Copy to Dr Katan

Corresp-Shekelle

The University of Texas
Health Science Center at Houston

SCHOOL OF PUBLIC HEALTH

1200 Herman Pressler
P.O. Box 20186
Houston, Texas 77225
(713)792-4400

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Scott Grundy, M.D., Ph.D.
Center for Human Nutrition
The University of Texas
Health Science Center at Dallas
5323 Harry Hines Blvd., Room G4.100
Dallas, TX 75235

file 1) R. Shekelle
2) Tabloc 90

Dear Scott:

Work on the IOM Committee on Diet and Health led me to review studies concerning effects of omega-6 PUFA on serum total cholesterol and LDL-C, particularly on the question whether isocaloric replacement of carbohydrate or oleic acid with linoleic acid decreases the concentration of LDL-C. I have summarized below my review of this material, and should very much appreciate learning how it may differ from your views. Please forgive the detail regarding methods of procedure, which I have set down as a place to begin.

I think the old experiments of Keys et al (1957) and of Hegsted et al (1965) are relevant to this question for the reasons given below. These two studies had many features in common, and can be considered together. Participants were physically and metabolically normal men, 32 to 62 years of age, who were hospitalized for chronic schizophrenia. All activities were supervised, and opportunites for obtaining extra food were very limited. Diets were constructed from ordinary mixed foods. A "control" diet was designed to approximate the usual American diet, and a low-fat basal diet was designed to which various oils and fats were added. Amount of fat and the fatty acid composition of each diet were determined analytically. Intake of dietary cholesterol on the low-fat basal diet was about 300 mg/day before addition of test lipids. Intake of total calories was adjusted individually in order to keep participants in caloric equilibrium.

The experiments were designed so that each man served as his own control. The order of presenting diets was varied so that effects of change in diet would not be confounded with changes over time in other factors. In the studies of Hegsted et al, comparisons were based on groups of 9-10 men who had consumed each diet for 4 weeks. In the studies of Keys et al, comparisons involved groups of 12-27 men who had consumed each diet for 2-9 weeks (usually 4 weeks). Serum total cholesterol and beta-lipoprotein cholesterol were determined in blood drawn on two separate days near the end of each dietary period.

Regression analyses indicated an independent effect of polyunsaturated fatty acids on serum total cholesterol for men consuming mixed-food diets providing 10-40% of calories from fat. The prediction equations indicated that isocaloric substitution of polyunsaturated fatty acids for monounsaturated fatty acids or carbohydrates in the amount of 10 percent of calories, without change in any other factors, would lower serum total cholesterol by 13-16 mg/dl. This effect of polyunsaturated fatty acids can be seen directly in those experiments where polyunsaturated fatty acids were exchanged for carbohydrate or for monounsaturated fatty acids with little change in intake of other nutrients. For example, in the experiments of Hegsted et al., mean serum total cholesterol decreased by 13 mg/dl (mean of periods 3 and 18 minus the mean of periods 1 and 6) and by 32 mg/dl (mean of periods 21 and 36 minus the mean of periods 19 and 24) when polyunsaturated fatty acids replaced monounsaturated fatty acids at 10% and at 20% of calories, respectively. In the JWX series of experiments conducted by Keys et al, serum total cholesterol decreased by 18 mg/dl when 14% of calories from monounsaturated fatty acids were replaced with polyunsaturated fatty acids.

Although these investigators published results only for serum total cholesterol, the following evidence supports the inference that they can be generalized to LDL-cholesterol. First, both groups of investigators measured beta-lipoprotein -- Keys et al by paper electrophoresis and Hegsted et al by an immunochemical procedure -- and both groups noted that results for beta-lipoprotein cholesterol closely paralleled those for total cholesterol. Second, the observed differences in mean serum total cholesterol -- e.g., the 13 to 32 mg/dl differences noted above when polyunsaturated fatty acids replaced monounsaturated fatty acids -- are too large to be accounted for by decrease just in HDL-cholesterol. Also, although interpreting the results of Becker et al (1983) is complicated by the large changes in plasma lipids that occurred when subjects went from mixed-food diets to liquid formula diets, their results were consistent with the idea that substituting linoleic acid for oleic acid lowered LDL-C. Finally, results from the LRC CPPT (Gordon et al., 1982) showed that increased intake of polyunsaturated fatty acids was associated with decrease in plasma total cholesterol, that the decrease occurred mainly in the LDL fraction, and that it was independent of change in body weight, saturated fatty acids, and cholesterol.

Evidence for the view that dietary polyunsaturated fatty acids do not lower LDL-cholesterol when substituted for monounsaturated fatty acids comes in part from the cross-over experiment which you and Mattson published in 1985. Twenty men (12 normotriglyceridemic and 8 hypertriglyceridemic) were maintained on liquid formula diets, one high in polyunsaturated fatty acids (S=4% of calories, M=6%, and P=29%) and the other high in monounsaturated fatty acids (S=3%, M=29%, and P=7%). Mean values on the high-poly and high-mono diets, respectively, were 191 and 197 mg/dl for plasma total cholesterol, 120 and 119 mg/dl for LDL-cholesterol, 36 and 40 mg/dl for VLDL-cholesterol, and 35 and 38 mg/dl for HDL-cholesterol. None of these differences was statistically significant. These results may be interpreted as indicating that a liquid formula diet providing 29% of calories from polyunsaturated fatty acids does not lower plasma LDL-cholesterol in comparison to a similar diet providing 7% of calories from PUFA. As you noted, however, alternative explanations of these results are possible. Mean plasma total cholesterol decreased by 41 mg/dl from values on admission to the end of the initial high-sat diet with the result that several patients had low serum total cholesterol levels before starting the test diets, and their further reductions were especially small. Patients with higher levels of total cholesterol on the high-sat had greater decreases when changed to the high-poly diet. For the 4 patients with highest levels of total cholesterol on the high-sat diet, the high-poly diet was associated with an average reduction of 64 mg/dl.

