Effects of dietary fatty acids on lipoproteins and cardiovascular disease risk: summary

Ernst J Schaefer

ABSTRACT  Cardiovascular disease is the leading cause of death and disability in the United States and other countries. To reduce the risk of cardiovascular disease, dietary saturated fat and cholesterol should be reduced. This section of the workshop included a discussion of pragmatic issues associated with translating complex scientific information on the fat and fatty acid content of foods for the public; an overview of and a theoretical framework for cholesterol and lipoprotein metabolism; information on the role of cholesterol in the control of low-density-lipoprotein cholesterol (from animal studies); epidemiologic studies on the association between dietary fat and fatty acids and lipids and lipoproteins; the appropriate experimental design for fatty acid studies; and clinical studies evaluating the effects of individual fatty acids on plasma lipids and lipoproteins. The evidence to date indicates that the individual fatty acids elicit distinctly different physiologic effects. There is still much to be learned about the effects of individual fatty acids on lipids and lipoproteins, their metabolic fate, and the responsible biological mechanisms. Am J Clin Nutr 1997;65(suppl):1655S–6S.

KEY WORDS  Cardiovascular disease, lipids, lipoproteins, fatty acids, cholesterol, metabolism

There is consensus that dietary saturated fat and cholesterol should be reduced in the diet of the general population to decrease the risk of cardiovascular disease (CVD) (1–3). CVD remains the leading cause of death and disability in the United States, as well as in many other developed countries. A diet high in saturated fat and cholesterol and a sedentary lifestyle predispose one to the development of risk factors associated with premature CVD. The National Cholesterol Education Program and other health agencies have recommended that total fat, saturated fat, and cholesterol be decreased to ≤ 30% of energy, < 10% of energy, and < 300 mg/d, respectively (Step 1 diet) to reduce heart disease risk in the general population (1). These recommendations are based on an impressive number of studies that have examined primarily the cholesterolemic effects of fatty acid classes. However, not all fatty acids within the same class behave the same physiologically. Thus, the purpose of this supplement is to discuss the different effects of individual dietary fatty acids on CVD risk factors.

The pragmatic issues associated with translating complex scientific information for the public on the fat and fatty acid content of foods were discussed by Edward Scarborough of the Food and Drug Administration (FDA). Currently, fatty acids are defined only chemically for nutrition labeling. Nutrition labels are present on all packaged foods and provide the consumer with information about the total fat and saturated fat content per serving. Additional information about the polyunsaturated and monounsaturated fat content and the stearic acid (18:0) content is voluntary. To go beyond a chemical definition for fatty acids to definitions based on potential physiologic effects, the overall effects of the specific fatty acids need to be considered, not just the effects on CVD risk factors, such as low-density-lipoprotein (LDL) cholesterol.

Although highly controlled feeding studies with individual fatty acids are useful, there is also a need for information about the use of specific fats in the marketplace. The FDA recognizes that food labeling by necessity will lag behind science and technology as the agency awaits consensus on various issues so that it can provide the most complete dietary advice to consumers in a manner that is easy to understand.

As a first step in understanding the potential effects of individual fatty acids on cardiovascular disease risk, John Dietschy provided an overview of cholesterol and lipoprotein metabolism and a theoretical framework. He emphasized that liver is the site of very-low-density lipoprotein biosynthesis and LDL production and removal. In humans and animals the hepatic LDL receptor regulates LDL concentrations in the plasma. Although LDL-receptor-independent clearance mechanisms are fairly constant, clearance of LDL mediated by the hepatic LDL receptor is regulated and can be variable. In humans, ~60% of LDL is cleared via the LDL receptor whereas 40% is cleared by non-LDL-receptor-mediated pathways.

With regard to the role of cholesterol in the control of LDL cholesterol, animal studies indicate that ~80% of cholesterol synthesis in the body occurs in extrahepatic tissues, with the remainder occurring in liver. Animals that have a lower rate of cholesterol synthesis in liver are more responsive to dietary cholesterol than are animals that have much higher rates. These differences appear to account for species differences between experimental animal models that are insensitive to dietary cholesterol (eg, rats) and those that are sensitive (eg, hamsters). Dietary cholesterol has been reported to increase liver cholesterol, resulting in down-regulation of LDL receptor mRNA concentrations. The evidence summarized by both John Dietschy and Robert Nicolosi indicates that the dietary satu-

1 From the Lipid Metabolism Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston.
2 Address reprint requests to EJ Schaefer, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, 711 Washington Street, Boston, MA 02111.
rated fatty acids lauric (12:0), myristic (14:0), and palmitic (16:0) acids raise total and LDL cholesterol by decreasing LDL-receptor-mediated clearance as the result of a reduction in LDL receptor activity whereas the unsaturated fatty acids [eg, oleic acid (9c-18:1)] act oppositely. However, 18:0 and elaic acid (9t-18:1) in the hamster model do not alter this system and appear to have a neutral effect. Liver cell cholesterol ester content is inversely related to LDL receptor activity. The effect of dietary saturated and unsaturated fatty acids on the ratio of hepatic free cholesterol and cholesterol esters appears to be a primary mechanism for the regulation of plasma LDL cholesterol.

