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Dietary Fat and Cholesterol
Lessons from the Past Decade

Expert groups in the United States, Europe and Canada in the late 1980s recommended that the general population reduce the amount of fat, in particular saturated fat, and cholesterol in their diets. These recommendations stemmed primarily from concern with the high incidence of cardiovascular disease (CVD) in these areas. Although there was a rationale for the recommendation to reduce the amount of saturated fat in the diet, the recommendations to reduce total fat and cholesterol in the diet of the general population were somewhat more tenuous. Nonetheless, governments and other health agencies responded by changing their food guides to reflect these recommendations. The food industry, in turn, responded by developing low fat, low saturated fat and cholesterol-free food products. The recommendations also stimulated research into the relationship between dietary fat and health. As a result, during the decade from 1990 to 2000 there was an appreciable refinement in the understanding of the role of dietary fat and cholesterol in diseases and disorders such as CVD, cancer, diabetes and obesity. Many questions still remain to be answered but the role of dietary fat has been clarified.

THE SCIENTIFIC LITERATURE SUGGESTS THAT REDUCING TOTAL FAT INTAKE IS OF LITTLE BENEFIT FROM A CARDIOVASCULAR RISK PERSPECTIVE WITHOUT A CONCOMITANT REDUCTION IN SATURATED FAT.

Scientific findings and meta-analyses of metabolic studies published over the past decade continued to support the importance of dietary saturated fat (SF) in altering risk factors associated with CVD. By contrast, several studies reported that the desired decrease in plasma cholesterol achieved by substituting carbohydrate (CHO) for dietary fat often is accompanied by lower levels of plasma high density lipoprotein (HDL) cholesterol and higher levels of plasma triglycerides. Studies also have shown that high intakes of *trans* fatty acids (TFA) raise plasma low density lipoprotein (LDL) cholesterol and lower plasma HDL cholesterol, thus bringing into question the practice of substituting hydrogenated vegetable oils for SF sources in food production and preparation.

Evidence amassed over the past decade indicates that dietary cholesterol is not a major factor affecting plasma cholesterol and lipoproteins in the general population. Results of recent meta-analyses, carefully controlled metabolic studies and analyses of epidemiological data indicate that earlier predictions overestimated the effect of dietary cholesterol on plasma cholesterol.

TOTAL DIETARY FAT

Limited studies have dealt specifically with the effect of dietary fat level *per se*. Nearly all metabolic studies that have examined the effect of dietary fat level on risk factors for CVD have been confounded by concomitant changes in the type of fat in the diet; lower dietary fat intakes usually were accompanied by lower intakes of SF. In fact, the scientific literature suggests that reducing total fat intake is of little benefit from a cardiovascular risk perspective without a concomitant reduction in SF. Barr et al[1] found that reducing total fat intake as a percent of energy had no effect on plasma total or LDL cholesterol levels if it was not accompanied by a reduction in SF intake. Changing subjects' intake from an average American (AA) diet (37% of energy as fat, 16% as SF) to an American Heart Association (AHA) Step I diet (30% energy as fat, 9% as SF) resulted in a significant decrease in plasma total and LDL cholesterol levels. By contrast, lowering total fat but maintaining the same level of SF as the AA diet (30% energy as fat, 15% as SF) had no effect on plasma total or LDL cholesterol levels.

Substituting monounsaturated fatty acids for saturated fat can counterbalance the atherogenic effects of a high carbohydrate diet.

Although substituting CHO for SF has been found to result in lower plasma total and LDL cholesterol levels, these beneficial effects are offset by an elevation in plasma triglyceride levels and a reduction in plasma HDL cholesterol levels.[2–4] Conversely, substituting monounsaturated fatty acids (MUFA) for SF can counterbalance the atherogenic effects of a high CHO diet. Kris-Etherton et al[5] reported that high fat, high MUFA diets were equally as effective as the AHA Step II diet in lowering plasma total and LDL cholesterol while not increasing triglyceride levels or decreasing HDL cholesterol levels. These findings are consistent with the observed beneficial effects of high fat, high MUFA diets compared with low fat, high CHO diets for subjects with non-insulin dependent diabetes mellitus.[6,7] However, the type of CHO influences the elevation in plasma triglyceride level; simple CHOs, in particular fructose and fructose-containing sugars (e.g. sucrose), produce a more severe hypertriglyceridemia than complex CHOs (e.g. starch and other polysaccharides).[3] In addition, higher fibre intakes moderate the hypertriglyceridemia induced by high CHO diets.

