

Dietary Treatment of Dyslipidemia: Overlooked and Undervalued?

BY DANA WHITHAM, MSc, RD, CDE

According to the Canadian Heart Health Survey, 36% of Canadian adults have an atherogenic lipid profile. Many, including some at low risk, are treated with medications.¹ Among patients with diabetes in Canada, 59% have dyslipidemia, as well as other co-morbid conditions.² Fortunately, dyslipidemia is a modifiable risk factor for cardiovascular disease (CVD). The atherogenic lipid profile includes increased concentrations of low-density lipoproteins (LDLs) and decreased concentrations of high-density lipoproteins (HDLs).

The mainstay of cholesterol lowering medications – the 3-hydroxy-3-methylglutaryl CoA reductase inhibitors (statins) – are some of the most frequently prescribed medications in Canada.¹ This is, no doubt, because of their efficacy in lowering cholesterol, their excellent overall safety profile, and the large body of clinical trial evidence associated with their use demonstrating reduced cardiovascular mortality in both primary and secondary prevention.^{4,5} New generation statins can lower LDL levels by >50%. In addition to their effect on lipids, statins have pleiotropic effects that likely include anti-inflammatory and anti-thrombotic properties.⁶ With all of the recent advancements in pharmacotherapy for dyslipidemia, or the “statin era” as some refer to it, the art of “lifestyle” therapy for cholesterol and cardiovascular risk reduction has been lost. The question we are left to answer is whether lifestyle changes are still relevant in the face of extremely effective cholesterol-lowering medications.

As with all medications, statins are not totally free of side effects, although true cases of myositis or rhabdomyolysis are extremely rare. Despite the fact that there are no differences in the number of complaints of myalgia between patients taking statins and placebo,⁷ (mild muscles aches *without* an elevation in creatinine kinase [CK]), statin intolerance continues to be a barrier to appropriate treatment. Combine this with occasional bad press and it is easy to highlight the importance of lifestyle treatment for dyslipidemia. Data from the Lipid Treatment Assessment Project found that 32% of individuals at low risk, 63% of individuals at moderate risk, and 83% of subjects at high risk for CVD did not achieve their lipid targets.⁸ Therefore, a gap exists that could be filled by dietary intervention.

The Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) recommends therapeutic lifestyle changes in all patients with dyslipidemia, with the addition of pharmacologic therapy based on cardiovascular risk factors and LDL levels. Diet therapy is considered the first-line approach in the treatment of individuals at *low risk* for heart disease and for many, LDL targets can be achieved with lifestyle changes alone. Individuals considered at *high risk* for heart disease (those with pre-existing CVD, diabetes, or with other multiple risk factors) are recommended to start pharmacologic treatment concurrently with lifestyle changes. In the update to the ATP III released by the NCEP in 2004, a “the lower, the better” approach to LDL reduction was suggested. In many cases, to achieve this safely, a combination of both diet and medications should be implemented.

To increase the effectiveness and acceptance of cholesterol-lowering diets, the use of functional foods is now recommended. NCEP guidelines recommend the use of a 25%-35% fat diet with <7% from saturated and *trans* fat and no more than 200 mg per day of dietary



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cholesterol. Therapeutic functional foods recommended by the NCEP include soluble fibre and plant phyto-sterols. Other functional foods such as nuts and soy protein may also be beneficial. These components, known to reduce cholesterol alone, in combination, and in concert with pharmacotherapy, are reviewed in this issue of *Endocrinology Rounds*.

Individual components

Saturated and trans fat: In a meta-analysis on the effect of decreasing total fat intake to <30% and maintaining saturated fatty acids (SFA) at <10% of total calories, LDL cholesterol was reduced by as much as 12%. Upon reducing SFA to <7% of calories, a further (4%) LDL reduction was observed.⁹ In the studies included in the analysis, the average reduction was in the 8%-10% range.

