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Dyslipidemia Management for Secondary Prevention in Women with Cardiovascular Disease: What Can We Expect From Non-pharmacologic Strategies?

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Abstract

Cardiovascular disease is the leading cause of death in women and the treatment of dyslipidemia is a cornerstone of secondary prevention. Pharmacologic therapy with statins can lower LDL-C by 30–50% and reduce the risk of recurrent coronary heart disease in both men and women. While significant reductions in LDL-C can be achieved with statin therapy, diet and lifestyle modification remain an essential part of the treatment regimen for cardiovascular disease. Moreover, a large proportion of the U.S. population is sedentary, overweight, and does not consume a heart-healthy diet. Non-pharmacologic treatment strategies also improve other cardiovascular risk factors and are generally easily accessible. In this review, we examine the effect of non-pharmacologic therapy on lipids as part of the secondary prevention strategy of cardiovascular disease in women.

Keywords

women; dyslipidemias; cardiovascular diseases; secondary prevention; diet; lifestyle

Introduction

Cardiovascular disease (CVD) is the number one cause of death among women and those over 40 years old have a greater than 50% lifetime risk of suffering a major adverse cardiovascular event.[1] Coronary heart disease (CHD) typically presents about ten years later in women, which is partially attributable to the adverse changes in lipid profile associated with menopause.[2] Despite later CHD onset, women younger than 75 years have up to twice the risk for early death after myocardial infarction compared to men of the same age.[3] Moreover, women with CHD or a risk-equivalent are less likely than men to achieve their goal LDL-cholesterol (LDL-C) level.[4]

Pharmacologic therapy for dyslipidemia is a cornerstone of CHD secondary prevention.[5] Statins can improve LDL-C levels by 30 to 50% and reduce the risk of CHD for both men and women.[6, 7] However, dietary and lifestyle modification are also integral components

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of a treatment regimen for CHD and even small changes can result in a significantly improved risk factor profile.[8] This is especially important given that less than half of U.S. adults meet the American Heart Association 2020 goal for physical activity and >75% consume a poor diet.[1] In this review we examine the role of nonpharmacologic strategies for the treatment of dyslipidemia in women with a history of cardiovascular disease.

Specific Diets and Macronutrient Intake

The type of food individuals consume and its preparation method can significantly influence the development of dyslipidemia. It is well-established that specific dietary macronutrients, such as saturated fats and cholesterol, have an adverse effect on the serum lipid profile. However, it is difficult for most individuals to completely eliminate the consumption of specific components. This has led to dietary recommendations that focus on consuming specific proportions of macronutrients, rather than the avoidance of one altogether.

The OmniHeart trial compared the effect of three diets that increased either the proportion of carbohydrates, protein, or unsaturated fatty acids.[9] Approximately 50% of the participants were women and of those over half were postmenopausal. All three diets also incorporated an increased intake of fruits, vegetables, and fiber. Participants' caloric intake was adjusted as needed to minimize weight change and they were instructed to maintain their baseline level of alcohol consumption and exercise. Individuals on all three diets experienced a >10mg/dL decrease in LDL-C. The protein diet group experienced the largest reduction in LDL-C of 14mg/dL, which was significantly more than the carbohydrate group's reduction of 11mg/dL. Those participants with a baseline LDL-C of 130mg/dL had an approximately 20mg/dL decrease in LDL-C no matter which diet they consumed, while individuals with a baseline LDL-C of < 130mg/dL had an approximate decrease in LDL-C of 5mg/dL.

The diets high in protein and unsaturated fats demonstrated significant decreases in triglycerides of 16mg/dL and 9mg/dL, respectively. There was no change in triglyceride levels for those who consumed the higher carbohydrate diet. All three diets showed a decrease in total cholesterol ranging from a reduction of 12mg/dL for the diet high in carbohydrates to 20mg/dL for the diet high in protein. A subgroup analysis stratified by gender showed a similar change in lipid levels for both men and women.

A trial by Dansinger et al. examined four commercially popular diets that recommend highly different macronutrient proportions.[10] The diets included 1) an Atkins diet based on restricting carbohydrate consumption to less than 20g per day, 2) an Ornish diet that was vegetarian and minimized calories from fat to <10%, 3) a Zone diet based on macronutrient proportions of 40% carbohydrates, 30% protein, and 30% fat, and 4) a Weight Watchers diet based a points system to count calories. Women were equally distributed among all four groups and made up half of the trial participants.

