Effect of Combining Psyllium Fiber With Simvastatin in Lowering Cholesterol

Abel E. Moreyra, MD; Alan C. Wilson, PhD; Ashraf Koraym, MD

Background: Soluble fiber supplements are recommended to reduce levels of low-density lipoprotein cholesterol (LDL-C). We evaluated the LDL-C-lowering effect of psyllium husk added to low-dose simvastatin therapy.

Methods: In a 12-week blinded placebo-controlled study, patients were randomized to receive 20 mg of simvastatin plus placebo, 10 mg of simvastatin plus placebo, or 10 mg of simvastatin plus 15 g of psyllium (Metamucil) daily. Levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglycerides, and apolipoprotein B were determined after 4 and 8 weeks of treatment.

Results: The study group comprised 68 patients. All treatments were well tolerated, and after 8 weeks the mean LDL-C levels in the group receiving 10 mg of simvastatin plus placebo fell by 55 mg/dL (1.42 mmol/L) from baseline, compared with 63 mg/dL (1.63 mmol/L) in the group receiving 10 mg of simvastatin plus psyllium (P = .03). The mean lowering of LDL-C in the group receiving 20 mg of simvastatin plus placebo was the same as that in the group receiving 10 mg of simvastatin plus psyllium. Similar results were seen for apolipoprotein B and total cholesterol. No significant changes from baseline triglyceride or high-density lipoprotein cholesterol levels occurred.

Conclusions: Dietary psyllium supplementation in patients taking 10 mg of simvastatin is as effective in lowering cholesterol as 20 mg of simvastatin alone. Psyllium soluble fiber should be considered as a safe and well-tolerated dietary supplement option to enhance LDL-C and apolipoprotein B lowering.

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It is now well established that individuals with elevated low-density lipoprotein cholesterol (LDL-C) levels are at increased risk for coronary heart disease. Early clinical trials for primary and secondary prevention of coronary artery disease demonstrated that lowering LDL-C levels with 3-hydroxy-3-methylglutaryl coenzyme A reductase enzyme inhibitors (statins) is effective in reducing morbidity and mortality among patients with elevated cholesterol. Statins are now widely used in combination with dietary intervention in the treatment of hyperlipidemia, and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) has recently issued an update based on the evidence of more recent statin trials that emphasizes the integral importance of therapeutic lifestyle changes. The NCEP ATP III guidelines recommend increased viscous (soluble) fiber (10-25 g/d) as a therapeutic option to enhance LDL-C lowering.

The cholesterol-lowering effect of the soluble fiber in psyllium husk has been evaluated in several studies and was found to lower serum cholesterol levels reproducibly. Two meta-analyses covering published and unpublished investigations report an overall 7% lowering of LDL-C and an absolute lowering of LDL-C by 1.12 mg/dL (0.03 mmol/L) per gram of psyllium soluble fiber. Long-term treatment with 10.2 g/d of psyllium for 26 weeks resulted in a reduction of serum total cholesterol by 4.7%, LDL-C by 6.7%, and the ratio of LDL-C to high-density lipoprotein cholesterol (HDL-C) by 3.3%. Although the exact mechanism of action of psyllium in lowering cholesterol is not fully understood, it has been suggested that the hypocholesterolemic effect may be mainly due to inhibition of bile acid reabsorption. In support of this, psyllium combined with half the usual dose of colestipol hydrochloride (a bile acid sequestrant resin) was reported to be as effective as using the full dose of colestipol. The method of administration of psyllium soluble fiber can also affect its ability to lower serum cholesterol; the maximum effect is seen when it is mixed with foods.

To our knowledge, there have been no controlled studies of the use of psyllium in...
combination with a statin. To evaluate the additional cholesterol-lowering effect of psyllium when added to simvastatin, we designed a study among patients with hyperlipidemia, comparing the effect of a low dose of simvastatin (10 mg) supplemented with psyllium (5 g three times daily with meals) with that of simvastatin (10 or 20 mg) with placebo powder in lowering serum cholesterol levels.