In studies assessing the impact of a combination of a low-saturated fat diet with statin treatment, a direct additive effect was demonstrated. A 5% decrease in LDL cholesterol was seen with the NCEP diet alone, a 27% decrease with statin treatment, and a 32% decrease was observed when these were combined.¹⁰

More and more Canadians are taking an active interest in their health. Nutrition label reading is a key component to healthy decision-making. Point of purchase programs, such as the "Health Check," and health claims such as "A healthy diet low in saturated and *trans* fat may help reduce the risk of heart disease," have assisted healthcare professionals in guiding patients towards making healthier choices in the marketplace.

Points to remember:

- Saturated plus *trans* fat should be limited to 7% of calories or approximately 15 grams/day for most high-risk individuals.
- Percent daily value (DV) for saturated and *trans* fat should not be greater than 20% in a serving.
- Encourage patients to reduce animal protein to 6-8 ounces daily (an amount equivalent to 2-3 decks of cards).
- Encourage consumption of 1% milk fat (M.F.) dairy products.

Soy protein: Soy protein is produced from raw whole soybeans via a process in which the indigestible components are removed. Soy protein is found in foods such as tofu, tempeh, soy milk, yogurt, and cheese. Vegetable proteins such as soy have been shown to reduce hepatic cholesterol synthesis and upregulate LDL receptors.¹¹ The substitution of vegetable protein (eg, soy) for animal protein has been shown to lower blood cholesterol levels. A meta-analysis of clinical studies on soy protein demonstrated that daily soy consumption (45 g/d) reduced LDL cholesterol by 12.9%.¹² Since 45 grams of soy is beyond what most individuals find to be an acceptable level, a study was designed to assess the amount of soy required to produce a physiologic effect. In a 6-week comparison

between 20, 30, 40, or 50 grams daily of soy protein, all levels were found to significantly decrease cholesterol.¹³ In the US, a food claim for soy protein states that a diet low in SFA with 25 grams per day of soy protein may reduce the risk of heart disease by lowering LDL cholesterol by approximately 4%.

Points to remember:

- Each soy serving contains 6.25 grams of soy protein, therefore 4 servings daily are required to achieve 25 grams.
- Try using frozen meals made with soy protein, soy milk, meat substitutes, or soy nuts as a means to increase intake.

Plant phytosterols: Phytosterols (plant sterols and stanols) are relative newcomers to the therapeutic treatment of dyslipidemia, despite initial studies conducted in the 1950s. Phytosterols function to lower LDL cholesterol by inhibiting cholesterol absorption from the intestine. Naturally-occurring plant sterols are found in vegetables, vegetable oils, nuts, and seeds. When used to create functional foods, phytosterols – if not properly solubilized – are virtually ineffective. As such, they are usually esterified with fatty acids and dissolved in a fatty medium such as margarine. Alternatively, phytosterols are available in powdered complexes or capsules and remain bioactive as long as they are combined with lecithin. In structure, plant sterols and stanols differ in a double bond in the sterol ring. In functionality, plant sterols diminish bile acid production, an effect that is not seen with plant stanols. Sterols and stanols also differ in terms of their efficacy in that, plant sterols have demonstrated decreases in LDL that are not consistently maintained in the long-term, especially in individuals with diabetes.^{14,15} Stanols, on the other hand, have demonstrated consistent and persistent LDL reductions.¹⁶ It has been hypothesized that in the case of plant sterols, an increase in cholesterol synthesis occurs in combination with a decrease in bile acid synthesis and this association is responsible for the lack of LDL lowering in the long-term. In a meta-analysis studying the effect of 2 grams of phytosterols per day on lipid profiles, a 10% reduction in LDL cholesterol was demonstrated without any significant effect on HDL cholesterol or triglyceride (TG) concentrations.¹⁷

In studies assessing the addition of phytosterols to pre-existing statin therapy, an additional reduction of between 6% and 20% has been demonstrated.¹⁴ This addition is, at the very least, equivalent to doubling the dose of the statin and since this option may be unavailable in some individuals, the use of phytosterols may help achieve targets. In a recent study assessing the compatibility of combining plant sterols and ezetimibe (which both work to block intestinal cholesterol absorption), LDL levels decreased by 5% with phytosterols alone, by 22% with ezetimibe alone, and by >25% when combined.¹⁸