SATURATED FAT INTAKE

A frequent approach in assessing the effect of dietary fat on risk factors for CVD, particularly prior to 1990, simply involved a comparison of the effects of certain fats (e.g. butter, lard, etc. compared with corn oil, canola oil, etc.). There is general consensus that SF have a major effect on plasma total and LDL cholesterol levels; however, few studies have examined the effect of dietary SF *per se*. As discussed in the previous section, the effect of SF is frequently confounded by the effect of total dietary fat. In addition, many of the studies reported over the past decade have centered on the effect of individual fatty acids on plasma lipids and lipoproteins.

Although not specifically designed to assess the effect of SF on the risk factors for CVD, several studies over the past decade have reported beneficial effects of lower SF intakes. Kris-Etherton et al[5] found that replacing SF with three different sources of MUFA resulted in lower plasma total and LDL cholesterol levels without the concomitant higher plasma triglyceride levels and lower plasma HDL cholesterol levels that accompanied a low fat, high CHO diet. Similarly, Judd et al,[8] in a study designed to assess the effect of TFA, found that plasma total and LDL cholesterol levels were significantly lower following a high oleic acid diet than a high SF diet. Likewise, Sanders et al,[9] in a study designed to compare the effect of n-3 and n-6 fatty acids, found that plasma total and LDL cholesterol and apolipoprotein B levels were lower when a combination of MUFA and either n-3 or n-6 PUFA replaced SF. Of particular interest is the controlled, multi-centre study by Ginsberg et al,[2] which compared the effect of the average American diet, the AHA Step I diet and a low fat diet (34%, 29% and 25% of energy as fat, and 15%, 9% and 6% as SF, respectively) on risk factors for CVD. Total and LDL cholesterol levels were progressively lower as total fat and SF in the diet were decreased. Dietary cholesterol, MUFA and PUFA were maintained essentially constant in the three diets (~275 mg/d, and 13% and 6.5% of energy, respectively). If total fat intake is not a significant factor in plasma lipid and lipoprotein levels, as discussed in the previous section, the changes would appear to be due to the decrease in SF intake. This was a multi-centre study and the effect of diet was consistent across sub-groups, suggesting that the favourable effect of a sequential decrease in SF intake can apply to the general population.

Studies reported over the past decade have confirmed the adverse effects of *trans* fatty acids on risk factors for cardiovascular disease.

Meta-analyses of the quantitative effects of dietary fatty acids on plasma lipid and lipoprotein levels[10–12] reinforce the concept of an adverse effect of dietary SF on risk factors for CVD. The three estimates coincided fairly closely; they predicted that each 1% increase in energy from SF would result in a 0.50–0.54 mmol/L increase in plasma cholesterol level, mainly LDL cholesterol. Gardner and Kraemer[13] confirmed the hypercholesterolemic effect of SF in a meta-analysis of studies on the effect of substituting MUFA or

PUFA for SF. Replacing 6% to 16% of energy from SF with either MUFA or PUFA resulted in a significant decrease in plasma total and LDL cholesterol levels. It is interesting to note that MUFA and PUFA were equally effective in lowering plasma total and LDL cholesterol levels when they replaced SF in the diet. In addition, no differences in plasma HDL cholesterol levels were seen when diets high in MUFA or PUFA were compared directly. By contrast, meta-analyses of more general studies designed to assess the effect of dietary fat and cholesterol on plasma lipids[10–12] reported a cholesterol-lowering effect of PUFA but no effect of MUFA.

Epidemiological studies,[14,15] such as the Nurses' Health Study,[15] also have reported a positive association between higher intakes of SF and increased risk of CVD. However, the results of cohort studies have been inconsistent. Extensive studies of American[16] and Finnish[17] men found no evidence of an association between SF intakes and CVD. Part of the inconsistency among cohort studies may be due to the dietary information used and variation in the length of the follow-up period.