At the end of the one year follow-up, there was no difference in weight loss between groups and participants in each group had lost approximately 3kg. Despite a progressive decrease in dietary adherence, there was a significant decrease in LDL-C ranging from 9mg/dL for participants in the Weight Watchers group to 13mg/dL for those in the Ornish diet group. The Atkins group had a non-significant decrease in LDL of 7mg/dL. The Ornish and Weight Watchers diet groups also had significant decreases in total cholesterol of 11mg/dl and 8mg/dL, respectively. All groups except for the Ornish diet had a significant increase of more than 3mg/dL of HDL.

Sacks et al. performed a trial with overweight adults to investigate the effects of four diets that differed in their proportion of fat, protein, and carbohydrate.[11]** Over 60% of

participants were women and approximately 20% were on lipid-lowering medications at baseline. After two years of follow-up, participants lost approximately 3kg of weight with no significant difference between groups. All diets showed a significant improvement in lipid profiles with a 12–17% reduction in triglycerides. The greatest reduction in triglycerides was observed in the high protein groups.

The low-fat diets and high-carbohydrate diets showed significantly larger decreases in LDL-C compared to the high-fat (5% vs. 1%) and low-carbohydrate diets (6% vs. 1%). However, the low-carbohydrate diet increased HDL 6% vs. an increase of 1% in the high-carbohydrate diet. Overall, the low-fat and average protein diets had the largest absolute decrease in LDL at two years follow-up of 6mg/dL. For the high-protein vs. low-protein groups there was no significant difference in LDL levels and a small decrease in HDL of 1mg/dL.

Individuals on high protein, low carbohydrate diets typically consume animal derived protein sources. This can result in weight loss and an improvement in triglyceride levels, but does not typically reduce LDL-C levels. Jenkins et al. investigated the effect of a low vs. high carbohydrate vegetarian diet on weight loss and lipid levels in a population of 50 overweight adults.[12]** The low carbohydrate group was instructed to consume their protein from plant sources, while the high carbohydrate group could consume eggs and dairy products. The majority of participants were female and more than 25% were taking cholesterol lowering medications at baseline.

After only four weeks of follow-up, both groups had significant improvements in their lipids and an approximate 5% reduction in body weight. However, the low carbohydrate group experienced a greater reduction in LDL-C (20% vs. 12%), triglyceride levels (29% vs. 18%), and total cholesterol (20% vs. 13%). These results suggest that for individuals who consume a high protein, low carbohydrate diet the consumption of protein derived from plants instead of animals can reduce both triglycerides and LDL-C. Jenkins et al. conducted a separate study to investigate the effect of a combination of foods that have been demonstrated to individually lower lipid levels; 61% of the participants were women, all of whom were post-menopausal.[13] The control group consumed a diet low in saturated fats and with an increased intake of whole grains, fruits, and vegetables. The intervention group was counseled to increase their intake of plant sterols, fiber, soy protein, and nuts. During the six month follow-up period participants in all groups lost between 1–2kg of body weight with no significant difference between groups. The intervention group had a significant reduction in LDL-C of 14% and a 10% reduction in total cholesterol, while the control group had a significant 4% reduction in LDL-C and a non-significant change in total cholesterol. There was no difference in lipid changes between men and women.

Mediterranean Diet

A Mediterranean-style diet is typified by the use of olive oil as the primary source of fat, an increased consumption of fish, a moderate amount of daily alcohol, and a high consumption of fruits, grains, and nuts. Populations along the Mediterranean Sea were noted to have lower rates of cardiovascular disease and this diet has garnered significant interest, especially since the Lyon Heart Study demonstrated a 65% relative risk reduction in cardiac death among those who consumed a Mediterranean style diet.[14]

The Medi-RIVAGE study compared the effects of a Mediterranean-style diet and an American Heart Association low fat diet on lipid profiles.[15] Over 60% of participants were women, the majority of whom were sedentary at baseline. After three months of follow-up, total cholesterol had significantly decreased in both the Mediterranean (8%) and low-fat (5%) groups and there was a non-significant decrease in LDL-C of 11% and 5%, respectively.

