Omega-6 polyunsaturated fatty acids and coronary heart disease1–3

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Most polyunsaturated fatty acids in the diet are of the omega-6 (n–6) type. These lower serum LDL cholesterol and, in clinical trials, the risk of heart disease. In this issue of the Journal, Jakobsen et al (1) illustrate the relation between fatty acids and heart disease from the observational side. They pooled data on diet and the incidence of heart disease in 340,000 people from the United States, Scandinavia, and Israel. The non-US cohorts made up 17% of subjects but 40% of the coronary events. The reason is probably that the Scandinavians and Israelis were mostly men, whereas 80% of the Americans were women.

Jakobsen et al’s (1) article focuses on the effects of replacing one macronutrient by another. Macronutrients present an issue not seen with vitamins, minerals, or drugs. Vitamins or drugs travel to a particular target in the body, exert their action, and are excreted. The fatty acids, sugars, and amino acids produced from macronutrients likewise affect target tissues but also provide calories. Adding a macronutrient to an existing diet will increase body weight, which will distort the effect on heart disease risk. Therefore, scientists study what happens when one kind of macronutrient isocalorically replaces another type. It is a matter of semantics whether the effect of such a replacement is ascribed to the macronutrient coming in or going out.

The Jakobsen et al (1) study is phrased in terms of such replacements. It shows that subjects with a low intake of saturated fatty acids and a concomitantly higher intake of carbohydrate suffered the same rate of coronary heart disease over the following 10 y as subjects who ate more saturated fatty acids and less carbohydrate. This agrees with the effect of replacing saturated fatty acids by carbohydrates on blood lipids: LDL and HDL cholesterol both fall, and the serum total-to-HDL cholesterol ratio remains unchanged (2). High-carbohydrate, low-fat diets also show little benefit for weight loss. The Jakobsen et al study therefore adds to growing doubts about whether such diets prevent heart disease.

Remarkably, subjects with a high intake of monounsaturated fatty acids (oleic acid) experienced significantly more coronary events than did those with a high intake of saturated fatty acids. Before we discard our olive oil bottles, we need to recognize that the major sources of monounsaturated fatty acids in the United States and Scandinavia were dairy, meat, and partially hydrogenated oils. A high intake of fat from these foods typifies an unhealthy lifestyle. Correction for confounders such as smoking, body mass index, and activity cuts the excess risk associated with high monounsaturated fatty acid intake in half, and therefore monounsaturated fatty acids may have acted as a surrogate for other risk factors. In countries in which olive oil is the main source, a high monounsaturated fatty acid intake is associated with lower rates of coronary heart disease.

Nonetheless, these data raise some concern about the advice to eat a Mediterranean diet. The low rate of coronary heart disease in Crete 50 y ago, when olive oil was a staple food, is suggestive, but such population comparisons do not constitute evidence-based medicine. The only experimental evidence we have on monounsaturated fatty acids comes from studies of blood lipids and other biomarkers. There are no clinical trials of monounsaturated fatty acids. In animal experiments, monkeys experienced as much atherosclerosis on diets rich in monounsaturated fatty acids as when consuming diets rich in saturated fatty acids (3). Extrapolations of such studies to humans are problematic, but it does stress that the scientific basis for monounsaturated fatty acids is incomplete.

Jakobsen et al (1) found that a low intake of saturated fatty acids and a proportionally higher intake of omega-6 polyunsaturated fatty acids was associated with a significant reduction of coronary heart disease. Confounding was again a problem: diets low in saturated fatty acids and high in polyunsaturated fatty acids are rich in vegetable oils, polyunsaturated margarines, lean meats, and low-fat dairy. That is what health-conscious people eat. Indeed, correction for smoking, body mass index, and other risk factors diminished the effect from a risk reduction by 31% to a risk reduction by only 13%, if 5% of energy from saturated fatty acids was replaced by that from polyunsaturated fatty acids. Is this 13% due to residual confounding by imperfectly measured aspects of a healthy lifestyle, or is it real?

Other types of research help us to decide.

The first type consists of metabolic trials of diet and blood lipids. These show that replacing 5% of energy from saturated fatty acids with polyunsaturated fatty acids reduces the serum total-to-HDL cholesterol ratio by 0.17 (2). In prospective observational studies, such a reduction in the total-to-HDL cholesterol ratio is associated with a reduction in heart disease risk of 9% (4).

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Clinical trials of polyunsaturated fatty acids and heart disease performed in the 1960s and 1970s form a second and, in my opinion, decisive source of information (5). The preliminary results of an ongoing meta-analysis of these trials (D Mozaffarian, personal communication, February 28, 2009) show a pooled relative risk of 0.84 (95% CI: 0.72, 0.97) when saturated fatty acids—mainly from dairy and meat—were replaced by polyunsaturates. This equals a 16% risk reduction. On average, these trials replaced 10% of energy from saturated fatty acids with polyunsaturated fatty acids. A 5% replacement should therefore reduce risk by 8%.

Thus, the effect of omega-6 fatty acids on blood lipids combined with prospective data on blood lipids and heart disease predicts a 9% risk reduction, the randomized clinical trials predict an 8% reduction, and the observational studies pooled by Jakobsen et al (1) predict a 13% reduction for people who eat 5% of calories as polyunsaturated instead of saturated fatty acids. Differences between these numbers may be due to chance or to short- compared with long-term effects.

The consistency between these various approaches yields confidence in the validity of their outcomes. It also refutes hypotheses that omega-6 polyunsaturated fatty acids increase heart disease risk. Such adverse effects may occur in cell culture and laboratory animals, but they apparently do not determine heart disease risk in humans.

Forty years ago, the American Heart Association recommended replacing saturated fatty acids with polyunsaturated fatty acids in the diet. It recently reaffirmed that recommendation (6). The Jakobsen et al study (1) underscores the soundness of this advice.

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REFERENCES