Many of the studies reported over the past decade have centered on the effect of specific fatty acids on risk factors for CVD.[18] In general, the plasma total and LDL cholesterol-raising effects of SF have been attributed to lauric, myristic and palmitic acids. A number of studies have indicated that myristic acid[19] and myristic acid plus lauric acid[20,21] are more hypercholesterolemic than palmitic acid. Tholstrup et al,[22] however, found that myristic and palmitic acids had similar effects on plasma total and LDL cholesterol levels. Lauric and myristic acids have also resulted in higher plasma HDL cholesterol levels than palmitic acid.[19–23] Stearic acid, by contrast, has not been found to be hypercholesterolemic and may even have some favourable effects on blood clotting activity.[20,24] On the other hand, the Nurses' Health Study,[15] a prospective cohort study, found that stearic acid increased the risk of CVD more than did other dietary SF.

TRANS FATTY ACIDS

The reports[25,26] that dietary TFA not only raised plasma LDL cholesterol levels but lowered HDL cholesterol levels aroused renewed interest in possible adverse effects of TFA. These reports also raised controversy with the practice of substituting hydrogenated fats for saturated animal fats in food processing and preparation. Studies reported over the past decade have confirmed the adverse effects of TFA on risk factors for CVD.[27] Judd et al[8] and Lichtenstein et al[28] substantiated the findings by the Dutch group[25,26] of a linear increase in plasma total and LDL cholesterol levels, and a linear decrease in HDL cholesterol level, with an increase in dietary TFA. Lichtenstein et al[28] also confirmed earlier studies[29,30] which found higher total-to-HDL cholesterol ratios with TFA intake. Studies on the effects of TFA on serum lipid levels also have reported higher levels of lipoprotein [a]; a specific risk factor for CVD.[28,30–32]

Studies involving comparison of TFA margarine with *trans*-free margarine[33,34] or non-hydrogenated vegetable oil[29] corroborated the hypercholesterolemic effect of TFA. In addition, prospective cohort studies in Finland[17] and the United States[35,36] and a case–control study in the United States[37] reported a strong relationship between CVD risk and TFA intake. In general, however, case–control studies that estimated the intake of TFA from food frequency data or tissue fatty acid composition did not find an association between TFA intake and myocardial infarction or sudden cardiac death.[38–40]

The accumulation of scientific data on the effect of TFA on plasma lipids and lipoproteins has moved agencies such as Health Canada and the US Food and Drug Administration to review their policies concerning TFA in nutrition labelling and nutrient content claims. Ample evidence supports the recommendation that consumers reduce intakes of both SF and TFA.

DIETARY CHOLESTEROL

Recommendations to reduce dietary cholesterol to 300 mg/day are based largely on population studies, such as the Seven Countries Study, and prediction equations derived from numerous controlled metabolic studies.[41,42] However, recent meta-analyses of studies reported over the past 30 years and carefully controlled metabolic and epidemiological studies reported during the past decade indicate that the earlier predictions of the effect of dietary cholesterol on plasma cholesterol were overestimated.

> AMPLE EVIDENCE SUPPORTS THE RECOMMENDATION THAT CONSUMERS REDUCE INTAKES OF BOTH SATURATED FAT AND *TRANS* FATTY ACIDS.

The effect of dietary fat and cholesterol on plasma lipids and lipoproteins has been assessed in three meta-analyses of the experimental data published over the past 30 years.[10–12] Hegsted et al,[10] in a re-evaluation of an earlier analysis[41] of the effect of dietary factors on serum total and LDL cholesterol, predicted an increase of 0.069 mmol/L in serum cholesterol for each 100 mg/day increase in dietary cholesterol on the basis of metabolic studies. They divided the 344 studies used in their analysis into metabolic studies (248), in which diets were prepared and fed under controlled conditions, and field studies (96), in which diets were modified through instruction or a combination of instruction and the provision of some foods. The estimated increase in serum cholesterol on the basis of the field studies with free-living subjects was 0.041 mmol/L for each 100 mg/day increase in dietary cholesterol. The authors suggested that, because field trials are more dependent on reported food intakes and food composition tables than are metabolic studies, the predicted effects of dietary fat and cholesterol on serum cholesterol levels were probably better represented by the analysis of the metabolic studies.

In a similar meta-analysis of 76 metabolic ward studies, Clarke et al[11] found essentially the same results: an increase of 0.065 mmol/L in serum cholesterol for each 100 mg/day increase in dietary cholesterol. Howell et al[12] conducted a similar meta-analysis of the data from 224 studies involving healthy free-living subjects between the ages of 18 and 69 years. They considered only studies that included a control group or in which subjects were randomly assigned, or that used repeat-measures design and controlled for confounding. They predicted a 0.057 mmol/L increase in serum cholesterol for each 100 mg/day increase in dietary cholesterol.