Singh et al. investigated the effect of a plant-based, Indo-Mediterranean diet compared to a National Cholesterol Education Program (NCEP) Step I diet among participants with a history of cardiovascular disease.[16] 90% of participants were male, although only about 25% were obese or overweight. After two years of follow-up, both groups had significantly improved lipid profiles. However, the group that consumed an Indo-Mediterranean diet had significantly greater reduction in LDL-C (18% vs. 14%), triglycerides (20% vs. 14%), and total cholesterol (12% vs. 9%) compared to the NCEP Step I diet.

Thomazella et al. conducted a secondary prevention trial comparing the effects of a Mediterranean diet and a NCEP diet that included phytosterol supplementation.[17]** While this trial only included men, the group's lipid profile was representative of appropriately treated secondary prevention patients with more than 80% taking statins at baseline and a mean LDL of less than 100mg/dL. Thus, the results may also be instructive when extrapolated to women. The study followed participants for three months, during which time statin dosages and exercise levels were not changed. Participants in both dietary groups lost approximately 1.5kg of body weight. However, in contrast to the results from the study by Singh et al., the NCEP diet group had a significantly decreased total cholesterol (9%) and LDL-C (12%), while the Mediterranean diet group had no significant change in either. There was a non-significant trend towards a reduction of triglyceride levels in both Mediterranean (15%) and NCEP (7%) diet groups.

Omega-3

A literature review by Harris found that omega-3 supplementation can be expected to lower triglycerides by 25–30%, while raising LDL-C by 5–10% and HDL-C by 1–3%.[18] However, trials investigating the effect of omega-3 on serum lipids have mostly been conducted using fish oil supplementation at doses of 3–6g/day, which realistically can only be achieved through pharmacologic supplementation.

The Diet and Reinfarction Study was the first randomized controlled trial to investigate the effect of increased fish intake on the secondary prevention of CHD.[19] There were three dietary intervention groups that were instructed to either 1) consume at least two portions of fatty fish per week, 2) reduce their fat intake to 30%, or 3) increase their fiber intake. At six months, the fish consumption group had a significant increase in total cholesterol of 2%, although this change was not significant by the end of the trial. Perhaps most striking, the fish consumption group experienced a significant reduction in all-cause mortality starting at four months and increasing to 29% by the end of the two year follow-up period. Although no significant change in serum cholesterol was reported, increased levels of omega-3 may affect platelet function and the clotting cascade, potentially contributing to the observed reduction in total mortality.

Alcohol

Moderate alcohol intake (1 drink/day for women and 2/day for men) can reduce the risk of recurrent CVD.[20] However, excessive consumption is harmful and associated with an adverse effect on cardiovascular risk factors and outcomes.[21] In a meta-analysis, Rimm et al. examined the effect of alcohol intake on lipids and found a 0.13mg/dL increase in HDL for every 1g/day of alcohol intake, with no significant difference between genders.[22] Therefore, a consumption of 14g/day of alcohol (one drink) would be expected to raise HDL-C by approximately 4%. The same amount of alcohol per day was also associated with an approximately 3% increase in triglycerides. Despite a greater expected increase in HDL-C and triglycerides for men who consume two drinks per day, the reduction in mortality appears to be the same for men and women.[23]

Hartung et al. investigated the effect of alcohol and physical activity on lipids among individuals who were sedentary and those who were runners.[24] Participants consumed three 12oz beers per day, containing approximately 40g of alcohol. Among the inactive participants, there was an almost 10mg/dL increase in HDL-C after three weeks of daily alcohol consumption, while no significant change in HDL was noted among participants who were regular joggers – suggesting that the HDL-related benefits of both activities are not cumulative.

Fiber

Brown et al. performed a meta-analysis of randomized trials in order to examine the effect of soluble fiber intake on serum lipids.[25] The included trials did not change the caloric intake of either the intervention or control groups. Of the 67 included trials, the mean age was 50 years and over 30% of participants were women. In the practical dose range of 2–10g/day of fiber intake per day, every one-gram increment of soluble fiber significantly reduced total cholesterol by 1.7mg/dL and LDL-C by 2.2mg/dL, without a significant effect on triglycerides. Surprisingly, there was a small but significant reduction in HDL by 0.1mg/dL for each gram of fiber consumed. There was no difference in effect size based on the type of fiber consumed. However, unlike a previous meta-analysis, these results did not show an increased lipid reduction effect in participants with hypercholesterolemia.[26]

Nuts

The consumption of nuts is associated with up to a 35% reduction in the risk of CHD for women.[27] Sabate et al. pooled the results of 25 trials in a meta-analysis to investigate the effect of increased nut consumption on lipids.[28]* The analysis was limited to trials that had no change in participant body weight and the included trials had an average nut intake of 2.4oz per day. Increased nut consumption resulted in a mean reduction in total cholesterol of 5.1% and a reduction in LDL-C of 7.4%. There was no significantly different change in lipids when stratified by gender or type of nut consumed.

