

The Effects of Probiotic Supplementation on Dyslipidemia

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Introduction

Dyslipidemia is a significant yet modifiable risk factor for atherosclerosis and cardiovascular disease (CVD). As CVD is the leading cause of death for men and women in the United States,¹ evaluating novel approaches to risk management is imperative. Standard care for dyslipidemia in those without familial hypercholesterolemia may involve therapeutic lifestyle changes including diet and exercise, as well as pharmacologic management. Despite the efficacy of pharmacologic therapy, not everyone who is suitable for lipid-lowering medications is treated. Barriers to medical treatment may include cost, preference to avoid medication, and statin-induced myalgias.

A growing number of clinical trials have demonstrated the potential to improve dyslipidemia through the use of probiotics. Probiotic supplements are typically prepared with species that are on the Generally Recognized as Safe list maintained by the Food and Drug Administration, including various species of lactic acid-producing *Lactobacillus* and *Bifidobacterium*. Such species are also commonly found in the gastrointestinal tracts of healthy individuals.² Scientific interest in the relationship between intestinal microbiota and cardiovascular health began in the 1960s, when it was identified that germ-free rats had increased absorption of cholesterol and conjugated bile acids, as well as higher blood cholesterol levels.³ In 1974, Mann⁴ described the Maasai tribesmen in Africa who regularly consumed several liters of fermented whole milk each day, yet had low rates of CVD, speculating that an element of the fermented milk was responsible for the hypocholesterolemic effect.

There are several proposed mechanisms of action for the cholesterol-lowering effects of probiotics. One mechanism is through cholesterol assimilation, where probiotic bacteria adhere to cholesterol molecules in the intestinal lumen and are excreted. In addition, some cholesterol may be taken up by the microbiota for incorporation into their cell membranes.⁵ Another mechanism suggests that short-chain fatty acids produced by probiotic bacteria interfere with the rate-limiting enzyme in hepatic cholesterol synthesis.⁶ Finally, certain bacteria can deconjugate bile acids through bile salt hydrolase (BSH) activity. The impact of BSH activity on serum cholesterol is twofold: first, deconjugation of bile acids leads to increased bile acid excretion and reliance on *de novo* cholesterol synthesis for production of new bile acids. Second, deconjugation decreases the solubility of cholesterol, thereby reducing the amount of cholesterol absorbed intestinally.⁶

The purpose of this review is to evaluate the current research and determine the effect of probiotic supplementation on total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) in adults with dyslipidemia.

Methods

The Academy of Nutrition and Dietetics (Academy) utilizes an evidence analysis process to gather, classify, and appraise relevant research, then summarize and grade the evidence.⁷ This methodology was utilized to systematically evaluate the relationship between probiotic supplementation and blood concentrations of TC, LDL-C, and HDL-C in adults with dyslipidemia. OVID Medline and Pub Med search

terms included cholesterol, probiotics, and dyslipidemias. Articles were limited to English language, humans, adults, and years 2011-2015, producing a total of 33 studies for consideration. Research involving pregnant women and co-interventions such as weight loss were excluded, and the results were further limited to randomized controlled trials (RCTs) with attrition rates below 20%, providing a total of nine studies for evaluation. Each study was critically appraised using the Academy's quality criteria checklist and assigned a positive, negative, or neutral rating. An expert panel of two registered dietitian nutritionists (RDNs), a cardiologist, and a cardiac rehabilitation registered nurse deliberated on the quality of the evidence and assigned a grade to the conclusion statement.

Results

Key variables of the nine studies and the associated impacts to baseline lipids are presented in Table 1. The studies ranged from 42 to 151 participants, including men and women with average ages of 43 to 67 years and average body mass indexes of 26 kg/m² to 31 kg/m². Average baseline TC, LDL-C, and HDL-C values were 186 to 258 mg/dl, 120 to 175 mg/dl, and 35 to 57 mg/dl, respectively. In seven of the nine studies, participants were instructed to maintain current dietary practices, with pre- and post-evaluation by dietary questionnaire. Five probiotic strains or combinations of strains at predetermined minimum doses in yogurt or capsule format served as interventions across the nine studies, and all studies were placebo-controlled. In four of the five studies utilizing yogurt as the intervention, both the treatment and placebo groups received conventional yogurt containing naturally occurring bacteria, with only the treatment groups receiving the additional probiotic supplementation as outlined in Table 1. Of the seven studies rated as positive, six demonstrated significant lipid reductions with probiotic supplementation that ranged from 4.1% to 19.7% in TC and 6.9% to 16.9% in LDL-C, compared with placebo. Only the two neutral studies demonstrated significant increases in HDL-C relative to placebo. Both yogurt and capsule delivery formats were associated with significant improvements in lipid profile. A combination of *L. acidophilus* and *B. lactis* Bb12 served as the probiotic intervention in four trials. Ejtahed⁸ studied 60 participants in Iran with type 2 diabetes mellitus (T2DM).