Although all of these analyses found a positive relationship between dietary cholesterol intake and plasma total cholesterol level, the estimated response to dietary cholesterol was much lower than previously estimated.[41] The prediction equations reported during the past decade[10-12,43] estimate a decrease in serum cholesterol level between 0.035 and 0.069 mmol/L for each 100 mg/day decrease in dietary cholesterol. These estimates are significantly lower than the earlier estimate by Hegsted et al[41] of a 0.175 mmol/L decrease for each 100 mg/day decrease in dietary cholesterol.

Although the scientific literature supports the premise that dietary cholesterol has a small but consistent effect on plasma total cholesterol level, the relationship between dietary cholesterol and plasma lipoproteins is not clear. Howell et al[12] found that changes in dietary cholesterol did not have a significant effect on plasma LDL cholesterol level. Hence, their prediction equation for the effect of dietary fat and cholesterol on plasma LDL cholesterol does not include dietary cholesterol as a bivariate predictor. By contrast, Hegsted et al[10] found that the effects of dietary fat and cholesterol on plasma LDL cholesterol were statistically significant. The predicted effects, however, were slightly lower than for the change in total plasma cholesterol level.

All of the prediction equations estimate a much greater effect on plasma cholesterol when SF intake is decreased to the recommended 8%–10% of energy compared with a 100 mg–200 mg decrease in dietary cholesterol. The estimated decrease in plasma total cholesterol in response to dietary cholesterol is relatively minor—the estimated change in plasma total cholesterol in response to a 100-mg change in dietary cholesterol represents only ~1% of the average adult's serum cholesterol value. Note that the estimated change falls within the variance (5%–10%) for repeat determinations of plasma cholesterol levels.

Although many controlled metabolic studies have assessed the effect of dietary cholesterol on plasma lipid and lipoprotein levels, there still is no clear consensus on the importance of dietary cholesterol in controlling risk factors for CVD. Lack of consensus probably stems from differences among studies in experimental protocol, variability in other dietary components and marked variation among subjects in response to dietary cholesterol. In addition, Hopkins[43] has reported that baseline dietary cholesterol has a major effect on the response to added dietary cholesterol; the lower the baseline cholesterol intake, the greater the response to added dietary cholesterol.

In an effort to overcome the effect of some of these factors, Ginsberg et al[44] assessed the effect of four levels of dietary cholesterol on the plasma lipid and lipoprotein levels of healthy young men. The study was a four-way crossover design in which each of the subjects consumed each dietary cholesterol level for a period of 8 weeks, with a "washout" between each test period. The basal diet was an AHA Step I diet (30% of energy as fat, 9% of energy as SF, 125 mg/day cholesterol), supplemented with 0, 1, 2 or 4 eggs per day. The diets provided 128 mg, 283 mg, 468 mg or 858 mg of cholesterol daily. Plasma total cholesterol increased by 0.038 mmol/L for each 100 mg of cholesterol added to the basal diet. This coincides with the lower estimates of the prediction equations discussed earlier. Essentially all of the increase in plasma total cholesterol was due to LDL cholesterol (0.036 mmol/L for each 100 mg of dietary cholesterol). This observation coincides with the report by Hegsted et al[10] that the effects of dietary fat and cholesterol on plasma LDL cholesterol roughly paralleled, but were slightly lower than, the effect on plasma total cholesterol. Similarly, Schnohr et al[45] found that adding two eggs per day to the average diet of 24 healthy Danish men and women resulted in an increase in plasma total cholesterol of ~0.042 mmol/L per 100 mg/day of added dietary cholesterol, with no effect on plasma LDL cholesterol level. Ginsberg et al[44] also found that added dietary cholesterol in the form of egg cholesterol had no effect on plasma HDL cholesterol or triglyceride levels. In addition, dietary cholesterol did not appear to increase the atherogenicity of the serum following a meal as assessed by cholesterol uptake by macrophages.

THE EARLIER PREDICTIONS OF THE EFFECT OF DIETARY CHOLESTEROL ON PLASMA CHOLESTEROL WERE OVERESTIMATED.