Horlick (1959, 1960) investigated the question whether corn oil would lower serum total cholesterol after serum total cholesterol had been brought to a basal level by consuming a diet from which all known hypercholesterolemic factors had been removed. The results indicated that substituting corn oil for carbohydratees in a basal diet providing 4% of calories from total fat had little or no effect on serum total cholesterol, although it may have affected the proportions of alpha- and beta-lipoproteins.

You and your colleagues (1986) also compared a mixed-food diet that provided 17% of calories from polyunsaturated fatty acids with the AHA phase I diet that provided 10% of calories from polyunsaturated fatty acids. Participants were 9 men residing in a VA domiciliary. As calculated from the formula of Keys et al, mean plasma total cholesterol should have been lower by 10 mg/dl, but in fact the two means were equal, 175 mg/dl. However, as you noted, chance cannot be ruled out as an explanation for this observation because the experiment lacked adequate power to detect a difference of 10 mg/dl; differences less than 12.3 mg/dl would not have been statistically significant.

Three other studies have been cited as indicating an absence of effect of polyunsaturated fatty acids on LDL-cholesterol. Brussaard et al (1980) compared diets (MOD & HIPUF) that provided 11 and 19% of calories from polyunsaturated fatty acids but were similar in intake of cholesterol, saturated fatty acids, and monounsaturated fatty acids. They concluded that the HIPUF diet was no more effective in depressing serum LDL-C than the MOD diet. However, this conclusion was based on an incomplete analysis of data that involved only intra-subject comparisons within each group. When the investigators compared differences between groups (i.e., between MOD and HIPUF) in changes from baseline to end of the test period, the results showed an effect of PUFA on serum total cholesterol as predicted by the equations of Keys et al (Katan, personal communication). Unfortunately, serum samples from group MOD during the test period were not analyzed for cholesterol fractions due to logistical constraints with the ultracentrifuge, so we don't know what happened to LDL-C.

The paper by Kuusi et al (1985) suffers from the same problem of incomplete analysis of data, but this can be overcome partially by additional analysis of the published data. Diet I was lower in saturated fatty acids and cholesterol and higher in polyunsaturated fatty acids than Diet II. Using the formula of Keys et al, the predicted differences in mean serum total cholesterol between Diets I and II were -12.5 mg/dl at 6 weeks and -11.9 mg/dl at 12 weeks with Diet I having the lower values. The observed differences in mean serum total cholesterol between Diets I and II for men were -11 and -15 mg/dl at 6 and 12 weeks, respectively. Corresponding differences in mean LDL-C were -5 and -9 mg/dl, and in mean HDL-C were -3 and -4 mg/dl. Results for women were similar but of smaller magnitude. The differences at 6 and 12 weeks were -6 and -5 mg/dl in total cholesterol, -8 and -2 mg/dl in LDL-C, and -3 and -1 mg/dl in HDL-C. Although these results are consistent with the changes predicted by the formulas of Keys and of Hegsted, interpretation regarding an independent effect of polyunsaturated fatty acids is difficult due to simultaneous change in saturated fatty acids and cholesterol.

Another experiment by Brussaard et al (1982) yielded a result that is apparently inconsistent with the result predicted by the formula of Keys et al. The basis for this inconsistency has not been determined. However, 12 of the subjects were young women, and it is possible that effects of the menstrual cycle on plasma lipids may have obscured effects of change in diet.

In summary, the evidence indicates to me that within the context of mixed-food diets that provide 10-40% of calories from fat, isocaloric substitution of omega-6 polyunsaturated fatty acids for carbohydrate or monounsaturated fatty acids lowers serum total cholesterol and LDL-cholesterol. A concomitant change in intake of saturated fatty acids is not necessary for this effect to occur. However, this effect may not occur under some conditions, e.g., when polyunsaturated fatty acids are substituted for carbohydrates in a diet that initially provides 4% of calories from total fat, or when diets that provide 20-30% of calories from polyunsaturated fatty acids are consumed. Further studies are needed in order to investigate these circumstances and clarify the mechanisms by which dietary factors affect plasma lipids and lipoproteins. However, in the context of ordinary American diets, the evidence indicates that increasing intake of linoleic acid from, say, 4-5% of calories to 8-10% of calories by isocaloric substitution for carbohydrate and/or oleic acid would results in a decrease in mean serum total cholesterol and LDL-C.

Clearly, other considerations need to be taken into account in determining whether such a change in diet would have a beneficial overall effect or not. I am not raising that question here, but only the question regarding an effect on LDL-C. As I said above, your assistance in understanding this complicated issue would be greatly appreciated.

With best regards,

Sincerely yours,

Richard B. Shekelle, Ph.D.
Professor of Epidemiology