### METHODS

#### PATIENTS

The study group comprised men (n = 40) and women (n = 28) aged 18 to 80 years, who met the NCEP ATP III criteria for drug treatment of hyperlipidemia and dietary intervention. All patients gave informed consent, and the Robert Wood Johnson Medical School Institutional Review Board approved the study. Patients were excluded if they had a body mass index (calculated as weight in kilograms divided by the square of height in meters) greater than 32, triglyceride levels greater than 400 mg/dL (>4.5 mmol/L), elevated liver enzymes aspartate aminotransferase or alanine aminotransferase greater than 1.5 times the upper limit of normal, allergy to psyllium or known hypersensitivity to statins, or weight change within 5% of the baseline weight before randomization. Women with childbearing potential who were not using a birth control method and pregnant or lactating women were excluded. Patients taking medications that affect lipid levels, including corticosteroids, thiazides, β-blockers, estrogens, and progesterones, at doses that could not be stably maintained for the duration of the study were excluded. Patients using the calcium channel blocker verapamil hydrochloride and immunosuppressive drug therapy were excluded. Other exclusions were active biliary disease, multiple lipid-lowering medications, myocardial infarction, coronary angioplasty, coronary artery bypass grafts, severe or unstable angina pectoris within 3 months before screening, uncontrolled hypertension, secondary causes of hyperlipidemia, type I or uncontrolled type II diabetes mellitus, unreliability as a study participant based on the investigator’s prior knowledge of the subject, and any significant factor that compromised the patient’s safety or compliance. Seventy-two patients were randomized to treatment, and 68 completed the study. One patient was excluded because of protocol violation, and 3 patients withdrew consent.

#### STUDY DESIGN

This randomized, double-blind, placebo-controlled, 3-arm parallel study consisted of a 4-week diet stabilization period that included a 2-week baseline evaluation phase, followed by an 8-week treatment period. During the initial period, patients were instructed in the NCEP Step 1 diet by a registered dietician and were told to discontinue therapy if they were taking lipid-lowering medication. At the start of the treatment period, patients were randomly assigned to receive one of the following treatments: (1) simvastatin (20 mg) plus placebo, (2) low-dose simvastatin (10 mg) plus placebo, or (3) low-dose simvastatin (10 mg) plus psyllium soluble fiber. Lipid and lipoprotein levels were evaluated 4 times during the baseline screening period, and the values at the week –1 visit and the randomization visit were used as the baseline. Patients returned to the clinic for evaluation at 4 and 8 weeks after randomization.

#### TREATMENT

Simvastatin (Zocor; Merck & Co, Inc, Whitehouse Station, NJ) was provided to the patients as single 10-mg or 20-mg tablets in foil packets, and they were instructed to take 1 tablet daily in the evening. The psyllium soluble fiber was supplied as 18 g of smooth-texture orange-flavored Metamucil (The Procter & Gamble Company) containing 5.1 g of psyllium husk and 3.6 g of soluble fiber; other ingredients included sucrose, citric acid, natural and artificial orange flavor, and coloring agents. The placebo powder was 18 g of Tang (Kraft Foods North America, Inc, Rye Brook, NY) containing no dietary fiber; other ingredients included sucrose, fructose, citric acid, orange juice solids, natural and artificial flavor, and color. Both powders were provided as single doses in individual opaque plastic packets with instructions to mix the powder with at least 8 oz (0.2 L) of liquid and consume 3 times daily with meals. Patients were advised to take other prescription medicine at least 2 hours before or 2 hours after taking the powders. Compliance with diet and medications was monitored throughout the study; unused study medication was collected, and the numbers of tablets and psyllium or placebo packets returned were recorded.

#### CLINICAL AND LABORATORY MEASUREMENTS

At the initial screening visit and the final visit of the study, each patient underwent routine physical examination and liver function tests, including aspartate transaminase and alanine transaminase. At the screening visit, a general medical history was obtained, the subject’s height and weight were measured, and blood samples were collected for clinical chemistry and fasting lipid profile. The lipid profile included total cholesterol, HDL-C, LDL-C, triglycerides, and apolipoproteins B and A-I (Apo B and Apo A-I). At other visits, only fasting lipid profiles were determined. Scheduled visits were at screening and at weeks –4, –1, 0 (randomization), 4, and 8. At each visit, a clinic nurse recorded weight, blood pressure, pulse rate, adverse events, and concomitant medications. Dietary data were collected by the registered dietician at baseline and during the study to monitor compliance with the NCEP Step 1 diet. Compliance with statin use was 91%; Metamucil and placebo compliance was 93% and 81%, respectively.

Serum lipid and lipoprotein levels were determined at the Robert Wood Johnson Medical School Lipid Metabolism Laboratory, which has been certified by the Centers for Disease Control and Prevention Lipid Standardization Program. Total serum cholesterol, HDL-C, and triglyceride levels were measured enzymatically using the Cholestech LDX System (Cholestech Corporation, Hayward, Calif). Serum LDL-C levels were calculated using the Friedewald equation. The Apo B and Apo A-I levels were measured immunochemically using a Behring BN 100 nphelometer (Dade Behring Inc, Newark, Del).

