Diet and Cholesterol Reduction

After a comprehensive assessment of recent clinical evidence, the most current National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines call for renewed emphasis on lowering levels of serum cholesterol (1). The ATP III update recommends that physicians set a low-density lipoprotein (LDL) cholesterol goal of less than 1.8 mmol/L (<70 mg/dL) for high-risk patients, based on studies such as the Heart Protection Study (2). Although the cut-points of 3.4 mmol/L (130 mg/dL) and 4.1 mmol/L (160 mg/dL) for LDL cholesterol in moderate- and low-risk individuals remain unaltered, it may not be long before they are also lowered.

Statins have been very successful in lowering cholesterol levels, but despite this, some people prefer to try diet first. Furthermore, a small number of individuals prefer to avoid the statin-related increased risk for myalgia, and a very small number of people have a contraindication to statins (3). The study by Gardner and colleagues in this issue (4) is an important reminder that diet, in addition to drugs, can play a role in achieving cholesterol targets. Gardner and colleagues, performing a 4-week study in which the investigators provided all of the food, found that a more "plant-based" diet low in saturated fat yielded an advantage of 0.18 mmol/L (7.0 mg/dL) in LDL cholesterol reduction compared with the control diet, a more traditional low-saturated-fat diet. Put in different terms, the plant-based diet achieved an additional reduction in LDL cholesterol level of 4.7 percentage points over the 4.6% reduction in the control group. The 9.3% total reduction in LDL cholesterol from baseline in participants following the plant-based diet is large enough that we would expect it to reduce all-cause mortality if sustained over time (5).

Gardner and colleagues asked whether plant-based foods have additional cholesterol-lowering benefits that are unrelated to their more favorable fatty acid profile. To determine this, the authors enriched their test diet with considerably more vegetables and whole grains than the control diet, together with soy, oats, wheat germ, almonds, peanuts, flaxseed, and garlic, all of which independently have been shown to reduce serum cholesterol. At the same time, the authors provided equal amounts of total fat, saturated fat, and dietary cholesterol in both the test and control diets. The difference in cholesterol lowering between treatments was therefore not due to differences in fatty acid profile or dietary cholesterol intake. The greater reduction in serum LDL cholesterol level seen on the test diet was probably due to its inclusion of foods with more fiber (41 g/2000 kcal vs. 22 g/2000 kcal)—specifically viscous fiber—and a higher proportion of vegetable protein and other cholesterol-lowering components found in plant-based foods.

The dietary approach in Gardner and colleagues' study reflects current thinking on how to increase the effectiveness of therapeutic diets. For example, ATP III guidelines advocated 2 g of plant sterols per day and 15 to 25 g of viscous fiber foods (such as oats and barley) per day (6), and the American Heart Association has highlighted the possible benefits of soy protein and nuts (7). Moreover, the U.S. Food and Drug Administration has permitted health claims for heart disease risk reduction for viscous fiber (oat β-glucan and psyllium), soy protein (25 g/d in 4 servings), plant sterols (1.6 g/d), and, most recently, nuts (for example, 42 g of almonds per day) (8). Viscous fibers increase bile acid losses; soy proteins and other vegetable proteins are associated with reduced hepatic cholesterol synthesis; plant sterols block cholesterol absorption; and nuts are sources of vegetable protein, plant sterols, and monounsaturated fat. Studies of each of these components have consistently shown favorable effects on the blood lipid profile. In effect, a combination of these food ingredients is the dietary equivalent of combining cholestyramine, a statin, and ezetimibe.

The recommended ATP III quantities are substantially greater than the amounts that Gardner and colleagues provided to their study participants and may require the use of specific foods containing concentrated sources of cholesterol-lowering ingredients. Gardner and colleagues wanted to measure the effects of a diet of routinely consumed foods. However, in other studies, the investigators have provided patients with combinations of cholesterol-lowering food components (a dietary portfolio) in the amounts advocated by the ATP III. These studies achieved 30% reductions in LDL cholesterol, much larger than that seen in Gardner and colleagues' study (8). A 30% reduction, if sustained in the real world where researchers do not provide the food, would be similar to the LDL cholesterol reductions seen in the statin trials, which reduced coronary heart disease (CHD) events by 25% to 35%. Furthermore, eating high levels of cholesterol-lowering foods in combination reduced the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol and the ratio of LDL cholesterol to HDL cholesterol, unlike in Gardner and colleagues' study. Nevertheless, Gardner and colleagues' approach may have more general application because it supports adherence to a plant-based diet (9). Diets with higher levels of cholesterol-lowering foods will provide an option for those in need of greater cholesterol reductions through diet. Nevertheless, the ingredients for both dietary approaches are available at local supermarkets and health food stores.