In an attempt to explain the lower response to added cholesterol in their study than predicted by Hegsted et al,[10] Ginsberg et al[44] suggested that the difference may have been due to the relatively low total fat and SF levels in their subjects' diets. However, Kestin et al[46] found no differences in plasma total or LDL cholesterol levels when ~520 mg/day of cholesterol was added to a high fat, high SF diet (40% and 15% of energy, respectively) or a moderate fat diet (35% and 12.5% of energy, respectively). In fact, the study by Ginsberg et al[44] was consistent with McNamara's conclusion,[47] based on a review of more than 100 studies, that there was an ~0.050 mmol/L change in plasma cholesterol for each

100 mg/day change in dietary cholesterol. Furthermore, McNamara[47] suggested that the polyunsaturated-to-saturated fatty acid (P:S) ratio of the diet did not affect the response to dietary cholesterol. On the other hand, Lichtenstein et al[48] found that adding ~300 mg/day of cholesterol to the diet resulted in significantly higher plasma total and LDL cholesterol levels on both a low fat–corn oil diet and a low fat–beef tallow diet. In addition, adding cholesterol to the diet eliminated the lower total and LDL cholesterol levels on the low fat–beef tallow diet compared with the baseline diet (30% and 35% of energy from fat, respectively).

THE RECOMMENDATION TO LIMIT CHOLESTEROL INTAKE MAY NOT BE APPROPRIATE FOR THE GENERAL POPULATION.

Ginsberg et al[44] observed a wide range in the response of individual subjects to dietary cholesterol. Three subjects actually had a decrease in plasma total and LDL cholesterol levels in response to added dietary cholesterol, whereas the responses of several subjects (regrettably the authors did not give the actual number) were more than twice the group average. Wide variations among individuals in response to dietary cholesterol also have been reported by other investigators.[49–51] Mistry et al,[49] for example, found that 1500 mg/day added dietary cholesterol resulted in a mean increase in plasma cholesterol level of 0.74 mmol/L, but that individual responses varied from a decrease of 0.15 mmol/L to an increase of 1.92 mmol/L. Furthermore, Katan et al[52] found that they could separate subjects into hypo- and hyper-responders to dietary cholesterol. The individuals who responded most to dietary cholesterol also responded to dietary SF; the correlation coefficient for individual responses to dietary cholesterol was 0.62. On the other hand, other researchers[41,46] did not find a relationship between the response to dietary cholesterol and SF.

Although not a direct study of the effect of dietary cholesterol on CVD, analysis of the data from the Health Professionals Follow-Up Study and the Nurses' Health Study[53] support the general premise that dietary cholesterol has little effect on CVD risk. As with other studies by the Harvard group, egg consumption was determined by a food frequency questionnaire. After adjusting for smoking and other covariates, the relative risk factors for egg consumption and CVD did not differ for egg intakes varying from <1 egg/week to ≥1 egg/day. Similarly, the adjusted relative risk did not differ for stroke incidence and egg consumption. Nor was there any evidence of increased risk of either CVD or stroke with either recent or long-term egg consumption.

SUMMARY

Appreciable clarity has been added over the past decade to the relationship between dietary fat and cholesterol and risk factors for CVD. There is general agreement that SF, in particular the fatty acids lauric, myristic and palmitic, increase plasma total and LDL cholesterol concentrations. There is also mounting evidence that TFA have adverse effects on risk factors for CVD. Not only do TFA raise plasma LDL cholesterol levels but they result in a concomitant decrease in plasma HDL cholesterol levels. Hence, there is ample evidence to recommend that consumers limit the intake of SF and TFA. By contrast, scientific reports of the past decade indicate that a reduction in total dietary fat by the substitution of CHO for fat may not be a prudent recommendation. High CHO diets have been found to increase plasma triglyceride levels and decrease plasma HDL cholesterol levels. Substitution of MUFA or PUFA for SF in the diet would appear to be a more effective way of lowering CVD risk than reducing total dietary fat *per se*. Evidence also has accumulated to suggest that the recommendation to limit cholesterol intake may not be appropriate for the general population. Although dietary cholesterol has been found to result in an overall increase in plasma total and LDL cholesterol levels, the magnitude of the increase for each additional 100 mg/day of dietary cholesterol is relative small. On the other hand, the marked variation in response to dietary cholesterol suggests that it would be prudent for individuals with elevated total or LDL cholesterol levels to restrict cholesterol intake.

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