#### STATISTICAL ANALYSIS

Differences in baseline demographic and clinical characteristics among the treatment groups were compared using analysis of variance for continuous variables and the χ² test for categorical variables. The efficacy evaluation was based on measurement and comparison of the mean levels of lipids and lipoproteins among treatment groups using generalized estimating equation methods to adjust for repeated measures within patients (baseline was included in the model). The GENMOD procedure of SAS version 8 (SAS Institute Inc, Cary, NC) was used to perform the analyses. In addition, an analysis of covariance model adjusting to baseline was done at weeks 4 and 8 on the change from baseline for each of the lipid measures and for the adjusted mean lipoprotein and apolipoprotein ratios.

#### RESULTS

Demographic and baseline clinical characteristics were similar among the treatment groups (Table 1). The mean age
Table 1. Patient Characteristics at Baseline by Treatment Group*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>10 mg of Simvastatin (n = 23)</th>
<th>10 mg of Simvastatin Plus Psyllium (n = 23)</th>
<th>20 mg of Simvastatin (n = 22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F ratio</td>
<td>16:7</td>
<td>17:6</td>
<td>15:7</td>
<td>.67</td>
</tr>
<tr>
<td>Age, y</td>
<td>64 ± 7</td>
<td>64 ± 9</td>
<td>63 ± 10</td>
<td>.91</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 ± 3†</td>
<td>27 ± 4</td>
<td>26 ± 4</td>
<td>.02</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On contact</td>
<td>150 ± 46</td>
<td>136 ± 48</td>
<td>158 ± 48</td>
<td>.32</td>
</tr>
<tr>
<td>At baseline</td>
<td>171 ± 34</td>
<td>172 ± 37</td>
<td>175 ± 35</td>
<td>.92</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>.60</td>
</tr>
<tr>
<td>≥2</td>
<td>9</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>CHD or CHD risk equivalent‡</td>
<td>10</td>
<td>18</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>.63</td>
</tr>
<tr>
<td>Previous lipid-lowering agent use</td>
<td>14</td>
<td>17</td>
<td>17</td>
<td>.82</td>
</tr>
<tr>
<td>Previous statin use</td>
<td>14</td>
<td>17</td>
<td>16</td>
<td>.34</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CHD, coronary heart disease.

SI conversion factor: To convert low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259.

*Data are given as number of subjects with the characteristic or as mean ± SD unless otherwise indicated.

†Significantly greater BMI in this group only compared with others.

‡Includes symptomatic carotid artery disease, peripheral arterial disease, and abdominal aortic aneurysm.

at baseline were 59.5 ± 2.15 mmol/L (range, 41.10-7.02 mmol/L), total cholesterol: 251 ± 60 mmol/L (range, 160-352 mg/dL), LDL-C: 46 ± 10 mg/dL (range, 30-83 mg/dL), HDL-C: 110 ± 20 mg/dL (range, 70-180 mg/dL), triglycerides: 157 ± 49 mg/dL (range, 49-290 mg/dL), Apo B: 150 ± 50 mg/dL (range, 80-237 mg/dL), and Apo A-I: 69 ± 16 mg/dL (range, 20-167 mg/dL).

Figure 1 shows plots of the mean levels of LDL-C, by treatment group, during the study. The baseline values for computing changes in LDL-C, as well as the other lipid variables, were obtained by averaging the levels at weeks −1 and 0. Most of the patients who enrolled had been taking some kind of statin therapy previously; only 3 had been taking Metamucil, all for constipation. The mean reductions in total cholesterol, LDL-C, and Apo B for the different treatment groups are shown in Table 2 and Figure 2.

At the end of 8 weeks of treatment, total cholesterol had dropped by 66 mg/dL (1.71 mmol/L) (−26%) in the group receiving 10 mg of simvastatin plus psyllium, a decrease slightly more than that achieved by treatment with 20 mg of simvastatin, which produced a drop of 61 mg/dL (1.58 mmol/L) (−24%) from baseline (P = .33) (Table 2). The LDL-C levels dropped 63 mg/dL (1.63 mmol/L) (−36%) in the group receiving 10 mg of simvastatin plus psyllium, with the additive effect equaling that seen with 20 mg of simvastatin (P = .70). Reductions from baseline in Apo B were more pronounced with the combination therapy at 50 mg/dL (−32%), compared with 43 mg/dL (−29%) with 20 mg of simvastatin (P < .05). Triglyceride levels were not significantly changed from baseline values in any of the treatment groups (Table 2 and Figure 3).