Phytosterols are not absorbed in the intestine, however, combining plant sterols and statins has been shown to increase absorption. When not combined with a statin, approximately 10%-18% of plant sterols and <0.2% of plant stanols are absorbed.¹⁹ It is theorized that statins increase serum sterol levels by decreasing biliary excretion, thus resulting in increased absorption of sterols from the intestine. Individuals with familial hypercholesterolemia tend to have higher levels of serum plant sterols, indicating that they may have an enhanced ability to absorb cholesterol from the intestine. High serum plant sterol levels have been linked with the increased development of coronary heart disease.¹⁴ Health Canada's adverse reaction database contains 4 reports in which plant sterols were suspected of hematologic adverse reactions. One study assessed the safety of providing plant sterols in combination with other therapeutic changes on serum sterol levels and red cell fragility. While serum sterol levels were higher, this increase was not found to be statistically significant. There was no effect on red cell fragility with the treatment of plant sterol-enriched margarine.²⁰ The NCEP guidelines suggest that the benefits of plant sterols on LDL reduction in high risk individuals outweigh any potential risks associated with its use.

Solubilized phytosterols are not currently available in Canada. Margarines such as Benecol™ (plant stanols), Becel Pro-Activ™ and Take Control™ (plant sterols) have been available in the US and many European countries for years. These margarines are not considered "family" margarines and should not be used by children or during pregnancy or lactation. Health Canada reports that the use of the margarine may pose a health risk to certain groups, including pregnant women, children, those at risk for hemorrhagic stroke, and people on cholesterol-lowering medications.²¹ The only option currently available in Canada is phytosterol capsules found in health food stores; the majority of these capsules contain plant sterols and not stanols. Because of the lack of long-term evidence to clearly demonstrate the safety of plant sterols, when given the choice, it might be prudent to recommend plant stanols as the phytosterol of choice for individuals treated with statins.

Points to remember

- Vegetable oils, nuts and seeds are natural sources of phytosterols.
- The therapeutic dosage of phytosterols is 2-3 grams per day.
- Check for a drug identification number (DIN) on the label of plant sterols.
- When available, recommend plant stanol margarine over plant sterols.

Almonds: The benefit of almonds on cholesterol is likely an additive effect of their protein, monounsaturated fat

content, and natural plant sterols. On their own, 1-2 ounces of almonds daily reduced LDL cholesterol by approximately 5%²². The Food and Drug Administration (FDA) has granted a health claim for nuts.

Points to remember

- 1-2 ounces of almonds is equal to approximately 15-30 nuts.
- 1 ounce of almonds is the equivalent of 2 tablespoons of almond butter.
- 1 ounce of almonds contains 165 calories, therefore substitute almonds for other snack foods because of excessive calories.

Soluble/viscous fibre

It has been hypothesized that soluble fibres alter the viscosity of stomach contents, thereby "trapping" nutrients and inhibiting bile acid re-uptake.²³ It has been suggested that a minimum daily intake of 3 grams of beta glucan and 9 grams of psyllium can provide a therapeutic benefit. Other viscous fibres include pectin (found in fruits and vegetables), guar (found in beans, peas and lentils), and a highly viscous blend of konjac mannan, sodium alginate, and xanthan gum called "PGX" (Table 1). In a meta-analysis of 67 trials, soluble fibre was shown to significantly decrease both total cholesterol (TC) and LDL cholesterol. In this study, common soluble fibres (eg, oats, psyllium, pectin and guar gum), led to an average LDL reduction of 5%.²⁴ A fibre must be viscous in order to effect cholesterol lowering; nonviscous fibres such as wheat bran have little effect. In a crossover study in subjects with insulin resistance, standard diets were supplemented with either 8-13 grams daily of wheat bran or glucomannan (isolated from konjac mannan). After just 8 weeks of treatment, LDL cholesterol was reduced by 22% after treatment with glucomannan.²⁵