The participants in Gardner and colleagues' study followed the study diet for only 1 month. Nevertheless, 1-year studies of plant sterols in self-selected diets and 4 months of metabolic studies of viscous fibers have shown that serum LDL cholesterol level decreases rapidly after patients start the diet and remains low as long as the diet is followed. Therefore, persons who adhere to the diet are

likely to sustain the reductions in LDL cholesterol seen in Gardner and colleagues' study.

Gardner and colleagues' study has 2 important messages. First, diets that "lump" foods rather than "split" them have a place. These diets combine several cholesterol-lowering foods in a specific diet rather than depending on a single cholesterol-lowering food. Second, the reduction in LDL cholesterol in Gardner and colleagues' study may explain why plant-based diets are associated with lower CHD risk, since the constituents of these diets are naturally occurring combinations of cholesterol-lowering dietary components. The experience of vegetarians provides an idea of the benefits of plant-based diets. Vegans who consume no animal products and therefore have relatively high intakes of plant-based foods have much lower levels of serum LDL cholesterol than people who eat a typical diet (10). Vegetarians have a reduced incidence of CHD, which contributes to overall longevity (11). After age 30 years, vegetarian Seventh-day Adventists have a life expectancy that is 5 years longer for men and 3 years longer for women than that of non-Adventist omnivores (11). The European Prospective Investigation into Cancer and Nutrition (EPIC)–Oxford study of 56 000 British men and women also showed a reduced risk for CHD in vegetarians (12). Furthermore, components of a plant-based diet, such as fruit fiber (13), nuts (11, 14), and whole grain cereals (15), have all been shown in observational studies to be associated with a reduced risk for heart disease in nonvegetarians. Vegetarian diets have resulted in angiographic improvement in established CHD (16). Although participants in Gardner and colleagues' study ate the plant-based diet for far too little time to expect an effect on cardiovascular end points, these other studies suggest that long-term increased consumption of plant-based foods leads to good outcomes. The authors of a comprehensive review of plant-based diets, longevity, and the Seventh-day Adventist experience came to the same conclusion (11).

At a time of renewed effort to reduce serum cholesterol levels, the plant-based diet studied by Gardner and colleagues occupies an intermediate, bridging position between conventional diets low in saturated fat (which achieve a 5% reduction in LDL cholesterol level) (17) and drug therapy (which achieves a 25% to 35% reduction in LDL cholesterol level). Gardner and colleagues' study also points to the advantage of combining several plant-based dietary strategies and forms a link with diets using more concentrated sources of the plant food components (which may achieve as much as a 30% reduction in LDL cholesterol level) (8, 18, 19). Either of these dietary approaches in combination with statins could reduce the amount of drugs required to achieve therapeutic goals and thereby avoid the rare potential side effects that are more likely to occur at higher statin doses (20).

Perhaps the most obvious significance of Gardner and colleagues' paper is the injection of new enthusiasm into the dietary management of hyperlipidemia. Previous studies have focused on saturated fat reduction with only modest results in general populations. The success of diets that combine foods containing active cholesterol-lowering components may make diet relevant in the age of powerful drugs like statins. Furthermore, plant-based diets, like statins, may have benefits other than cholesterol reduction, such as effects on C-reactive protein (8) and, in the case of the high-fiber components, satiety and colonic health. The unanswered question regarding plant-based diets enriched with cholesterol-lowering components is the extent to which they reduce cardiovascular disease. The major barrier to testing this hypothesis is sustained adherence to the diet, a question that short-term studies do not answer (6).

David J.A. Jenkins, MD, PhD, DSc
Cyril W.C. Kendall, PhD
Augustine Marchie, MSc
St. Michael's Hospital and University of Toronto
Toronto, Ontario M5C 2T2, Canada

Potential Financial Conflicts of Interest: *Consultancies:* D.J.A. Jenkins (Solae, Almond Board of California); *Honoraria:* D.J.A. Jenkins (Oldways Preservation and Exchange Trust, Almond Board of California, Dried Plum Board of California), C.W.C. Kendall (Almond Board of California, Loblaw Brands Ltd., Unilever); *Stock ownership or options (other than mutual funds):* D.J.A. Jenkins (Pacific Health Laboratories, Inc.); *Grants received:* D.J.A. Jenkins and C.W.C. Kendall (Barilla, Solae, Unilever, Hain Celestial Group, Loblaw Brands Ltd., Sanitarium Co., Almond Board of California, International Tree Nut Council); *Other:* D.J.A. Jenkins (Loblaw Brands Ltd., Sanitarium Co., Herbalife International, Nutritional Fundamentals for Health, Pacific Health Laboratories, Inc., California Strawberry Commission, Metagenics).