Among participants with a triglyceride level ≥ 150 mg/dL there was a 10% reduction in triglycerides, while individuals with a triglyceride level <150 mg/dL had no significant change. Participants with 20% of their dietary energy intake from nuts had a larger decrease in total cholesterol, LDL, and triglycerides compared to those who consumed 10% of their energy from nuts. A larger improvement in lipid levels was also observed in normal weight participants compared to those who were overweight and obese. Additionally, individuals with a baseline LDL >160 mg/dL had a greater reduction in total cholesterol and LDL compared to participants with a LDL <130 mg/dL.

Smoking

Although women typically experience CVD about 10 years later in life than men, an observational study revealed that among female smokers with acute coronary syndrome, the difference in age of CVD onset decreased to only one year.[29] Craig et al. investigated the effect of smoking on lipids in a meta-analysis of 54 studies.[30] Smokers were more likely to have an elevated total cholesterol (3%), triglycerides (9%), LDL-C (2%), and a lower HDL (6%). Moreover, heavy smokers had an elevation in triglyceride level nearly twice as high as light smokers (18% vs. 11%) and nearly twice the decline in HDL-C level (9% vs. 5%).

The PROCAM study investigated the association between smoking and serum lipids in a prospective analysis of 30,908 participants.[31] Women and men who smoked had a HDL-C level approximately 6% lower than non-smokers. However, the change in lipids associated

with smoking was two-fold greater for total cholesterol and an almost four-fold greater for LDL-C in women compared to men.

Gepner et al. investigated the effect of smoking cessation on lipids in a trial of 1,504 active smokers.[32]* After one year, those who quit had an increase in HDL-C of approximately 6%, despite gaining about 9 pounds more body weight than those who continued to smoke. Although not quantified, the increase in HDL-C was greater for women than men and greater for those with a lower baseline HDL-C level.

Exercise

A meta-analysis by Kelley et al. pooled results from 41 randomized trials conducted exclusively in women to evaluate the effect of exercise on lipids.[33] The average length of the exercise programs was approximately six months with 3–4 days of exercise per week and an average BMI of approximately 26 kg/m² at baseline. The exercise groups had significant improvement in all major lipids, most significantly with a 5% reduction in triglycerides, a 3% reduction in LDL-C, and a 3% increase in HDL-C. Additionally, when trials conducted in pre- and post-menopausal women were compared there was no significant difference in the effect size.

Barnard et al. conducted a three week trial among pre and post-menopausal women to investigate the effect of combined dietary and exercise intervention.[34] Participants had daily aerobic exercise and consumed a low-fat diet that did not include caloric restriction. Although post-menopausal women had significantly higher lipid levels at baseline, both groups experienced approximately 20% reductions in total cholesterol, LDL-C, and triglycerides. In addition, both groups had an approximately 20% increase in HDL-C levels.

Fahlman et al. investigated the effect of aerobic exercise and resistance training on lipids in women aged 70–87.[35] After ten weeks, there were no significant differences in caloric intake or body weight within any of the groups. However, both the aerobic and resistance training groups had a significant increase in HDL-C (25% and 8%) and decrease in triglycerides (39% and 11%), while the control group had a 8% decrease in HDL and a 27% increase in triglycerides.

Despite a 25% reduction in cardiovascular death, traditionally only about 20% of eligible patients participate in cardiac rehabilitation after hospital discharge, with even fewer continuing long-term.[36, 37] Taylor et al. conducted a meta-analysis of 48 randomized trials investigating the effect of an exercise-based cardiac rehabilitation program lasting for at least 6 months; 27 of the trials included both men and women, although only about 20% of those participants were women.[38] There was a significant reduction of 14mg/dL of total cholesterol and 20mg/dL of triglyceride levels, but no significant change in LDL-C or HDL-C.