Insoluble fibre, while having no therapeutic effect on cholesterol, has been implicated in the prevention of CVD. Substantial evidence exists to substantiate the claim that a diet high in cereal fibres and whole grains helps reduce the risk of heart disease. Cross-sectional epidemiological studies reveal an inverse association between fibre intake and CVD.²⁶ Prospective population studies (eg, the Nurses Health Study) found that the highest quintile of cereal fibre intake (7.74 g/d) resulted in a 34% decrease in the risk of CVD compared to the lowest quintile (2.2 g/d).²⁷ Despite this substantial benefit, the intake of whole grains in the United States is <1 serving per day.²⁸ Whole grains have demonstrated improvements in key risk factors for heart disease, such as diabetes and obesity. In summary, while soluble fibre has a small, but significant effect, on lowering cholesterol, insoluble fibre (eg, whole grains and cereals) may provide substantial benefits on rates of CVD and should not be overlooked.

Food	Serving	Soluble fibre (g)	Insoluble fibre (g)	Total (g)
Bran buds with psyllium™	1/3 cup	3.0	9.7	12.7
Orange	1 medium	1.9	1.4	3.3
Pear (with skin)	1 large	1.9	4.7	6.6
Sweet potato (flesh)	1/2 cup	1.8	2.2	4.0
Kidney beans	1/2 cup	1.7	7.4	9.1
Green beans	1 cup	1.7	3.7	5.4
Oatmeal (cooked)	1 cup	1.0	2.9	3.9
Okra	1/2 cup	1.0	3.1	4.1
Barley (cooked)	1/2 cup	0.8	2.2	3.0
Rye bread	2 slices	0.7	1.1	1.8

Points to remember

- Daily intake of 25-35 grams of total fibre should be encouraged
- Daily intake of 5-10 grams of soluble fibre should be encouraged
- Oats, oat bran, oat-based or All Bran Buds™ with psyllium cereal are recommended for breakfast.
- “Whole wheat” does not mean “whole grain.” Look for breads made with whole grain flour.
- Encourage 5-10 servings per day of fruits and vegetables.

Combination diets

Portfolio diet: Individually, plant sterols, almonds, soy protein, and fibre reduce LDL cholesterol in the range of 5%-15%. With a low-saturated fat diet (<7% of calories), it is estimated that the additional individual components would achieve only a 5% reduction.²⁹ To test the effect of these components in combination, a metabolically-controlled portfolio of foods was provided to subjects. All were instructed to follow a 7% saturated fat diet with <200 mg of cholesterol in accordance with the NCEP guidelines. In addition, approximately 2 grams of plant sterols in the form of a supplemented margarine, 10-20 grams of viscous fibre, 50 grams of soy protein, and 2 ounces of almonds were provided daily. The diet was strictly vegetarian and did not allow milk products, eggs, or animal protein of any kind. In the original portfolio study, LDL was decreased by 29.6%, on par with a first-generation statin.²⁹

In a subsequent study that assessed whether the combination of the above-mentioned therapeutic foods could have an additive effect in an ad lib situation, 66 hyperlipidemic subjects were studied for a period of 1 year. Approximately one-third of the

participants had a decrease in LDL cholesterol of >20%, a reduction associated with a 25%-35% decrease in cardiac death.³⁰ The mean LDL reduction in this self-selected study was 13%, significantly less than the original study. The authors concluded that since the majority of the participants were already meeting the fat and cholesterol targets set out by the NCEP, any reduction would ultimately be an indication of the combined effect of the soy, almonds, sterols, and fibre.

In a further publication from these authors, both the portfolio diet and treatment with a statin reduced C-reactive protein (CRP) levels from baseline after only 4 weeks of treatment. In this case, the diet outperformed the statin, with a reduction of 23.8% versus 16.3%, respectively.³¹ Although impressive, this difference was not statistically significant.

These studies demonstrate that in motivated individuals, a diet portfolio of therapeutic foods is on a par with first-generation statins, not only in terms of their cholesterol-lowering abilities, but also for their anti-inflammatory effects.

