subjects needing lipid-lowering drugs, were deemed unrealistic by [Ramsey et al.](#)^[7].

In more recent trials, [Singh et al.](#)^[10], in India, found that a fat-reduced diet (less than 25% of energy) decreased blood total and LDL cholesterol concentrations and body weight by 5.4%, 5.6% and 3 kg in patients with myocardial infarction. A diet additionally rich in fruit, vegetables, nuts, and grain products reduced these values by 12.7%, 12.3% and 7 kg, respectively. [Hunninghake et al.](#)^[6] observed among hypercholesterolaemic men and women with proven coronary heart disease, living in a community setting, that the benefit of a 5% reduction in LDL cholesterol by the National Cholesterol Education Program step 2 diet, was possibly offset by the accompanying reduction in the level of HDL cholesterol. Similarly, in the trial by [Knopp et al.](#)^[11] HDL cholesterol levels were lowered along with the levels of LDL cholesterol (8.4% and 13%), in men with hypercholesterolaemia when dietary fat was reduced from a baseline level of 34–36% of total calories from fat to 25% and 22%. Conversely, less extreme restriction of dietary fat intake to 26% and 27% reduced LDL cholesterol to a similar extent (13.4% and 5.3%) without lowering HDL cholesterol. [Stefanick et al.](#)^[12] examined the effects of changes in diet and exercise, alone and together, on plasma lipoproteins, in subjects without history of coronary heart disease and with low HDL and moderately increased LDL cholesterol. The National Cholesterol Education Program step 2 diet failed to lower LDL cholesterol levels significantly in either men or women compared to controls; when the diet was combined with aerobic exercise, however, the resulting reductions in LDL cholesterol levels were significant (also significant in men compared to the exercise group), with no adverse effects on HDL cholesterol. In earlier research, the same authors demonstrated that weight loss significantly increased HDL cholesterol levels, but did not lower total or LDL cholesterol in moderately overweight men^[13] and that physical activity prevented the lowering of HDL cholesterol levels which usually results from a low-fat diet in overweight men and women^[14]. Subsequently, the updated National Cholesterol Education Program guidelines emphasized the incorporation of weight loss and physical activity into dietary therapy for cholesterol management^[4]. In the study by [Nicklas et al.](#)^[15] obese, postmenopausal women with elevated baseline concentrations of LDL cholesterol ($> 4.14 \text{ mmol} \cdot \text{l}^{-1}$) showed reductions in

levels of triacylglycerol (19%), total cholesterol (13%), and LDL cholesterol (14%) concentrations with an American Heart Association diet step 1^[16] and weight loss, whereas women with lower initial LDL cholesterol concentrations had minimal changes in triacylglycerol, total cholesterol, and LDL cholesterol concentrations. The effect of a reduction in dietary fat intake was to lower total cholesterol and LDL cholesterol concentrations, whereas the American Heart Association diet and weight loss had opposite effects on HDL cholesterol concentrations. The decrease in HDL cholesterol concentrations was similar across hypercholesterolaemic, normocholesterolaemic and mildly hypercholesterolaemic groups (9%). The same authors^[17] observed in middle-aged and older men with exercise-induced silent myocardial infarction, that an American Heart Association step 1 diet significantly lowered triglycerides (26%), total cholesterol (12%), LDL cholesterol (10%) and HDL cholesterol (7%). Subsequent weight loss in conjunction with the American Heart Association diet resulted in an additional decrease of 24%, 10%, and 10%, respectively, and an increase in HDL cholesterol of 8%. Schaefer *et al.*^[8] found in both normolipidaemic and hypercholesterolaemic subjects that consumption of a National Cholesterol Education Program step 2 diet was associated with significant changes in levels of total cholesterol (−20% and −16%, respectively), LDL cholesterol (−21% and −18%) and HDL cholesterol (−16% and −15%). There was a wide range of diet responsiveness in the total group, with LDL cholesterol changes ranging from +5% to −40%. In the study by Walden *et al.*^[18] a National Cholesterol Education Program step 2 diet in hypercholesterolaemic men and women, with and without elevated triglycerides, significantly reduced LDL cholesterol in women (7.6% and 8.1%) and men (8.8% and 8.1%) with hypercholesterolaemia and combined hyperlipidaemia. Candidates for drug therapy were reduced from between 27% and 37% to 20%. HDL cholesterol was significantly decreased in women (−6.4% and −4.7%) but not in men.

