strategy already has been demonstrated, but determination of potential long-term toxicity will require more time.


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# Diet First, Then Medication for Hypercholesterolemia

James W. Anderson, MD

MANAGING DIET IS THE KEY TO TREATING ALL COMmon lipid disorders. Previous observations suggest that intensive dietary intervention can decrease serum cholesterol and low-density lipoprotein cholesterol (LDL-C) levels by approximately 30%.[1] The findings of Jenkins and colleagues[2] reported in this issue of THE JOURNAL indicate that intensive dietary therapy may be just as effective in reducing cholesterol levels as the starting dosage of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) drug.

In their preliminary investigation, Jenkins et al randomly assigned 55 healthy hyperlipidemic men and women to receive 1 of 3 treatments: a very low-saturated-fat diet based on whole-grain wheat cereals and low-fat dairy foods (control group); the same diet plus lovastatin, 20 mg/d (statin group); or a diet high in plant sterols, soy protein, viscous fibers, and almonds (dietary portfolio group). Based on data from the 46 patients who completed the 4-week study, the authors report that the statin and dietary portfolio treatment groups had approximately 30% reduction in LDL-C compared with an 8% reduction in the control group; they report roughly comparable results using an intention-to-treat analysis. These results are potentially important, given the expense, safety concerns, and intolerance related to statin use. Moreover, if confirmed in other rigorous investigations, these findings could have far-reaching implications for a large number of patients with dyslipidemia; those who are motivated to adopt prudent diets might achieve meaningful lipid reductions without pharmacotherapy.

**See also p 502.**

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Statin intolerance is a common reason patients are referred to lipid specialty clinics. Individuals with statin intolerance, who have been treated with multiple statins, often develop nonspecific musculoskeletal complaints without alterations in serum creatine kinase.[3] Clinically important myositis or rhabdomyolysis with statins is uncommon, but when it does occur, it is often dose-related, and is increased when statins are used with other agents that share common metabolic pathways or agents that are associated with musculoskeletal complaints.[4] Statin-intolerant individuals, especially those with serum LDL-C levels greater than 200 mg/dL (5.18 mmol/L), need intensive nutritional management. Other individuals, such as elderly patients who are concerned about the cost of statins or patients who are interested in nonpharmacological therapy, may be particularly receptive to intensive dietary therapy.

Intensive nutrition management requires the addition of soy protein,[5] soluble (viscous) fiber,[6] and plant sterols[7] to the low-saturated-fat, low-*trans*-fatty-acid, low-cholesterol features of the American Heart Association diets.[8] Intensive intervention with high-fiber, low-fat diets decreases serum LDL-C, but only by 16% from baseline values according to a meta-analysis of 12 controlled studies of individuals with diabetes.[9] Thus, complementary nutrition measures are required to achieve serum cholesterol and LDL-C reductions of greater than 30%. Incorporating 3 to 6 g/d of soluble fiber from oat products or psyllium may decrease serum LDL-C levels by approximately 7%.[6] Including 2 to 3 g/d of plant sterols into the regimen may reduce serum LDL-C by another 10% to 15%.[7] Psyllium and plant sterols are available in gel capsules and soluble fiber in palatable wholegrain oat cereals.

Of all the cholesterol-lowering nutrients, soy protein has the broadest range of effects on serum lipoproteins and cardiovascular risks. Soy protein significantly decreases serum cholesterol, LDL-C, and triglyceride levels; slightly increases serum high-density lipoprotein cholesterol (HDL-C) levels[5]; and may selectively decrease the amount of atherogenic small, dense LDL particles.[10] In addition to its beneficial effects on serum lipids, soy protein and its isoflavones reduce the risk of atherosclerotic disease by improving vascular reactivity, decreasing in vivo oxidation, preventing inflammation, and reducing platelet aggregation.[11] Soy protein also favorably affects coronary artery vascular reactivity in monkeys[12] and may enhance postischemic reperfusion in humans.[13] In addition, soy protein intake lowers in vivo oxidation of LDL-C[14] and serum homocysteine levels[15] and may decrease C-reactive protein levels.[2]

Although soy isoflavones may contribute to the hypocholesterolemic benefits of soy protein,[5] recent data suggest that bioactive peptides may play a more important role.[16] Soy protein is hydrolyzed in the intestine, and it appears that small peptides containing 4 to 6 amino acids are absorbed into the portal circulation.[16] These soy peptides appear to activate hepatic LDL receptors with in vitro models[17] and increase messenger RNA expression of LDL receptors in circulating human monocytes.[18] Soy protein, peptides, and isoflavones may work together to produce effects on lipid metabolism and gene expression. In animal models, soy protein hydrolysates selectively decrease visceral adipose tissue[19] and may have effects on enzymes involved in lipid metabolism,[20] including the expression of their messenger RNA.[21] In humans, soy protein intake appears to promote insulin sensitivity.[22]

The findings of Jenkins et al[2] suggest that intensive nutritional therapy that includes low intake of saturated fat, *trans*-fatty acid, and cholesterol, with emphasis on soy protein, soluble fiber, plant sterols, and almonds, may be a useful first-line intervention for select patients with dyslipidemia. However, several caveats must be considered before this diet can be recommended for widespread application. For instance, the investigation was of short duration, the sample size was small, and only hyperlipidemic participants who were otherwise healthy were included. Moreover, even though the authors note that adherence, as expressed by percentage of prescribed calories recorded as consumed during week 4, exceeded 90% in all 3 study groups, 40% of those in the dietary portfolio group who completed the study and provided comments indicated that greater food variety was required, and 27% felt that the food volume was too great. In addition, there was no discussion of adverse effects, such as gastrointestinal symptoms related to the diets. Also, because the treatment diets were prepackaged and provided to study participants, it is unclear, as the authors suggest, whether adherence or outcomes would be similar for patients who would have to assemble similar foods for themselves on a routine basis. Although the authors did not provide information on the costs of such a dietary approach, it seems possible that a plant-based diet would be less expensive than a diet focused on animal protein and including fast foods and convenience foods.

In addition to specific dietary intervention, overweight or obese individuals with hyperlipidemia should reduce their weight to reach a body mass index of 25 or less unless there are specific contraindications. Obesity poses an independent risk for cardiovascular disease.[23,24] Weight loss can significantly decrease serum LDL-C and triglyceride levels while slightly increasing serum HDL-C levels.[23,25] Energy-restricted diets that emphasize higher carbohydrate, higher fiber, and lower saturated fat and cholesterol promote weight loss and improve serum lipids. Increasing soy protein intake may further help to correct weight and lipid problems.[26] In addition, most individuals should be counseled to engage in 30 to 60 minutes of moderate physical activity daily.

Dietary management is an essential part of the treatment for lipid disorders, although adherence to strict and intensive dietary interventions requires motivation by patients,

encouragement by physicians, and, perhaps, counseling by dietitians and nutrition experts. For most patients, dietary intervention should be the first line of therapy (perhaps for 6 to 12 weeks) before introducing pharmacotherapy for hyperlipidemia.

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