Participants who consumed probiotic yogurt for 6 weeks experienced 4.5% and 7.5% decreases in TC and LDL-C, respectively, compared with placebo ($P < .01$). Nabavi's⁹ study intervention and results among 72 Iranians with non-alcoholic fatty liver disease were almost identical to those of Ejtahed. A third study in Iran involving 42 participants with T2DM by Mohamadshahi¹⁰ demonstrated that reductions in TC and LDL-C were not significant compared with placebo; however, TC and LDL-C decreased 11.7% ($P = .044$) and 22.7% ($P = .013$), respectively, compared with baseline. An increase of 11.5% in HDL-C ($P = .023$) occurred in the probiotic group, compared with placebo. Finally, Ivey¹¹ conducted a factorial study of 151 participants in Australia to evaluate the impact of *L. acidophilus* and *B. lactis* Bb12 yogurt and capsules on the features of metabolic syndrome, but the lipid changes relative to placebo were not significant. A limitation of this study was the use of cholesterol-lowering medications by 78% of participants during the trial.

A study of 64 participants in Thailand by Rerksuppaphol¹² used *L. acidophilus*, this time combined with *B. bifidum* and delivered in a capsule form. Relative to placebo, those consuming the combined probiotics experienced decreases in TC and LDL-C of 19.7% ($P < .001$) and 16.9% ($P < .01$), respectively. A portion of this demonstrated improvement in lipid profile was attributable to significant increases of 9.4% and 14.2% in TC and LDL-C, respectively, experienced by the control group. Additionally, those consuming the probiotic exhibited a 5.4% decrease in HDL-C compared with placebo ($P = .04$). Participants in both groups were instructed to minimize fat intake during the study, but were given no other dietary guidance. The lack of dietary control was considered a limitation of the study.

Table 1. Changes in Lipid Profile with Probiotic Treatment Versus Placebo

Study, Year, Quality Rating	Probiotic Strain and Dose (in CFU)	Weeks in Study	TC (mg/dl) Baseline	TC Change	LDL-C (mg/dl) Baseline	LDL-C Change	HDL-C (mg/dl) Baseline	HDL-C Change
Ejtahed 2011 +	<i>L. acidophilus</i> , <i>B. lactis</i> Bb12 1.1x10 ⁹ , 1.2x10 ⁹	6	201	-4.5% P<.01	122	-7.5% P<.01	48	NS
Nabavi 2014 +	<i>L. acidophilus</i> , <i>B. lactis</i> Bb12 1.3x10 ⁹ , 1.2x10 ⁹	8	197	-4.1% P<.01	120	-6.9% P<.01	48	NS
Mohamadshahi 2014 ⊖	<i>L. acidophilus</i> , <i>B. lactis</i> Bb12 1.1x10 ⁹ , 1.1x10 ⁹	8	219	-10.2% P=.11*	133	-17.2% P=.06*	44	11.5% P=.023
Ivey 2015 +	<i>L. acidophilus</i> , <i>B. lactis</i> Bb12 3.0x10 ⁹ , 3.0x10 ⁹	6	206	NS	125	NS	53	NS
Rerksuppaphol 2015 +	<i>L. acidophilus</i> , <i>B. bifidum</i> 1.0x10 ⁹ , 1.0x10 ⁹	6	237	-19.7% [†] P<.001	158	-16.9% [†] P<.01	57	-5.4% P=.04
Jones 2012 +	<i>L. reuteri</i> NCIMB 30242 2.8x10 ⁹	6	258	-4.8% P=.031	169	-8.9% P=.016	55	NS
Jones 2012 +	<i>L. reuteri</i> NCIMB 30242 5.8x10 ⁹	9	246	-9.1% P=.001	175	-11.6% P=.001	51	NS
Fuentes 2013 +	<i>L. plantarum</i> (3 strains) 1.2x10 ⁹	12	247	-13.6% P<.05	167	-8.8% NS [‡]	44	5.7% NS [‡]
Rajkumar 2014 ⊖	VSL#3 (8 strains) 112.5x10 ⁹	6	186	Not stated	124	-7.0% [‡] P<.05	35	18.5% [‡] P<.01

CFU = colony forming units; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol
+ Positive quality study ⊖ Neutral quality study NS = not significant (P>.05)

* NS compared with placebo, but significant changes of -11.7% (P=.044) and -22.7% (P=.013) in TC and LDL-C, respectively, compared with baseline.