Mediterranean diets (including n-3 fatty acids): Cardiac outcomes were improved within 2-3 years of following a diet low in saturated fat, high in fibre, and increased n-3 fatty acids from either fish or plant sources.^{32,33} In the Lyon Diet Heart Study (LDHS), an n-3 enriched Mediterranean diet was shown to reduce all-cause mortality in 600 secondary prevention subjects. In particular, sudden death from a cardiac event was reduced by 65% over a 4-year period.³³ This drastic effect on CVD risk was demonstrated regardless of any effect on traditional risk factors for heart disease (eg, high cholesterol or blood pressure). People on the Mediterranean diet consumed less total fat, saturates, linoleic acid, and had a 3-fold increase in n-3 fatty acid alpha linolenic acid (ALA).

Singh et al adopted the Lyon Diet protocol to study an IndoMediterranean diet in 100 patients with established CVD. A diet rich in whole grains, legumes, walnuts, fruit, vegetables, mustard, and soy oil provided 4.1 g of ALA daily compared to the control diet (NCEP), which contained only 1.9 grams per day. The atherogenic lipid profile was favourably altered by the diet; LDL significantly decreased and HDL increased. The IndoMediterranean diet was also associated with a significant reduction (50%) in both fatal and nonfatal MI and a reduction in sudden death.³⁴

While it appears there may be multiple benefits from statins, the principle cause for the reduction in mortality associated with their use is likely through a direct effect on cholesterol reduction. In contrast,

the beneficial effect of a healthy whole diet approach on cardiovascular mortality is independent of any lipid changes. One study assessed the effect of a Mediterranean type of diet combined with simvastatin over 12 weeks.³⁵ After 12 weeks on the Mediterranean diet, LDL decreased by 11%, compared to 30% with simvastatin and 41% when the 2 treatments were combined.

These studies again demonstrate the independent and additive effect of lifestyle changes in combination with pharmacotherapy.

Points to remember:

- More information and sample portfolio menus can be found at www.portfolioeatingplan.com.
- Encourage fatty fish consumption (salmon, trout, herring, mackerel, sardines) twice a week.
- Ensure that all omega 3 supplements come from a reputable source and contain a drug identification number (DIN).
- An increase in ALA consumption to a goal of 2 grams per day should be encouraged. Many products contain additional *n*-3 fatty acids, such as milk, yogurt, and eggs.

Conclusions

Diet intervention for the treatment of dyslipidemia is effective alone, and in combination, with statin therapy. While the additional reduction may seem small or insignificant, there are many instances when diet therapy can help achieve lipid targets, eg, when targets cannot be achieved with statin treatment alone, when there are intolerable statin side effects, when certain patients prefer to avoid medications if possible, and when patients find pharmacologic treatment too costly. It seems reasonable to broaden our approach to cardiac health and remember that the effects of a healthy diet go beyond any therapeutic changes to cholesterol. The time has come to reassert the importance of healthy eating for managing not only lipids, but overall heart health.

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Abstract of Interest

Effect of statins on noncholesterol sterol levels: implications for use of plant stanols and sterols.

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Normal serum contains small amounts of noncholesterol sterols, including those reflecting cholesterol absorption and those that are markers of cholesterol synthesis. Absorption marker sterols include serum plant sterols, whereas cholesterol precursor sterols correlate with whole-body synthesis of cholesterol. Thus, serum noncholesterol sterols, and especially their ratios to cholesterol, can be used to evaluate the major features of cholesterol metabolism (ie, synthesis and absorption). Statin treatment reduces serum cholesterol precursors but increases serum plant sterols severalfold, especially in subjects with high-absorption marker sterol levels indicative of efficient cholesterol and sterol absorption in general. Statin therapy is most effective in subjects with high serum cholesterol precursor levels. In subjects with high-absorption sterol markers, dietary cholesterol absorption inhibition (eg, with plant stanol and sterol ester margarine) needs to be combined with a statin to achieve effective

serum cholesterol reduction. However, whereas dietary plant stanol esters reduce statin-induced elevations of serum plant sterol levels, serum plant sterol levels remain elevated during dietary plant sterol ester consumption. The clinical implication of high serum plant sterol levels is under active investigation. *Am J Cardiol* 2005;96(1A):40D-46D

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