Factors that may contribute to the contradictory findings and the limited effects of low fat diets on blood cholesterol

Variation of dietary and lifestyle factors tested

In cholesterol-lowering dietary trials, the diets did not vary only in relation to the content of total and

saturated fat and cholesterol (American Heart Association, National Cholesterol Education Program step 1 and 2 diets, less fat than the National Cholesterol Education Program step 2 diet, etc.) but also in relation to other dietary components (e.g., more fruits, vegetables, grains and fewer calories in order to induce weight loss) and additional life-style factors such as exercise. In some of the trials these factors were incorporated into the study design. In others, the alteration of the fat content of a diet may have indirectly led to alterations in other components of the diet and/or additional changes in lifestyle. It is thus very difficult to determine which dietary and non-dietary factors are responsible for an effect^[1].

Non-adherence to dietary advice

It is recognized that adherence to dietary advice is poor and dependent on factors such as strictness of diet, the individual's perception of being at risk, the perceived costs and benefits of a change in diet, as well as the trial setting (metabolic-ward conditions, outpatient environment, etc.). Furthermore, there are intrinsic problems in the assessment of dietary intake and dietary compliance in free-living subjects who self-select their food. Additionally, dietary trials, in general, cannot be blinded and changes in the diet of the 'control' group may bias the results of a dietary trial^[1,18,19].

Variation in response to cholesterol-lowering diets

Some studies indicate that baseline LDL cholesterol concentration is a major determinant of LDL cholesterol reduction associated with reduced-fat diets^[20]. For example, in the survey by Nicklas *et al.*^[15], the lipoprotein lipid responses to an American Heart Association diet^[16] and weight loss could be demonstrated only in women with elevated LDL cholesterol concentrations at baseline. In contrast, another study showed that reductions in triacylglycerol, HDL cholesterol, and LDL cholesterol concentrations were similar in hypercholesterolaemic and normocholesterolaemic subjects after a National Cholesterol Education Program step 2 diet^[8]. In a more recent analysis by Schaefer *et al.*^[21], the observation that baseline LDL cholesterol concentration is a major determinant of LDL cholesterol reduction associated with reduced-fat diets was confirmed by multivariate-regression analyses in men, but not in women. Age was also identified as a predictor of response in both sexes. Failure to consider the range of response

among subgroups of study participants may explain the results of some studies which showed that a low fat diet had only limited impact on blood cholesterol levels^[22,23].

Conclusions

The controversial results of trials testing the effect of a fat-reduced diet on blood lipid profile, and the rather small effects in the study by Aquilani *et al.*^[9] limited to a very low fat diet, may in part be explained by non-compliance to dietary advice, and variation in response to cholesterol-lowering diets in subgroups of study participants. Genetic influences underlying the latter remain to be identified. Furthermore, the National Cholesterol Education Program step 2 diet may have limited effect without the incorporation of exercise and weight loss goals, as recommended in the second National Cholesterol Education Program expert report^[4] or in the newest European recommendations^[5]. In addition, dietary fat reduction should not be considered in isolation; fat reduction results in major dietary changes and other factors such as content of fibre, vegetables and fruit in the diet which may influence the serum lipid profile. In this context, the very low fat diet used by Aquilani *et al.*^[9] should be further investigated because of the fact that it did not have a HDL serum cholesterol-reducing effect as seen in many other studies.

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