[†] Control group experienced significant increases in TC and LDL-C of 9.4% (P<.001) and 14.2% (P<.01), respectively.

[‡] NS compared with placebo, but significant changes of -14.7% (P<.05) and 6.6% (P<.05) in LDL-C and HDL-C, respectively, compared with baseline.

[‡] Compared with baseline, but stated as significant compared with placebo.

Jones^{13,14} published two studies in the Czech Republic to examine the impact of *L. reuteri* NCIMB 30242 (Cardioviva) on dyslipidemia. The first study provided 114 participants with *L. reuteri* yogurt for 6 weeks. TC and LDL-C were reduced by 4.8% (P=.031) and 8.9% (P=.016), respectively. A second study provided 127 participants with *L. reuteri* in capsule form for 9 weeks. Compared with placebo, *L. reuteri* supplementation decreased TC and LDL-C by 9.1% and 11.6%, respectively (P=.001). In addition, significant improvement in other CVD risk markers, including apoB-100, fibrinogen, and hsCRP levels were observed.

Fuentes¹⁵ studied the impact of three strains of *L. plantarum* (AB-LIFE: CECT 7527, 7528, and 7529) on the lipid profile of 60 participants in Spain. Compared with placebo, participants supplemented with *L. plantarum* experienced a decrease of 13.6% ($P < .05$) in TC and a non-significant decrease of 8.8% in LDL-C. Fuentes stratified participants by baseline TC into high and low initial value categories. Those with the highest initial TC levels (251-300 mg/dl) experienced the greatest improvements with probiotic treatment: reductions in TC and LDL-C of 17.4% and 17.6%, respectively, compared with baseline; however, even participants with the lowest initial TC values saw reductions of 9.4% and 11.5% in TC and LDL-C, respectively.

Rajkumar¹⁶ studied the effects of omega-3 and probiotic supplementation (alone and in combination) on the lipid profile of 60 overweight adults in India. VSL#3 is a high-potency combination of eight strains of bifidobacteria, lactobacilli, and streptococci. Compared with baseline values, those supplemented with VSL#3 experienced a decrease in LDL-C of 7% ($P < .05$) and an increase in HDL-C of 18.5% ($P < .01$).

Review of the research determined that in adults with dyslipidemia, there is fair (grade II) evidence supporting the use of probiotics to reduce TC and LDL-C when consumed in yogurt or capsule form for 6 to 12 weeks. The effect of probiotics on HDL-C remains unclear. Probiotic strains with their minimum daily doses analyzed include: *L. acidophilus* (1.11×10^9 CFU) with *B. lactis* Bb12 (1.08×10^9 CFU), *L. acidophilus* (3.0×10^9 CFU) with *B. bifidum* (3.0×10^9 CFU), *L. reuteri* NCIMB 30242 (2.8×10^9 CFU), *L. plantarum* CECT 7527, 7528, and 7529 (1.2×10^9 CFU), and VSL#3 (112.5×10^9 CFU).

Discussion

The results of the aforementioned RCTs are consistent with several probiotic meta-analyses¹⁷⁻¹⁹ published in 2015, which reported average reductions in TC and LDL-C of 6.6 to 10.4 mg/dl and 7.3 to 8.9 mg/dl, respectively, compared with placebo. The meta-analyses did not identify significant improvements in HDL-C. Trends noted across the published research on probiotics include greater lipid reduction with higher baseline TC values, longer intervention periods, and the use of lactobacilli strains. The large number of positive quality, recently published RCTs is a strength of this review. The lack of published research studying participants following typical American diets limits generalizability of the results. The impact of probiotics on lipid profiles of individuals consuming an American diet and those using typical lipid-lowering medications such as statin-monotherapy should be the focus of future studies.

Conclusion

A review of nine recent RCTs indicates that supplementation with formulated combinations of probiotic strains significantly decreases TC and LDL-C in adults with dyslipidemia. While additional evidence is warranted prior to RDNs providing specific strain recommendations, lifestyle intervention that combines diet and exercise remains the pillar of primary care treatment in this population.

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