Epidemiologic studies have played a large role in shaping consensus on the association between dietary fat and blood lipids and lipoproteins. The review by Arlene Caggiula and Vikkie Mustad pointed out that epidemiologic studies have been limited largely to total fat and fatty acid classes. Most notably, there is a consistent relation between saturated fat intake and serum total cholesterol concentrations whereas the relations for mono- and polyunsaturated fatty acids are less consistent. Epidemiologic data available on the effect of individual fatty acids and blood lipids are limited mainly because of methodologic issues associated with obtaining accurate dietary intake data. Although associations between saturated fat and plasma cholesterol have been shown to be significant and positive, the correlations and regression coefficients are generally low and reflect the large variability associated with assessing nutrient intake as well as the historical use of only single-point measures of plasma cholesterol.

Both human and animal studies are important in advancing our knowledge of the effects of individual fatty acids on plasma lipids and lipoproteins and the underlying mechanisms of action. The human studies are essential because they provide the definitive clinical outcome about how fatty acids affect plasma lipids and lipoproteins. Animal studies, likewise, are invaluable because many mechanistic experiments can be conducted that otherwise could not be done in humans. Thus, human and animal studies complement each other in providing a comprehensive understanding of the biological mechanisms by which individual fatty acids exert their diverse effects.

As for all scientific investigations, the appropriate experimental design is crucial for fatty acid studies. John Dietschy and Penny Kris-Etherton described key design considerations for animal and human studies, many of which are common to both. Important design criteria include having an appropriate control group and an adequate number of subjects or animals as well as ensuring that the study is of sufficient duration for evaluating the endpoint of interest. Due consideration must be given to the animal model selected or the human population evaluated. The animal model should provide data that can be extrapolated to humans. With human populations, sex, age, race, and health status need to be considered.

Having an appropriate experimental diet is necessary for ensuring the validity and usefulness of the collected data. The diet design issues for human and animal studies are similar. All experimental diets must be well defined and of known nutrient composition and must meet the target nutrient specifications throughout the study. Although the ideal diet design would change just the fatty acid of interest, in practice when one fatty acid is manipulated, this is done at the expense of either adding the fatty acid of interest to a base diet (and thus increasing the total fat content of the diet but maintaining the absolute level of the other fatty acids) or substituting the fatty acid of interest for another fatty acid in the diet (eg, for one that has a neutral effect on the endpoint of interest). Other key diet design issues include adding sufficient dietary cholesterol for a fatty acid effect to be observed, feeding all foods with use of metabolic-ward conditions and procedures, and ensuring that energy balance is maintained throughout the study. If a "designer" fat is required for a study, it must be verified that the digestion and absorption of this fat are indistinguishable from other fats in the diet. In some instances, as William Harris noted for n-3 fatty acids, supplements can be a suitable alternative to a controlled feeding study.

There is consensus in the scientific community that dietary saturated fat and cholesterol raise LDL cholesterol and contribute to excess cardiovascular disease risk. Therefore, professional and government groups have recommended for the general population that saturated fat be restricted to <10% of energy and cholesterol be restricted to <300 mg/d (1-3). There is consensus that dietary fatty acids affect LDL-cholesterol concentrations by mediating its clearance and causing up- or down-regulation of LDL receptor activity. Excess saturated fat in the diet results in decreased LDL receptor activity.

There is also consensus in the scientific community that dietary saturated fatty acids raise LDL cholesterol compared with polyunsaturated fatty acids by decreasing LDL-receptor-mediated clearance caused by decreased LDL receptor activity, which is in part due to decreased amounts of mRNA for the LDL receptor. With regard to saturated fats, there is consensus that 12:0, 14:0, and 16:0 all raise LDL cholesterol relative to carbohydrate. In contrast, there is strong evidence that 18:0 is neutral or actually lowers LDL cholesterol slightly relative to carbohydrate. This is also true for 9c-18:1. Linoleic acid (18:2n-6) lowers LDL cholesterol. Therefore, 18:0 should not be grouped with other saturated fatty acids with regard to LDL effects. Emerging evidence suggests that 9t-18:1 has effects between those of saturated and unsaturated fatty acids. However, future studies are needed to resolve this point. There is also consensus that eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (20:6n-3), when given as fish oil in fish oil capsules, lower triacylglycerol relative to placebo and have little effect on other lipoproteins. There are too few data about α-linolenic acid (18:3n-3) for conclusions to be drawn about its effect on LDL-cholesterol concentrations.

Despite the above information, there is still much to be learned about the effects of each individual fatty acid on lipids and lipoproteins, their metabolic fate, and the biological mechanisms responsible for their diverse effects. This theme occurs repeatedly throughout the papers in this supplement and points to the need for further scientific inquiry in this field.

REFERENCES