There was no significant change from baseline in HDL-C in the psyllium supplement group, although a blunting of the HDL-C increase with statin treatment was observed. Similar results were seen in the Apo A-I levels.

The baseline ratios for lipoprotein (LDL-C/HDL-C) and apolipoprotein (Apo-B/Apo A-I) were 3.66 and 3.28, respectively, in the group receiving 10 mg of simvastatin; 3.86 and 3.43, respectively, in the group receiving 20 mg of simvastatin and the group receiving 10 mg of simvastatin plus psyllium (P = .05). Triglyceride levels were not significantly changed from baseline values in any of the treatment groups (Table 2 and Figure 3). There was no significant change from baseline in HDL-C in the psyllium supplement group, although a blunting of the HDL-C increase with statin treatment was observed. Similar results were seen in the Apo A-I levels.

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Most of the patients tolerated the combination therapy well, with good compliance. The NCEP ATP III guidelines were applied to each individual to determine his or her LDL-C goal of therapy based on risk categories (Table 3). Sixty-one percent (14/23) of patients who...
Table 2. Absolute Change From Baseline in Serum Lipid and Lipoprotein Levels, by Week and Treatment Group*

<table>
<thead>
<tr>
<th>Lipid Variable</th>
<th>Week</th>
<th>Change From Baseline, mg/dL</th>
<th>Generalized Estimating Equation P Value</th>
<th>10 mg of Simvastatin (n = 23)</th>
<th>10 mg of Simvastatin Plus Psyllium (n = 23)</th>
<th>20 mg of Simvastatin (n = 22)</th>
<th>20 mg of Simvastatin vs 10 mg of Simvastatin</th>
<th>10 mg of Simvastatin vs 10 mg of Simvastatin Plus Psyllium</th>
<th>20 mg of Simvastatin vs 10 mg of Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>4</td>
<td>-47</td>
<td>-59</td>
<td>-53</td>
<td>.33</td>
<td>.04</td>
<td>.30</td>
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<tr>
<td></td>
<td>8</td>
<td>-57</td>
<td>-66</td>
<td>-61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low-density lipoprotein</td>
<td>4</td>
<td>-45</td>
<td>-57</td>
<td>-53</td>
<td>.70</td>
<td>.03</td>
<td>.07</td>
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<td>cholesterol</td>
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<td>.05</td>
<td>.05</td>
<td>.88</td>
<td></td>
<td></td>
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<tr>
<td>Apolipoprotein B</td>
<td>4</td>
<td>-39</td>
<td>-51</td>
<td>-41</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>8</td>
<td>-47</td>
<td>-50</td>
<td>-43</td>
<td>.003</td>
<td>.11</td>
<td>.20</td>
<td></td>
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</tr>
<tr>
<td>Apolipoprotein A-I</td>
<td>4</td>
<td>11</td>
<td>7</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>8</td>
<td>13</td>
<td>8</td>
<td>17</td>
<td></td>
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</tr>
<tr>
<td>High-density lipoprotein</td>
<td>4</td>
<td>3</td>
<td>-1</td>
<td>5</td>
<td>&lt;.001</td>
<td>.01</td>
<td>.31</td>
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<tr>
<td>cholesterol</td>
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<td>-3</td>
<td>4</td>
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<td></td>
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</tr>
<tr>
<td>Triglycerides</td>
<td>4</td>
<td>-14</td>
<td>-11</td>
<td>-21</td>
<td>.93</td>
<td>.56</td>
<td>.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>-23</td>
<td>-17</td>
<td>-8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SI conversion factors: To convert total, low-density lipoprotein and high-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*Data are given as means from analysis of covariance adjusted for baseline unless otherwise indicated.

Figure 2. Charts showing mean percentage changes from baseline at 4 and 8 weeks in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B.

Figure 3. Charts showing mean percentage changes from baseline at 4 and 8 weeks in triglycerides, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein A-I.
received the psyllium supplement with 10 mg of simvastatin achieved their LDL-C goal, compared with 50% (11/22) of those receiving 20 mg of simvastatin, but the difference was not statistically significant (P = .46). Adverse effects were ascertained at follow-up visits. No serious adverse events occurred, and only 3 adverse events were reported, including 2 gastrointestinal (1 in each of the groups receiving the placebo powder) and 1 instance of muscle ache in the group receiving 20 mg of simvastatin.