Requests for Single Reprints: David J.A. Jenkins, MD, PhD, DSc, Clinical Nutrition and Risk Factor Modification Center, St. Michael's Hospital, 61 Queen Street East, Toronto, Ontario M5C 2T2, Canada; e-mail, cyril.kendall@utoronto.ca.

Current author addresses are available at www.annals.org.

Ann Intern Med. 2005;142:793-795.

References

1. **Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al.** Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227-39. [PMID: 15249516]

2. **Collins R, Armitage J, Parish S, Sleigh P, Peto R.** MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361:2005-16. [PMID: 12814710]

3. **Larosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al.** Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005. [PMID: 15755765]

4. **Gardner CD, Coulston A, Chatterjee L, Rigby A, Spiller G, Farquhar JW.** The effect of a plant-based diet on plasma lipids in hypercholesterolemic adults. A randomized trial. Ann Intern Med. 2005;142:725-33.

5. **Holme I.** An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence. Circulation. 1990;82:1916-24. [PMID: 2242517]

6. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment

of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285:2486-97. [PMID: 11368702]

7. **Krauss RM, Eckel RH, Howard B, Appel LJ, Daniels SR, Deckelbaum RJ, et al.** AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation. 2000;102:2284-99. [PMID: 11056107]

8. **Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, et al.** Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. JAMA. 2003;290:502-10. [PMID: 12876093]

9. **Denke MA.** Reviewing your investment strategy: where does diet fit in your personal portfolio [Editorial]. Am J Clin Nutr. 2005;81:339-40. [PMID: 15699219]

10. **Sacks FM, Donner A, Castelli WP, Gronemeyer J, Pletka P, Margolius HS, et al.** Effect of ingestion of meat on plasma cholesterol of vegetarians. JAMA. 1981;246:640-4. [PMID: 7019459]

11. **Fraser GE.** Diet, Life Expectancy, and Chronic Disease: Studies of Seventh-Day Adventists and Other Vegetarians. New York: Oxford Univ Pr; 2004:1-392.

12. **Key TJ, Appleby PN, Davey GK, Allen NE, Spencer EA, Travis RC.** Mortality in British vegetarians: review and preliminary results from EPIC-Oxford. Am J Clin Nutr. 2003;78:533S-538S. [PMID: 12936946]

13. **Pereira MA, O'Reilly E, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, et al.** Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies. Arch Intern Med. 2004;164:370-6. [PMID: 14980987]

14. **Hu FB, Stampfer MJ, Manson JE, Rimm EB, Colditz GA, Rosner BA, et al.** Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. BMJ. 1998;317:1341-5. [PMID: 9812929]

15. **Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, et al.** Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. Am J Clin Nutr. 1999;70:412-9. [PMID: 10479204]

16. **Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, et al.** Intensive lifestyle changes for reversal of coronary heart disease. JAMA. 1998;280:2001-7. [PMID: 9863851]

17. **Ramsay LE, Yeo WW, Jackson PR.** Dietary reduction of serum cholesterol concentration: time to think again. BMJ. 1991;303:953-7. [PMID: 1954418]

18. **Kendall CW, Jenkins DJ.** A dietary portfolio: maximal reduction of low-density lipoprotein cholesterol with diet. Curr Atheroscler Rep. 2004;6:492-8. [PMID: 15485596]

19. **Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, et al.** Direct comparison of a dietary portfolio of cholesterol-lowering foods with a statin in hypercholesterolemic participants. Am J Clin Nutr. 2005;81:380-7. [PMID: 15699225]

20. **Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C, et al.** ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins. Stroke. 2002;33:2337-41. [PMID: 12215610]

Current Author Addresses: Dr. Jenkins: Clinical Nutrition and Risk Factor Modification Center, St. Michael's Hospital, 61 Queen Street East, Toronto, Ontario M5C 2T2, Canada.
Dr. Kendall and Mr. Marchie: Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario M5S 3E2, Canada.