The objective of this study was to determine whether the addition of psyllium soluble fiber to a small dose of statin would be as effective in lowering cholesterol as doubling the dose of statin. The data show that a low dose (10 mg) of simvastatin supplemented with psyllium (5 g three times daily with meals) achieved the same LDL-C– and Apo B–lowering results as doubling the simvastatin dose to 20 mg. These results are in agreement with the NCEP ATP III recommendation that dietary supplementation with viscous soluble fiber is an effective therapeutic option to lower LDL-C. Psyllium is a natural hydrophilic fiber with hypocholesterolemic effects that is safe and well tolerated when used as an adjunct to a low-fat diet. Although by itself it produces a modest (5%-6%) effect in lowering LDL-C, consistent results in clinical trials and meta-analyses have encouraged physicians to recommend its use in combination with dietary interventions.5-7 The mechanism of cholesterol lowering by psyllium is believed to lie in the ability to modify the enterohepatic circulation of bile acids, increasing bile acid synthesis and diverting hepatic cholesterol to bile acid production. This is in line with the additive effect observed when combined with statin therapy, which inhibits cholesterol synthesis directly in the liver through 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition. The observed percentage of LDL-C lowering achieved by adding psyllium to statin in this study is in the general ballpark of that reported for doubling the dose of most statins (ie, approximately 6%).11

The effects of combination therapy with psyllium or statin alone on triglyceride levels were not statistically or clinically significant. Triglyceride levels are sensitive to dietary changes, and the sugar in the powder solutions might have contributed to increased triglycerides. Also, if the mechanism of action of psyllium is similar to that of bile acid–binding resins, then an increase in triglycerides would not be unexpected because resin use is often associated with elevated triglycerides. The decrease in triglycerides at 8 weeks was most marked among those patients taking 10 mg of simvastatin plus placebo, suggesting that they responded most to the dietary regimen. These patients were also the heaviest.

We observed no increase in HDL-C and a blunting of the Apo A-I increase compared with placebo when psy-
lium was combined with simvastatin. Small reductions in HDL-C have previously been reported with the administration of psyllium and other dietary fibers. This, together with the observed changes in triglycerides, may explain the blunting effect, although interpretation of these results is limited because of the small size of the effects and the sample size. Further evaluation is required to determine the clinical significance of these effects.

The 2004 update of the NCEP ATP III guidelines includes a wider patient population requiring more aggressive LDL-C control. The guidelines continue to suggest the use of soluble fiber as an integral part of the therapeutic lifestyle change intervention.

Guidelines recommend a daily intake of 20 to 30 g of total dietary fiber but do not elaborate on the different effects of soluble and nonsoluble fibers. Dietary soluble fibers, including psyllium supplements, can have a healthy effect in many ways. A pooled analysis of 10 prospective cohort investigations of dietary fiber intake and coronary heart disease protection found that the risk reduction for coronary mortality was stronger with soluble fiber (relative risk, 0.46; 95% confidence interval, 0.28-0.74; for each 10-g/d increment) than for insoluble fiber (relative risk, 0.80; 95% confidence interval, 0.69-0.92). In addition, increased soluble fiber intake has been shown to favorably improve the dietary glycemic index. The benefit may be especially strong in the United States, where the typical diet is often deficient in dietary and soluble fiber. In a randomized trial of a popular low-carbohydrate diet, participants reported reducing fiber intake by 42% compared with baseline. Recently released results of clinical trials using high doses of statins to lower lipids have substantiated the concept that “lower is better,” which is to say that intensive lipid-lowering statin regimens provide a greater protection against cardiovascular events (fetal and nonfetal myocardial infarction) than standard regimens. In response to this evidence, physicians may begin to use higher doses of statins or use combination drug therapy aimed at inhibiting both sources of cholesterol, production in the liver with statins and absorption in the intestine with ezetimibe. Although statins are safe and well tolerated, adverse effects have been demonstrated to bear a direct relationship to the dose level. Adverse effects may also be exacerbated by combination therapy with fibrates or 1 g/d or more of niacin (rhabdomyolysis) or with ezetimibe (liver transaminase elevation), thereby raising concerns among patients and physicians.

In summary, although combination therapies are common in the practice of medicine, physicians have been cautious when it comes to the treatment of dyslipidemia because of the increased likelihood of the patient developing undesirable adverse effects or liver dysfunction. Psyllium supplementation should be considered as a safe and well-tolerated dietary alternative to escalating the dose of statin to enhance LDL-C lowering.

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