Weight loss

Excess body weight is a significant risk factor for cardiovascular disease and 64% of U.S. women are either overweight or obese.[39] Melanson et al. investigated the effect of dietary and exercise-induced weight loss in a group of sedentary, overweight women.[40] During the trial, participants walked on average 5 days per week and consumed calorie-restricted diets with either chicken or beef as their main source of protein. At the end of 12 weeks, individuals in both groups had lost approximately 6 kg of body weight and had similar improvements in lipids with approximately a 9% reduction in total cholesterol and LDL-C.

Wood et al. investigated the effect of weight loss caused by either caloric restriction or exercise on serum lipids.[41] Both intervention groups lost a significant amount of body weight compared to the control group, but the caloric restriction group lost almost twice as much weight as the exercise group (7kg vs. 4kg). Both groups had a significant increase in HDL of approximately 10% and a decrease in triglycerides of approximately 11%. There were non-significant decreases in LDL-C and total cholesterol for both intervention groups.

A meta-analysis by Poobalan investigated the effect of weight loss on lipids in overweight and obese individuals.[42] Weight loss was significantly associated with reductions in total cholesterol, triglycerides, and LDL-C, but not HDL-C. Based on their pooled results, for every 10 kg of weight loss there would be an expected decrease of 9mg/dL of total cholesterol, 11 mg/dL for triglycerides, and 7 mg/dL for LDL.

Conclusions

Women with a history of cardiovascular disease should be treated to a goal LDL-C of at least <100mg/dL and preferably <70 mg/dL.[5] While statins can dramatically lower lipids and reduce cardiovascular events and mortality in women, non-pharmacologic treatment strategies should also be an integral component of a secondary prevention strategy.[7] Larger improvements in serum cholesterol levels can generally be expected for individuals who have more severe lipid abnormalities at baseline, regardless of whether the treatment is pharmacologic or non-pharmacologic. It is also especially important that women be advised to quit smoking, because they have a significantly worse lipid profile and an earlier onset of CVD compared to men. A summary of the lipid profile changes observed for different non-pharmacologic treatment strategies is presented in Table 1.

A large proportion of the U.S. population is sedentary, overweight, and does not consume a heart-healthy diet. However, only a relatively small change in diet and lifestyle is required to achieve a significant improvement in serum lipids. Dietary and lifestyle modifications generally result in smaller lipid profile changes than statin therapy, but have the added benefit of improving other cardiovascular risk factors. Non-pharmacologic treatment strategies can also improve lipids for individuals who are already on statin therapy and are comparably efficacious between the men and women. Overall, non-pharmacologic strategies can significantly improve lipid profiles in women with a history of CVD and the fundamental importance of diet, exercise, and other therapeutic lifestyle modifications cannot be overemphasized.

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Table 1
The effect of non-pharmacologic treatment strategies on lipid profiles among selected trials.

Author (year)	Intervention arms	Follow-up	LDL-C (mg/dL)	HDL-C (mg/dL)	triglycerides (mg/dL)	total cholesterol (mg/dL)
Appel et al. (2005) ⁹	↑ carbohydrates	6 weeks	-12	-1	NS	-12
	↑ protein		-14	-3	-16	-20
	↑ unsaturated fat		-13	NS	-9	-15
Dansinger et al. (2005) ¹⁰	Atkins	1 year	NS	3	NS	NS
	Ornish		-13	NS	NS	-11
	Zone		-12	3	NS	NS
	Weight Watchers		-9	3	NS	-8
Sacks et al. (2009) ¹¹	Low fat vs. high fat	2 years	-5	NS	NS	-6
	Average protein vs. high protein		NS	-1	NS	NS
	Low carb vs. high carb		6	2	NS	6
Jenkins et al. (2009) ¹²	low-carb, plant derived protein	4 weeks	-36	NS	-76	-52
	high-carb, animal derived protein ("lacto-ovo")		-22	NS	-40	-32
Jenkins et al. (2011) ¹³	low saturated fat (control)	6 months	-6	NS	NS	NS
	sterols, fiber, soy, nuts – 2 counseling sessions		-25	NS	NS	-26
	sterols, fiber, soy, nuts – 7 counseling sessions		-26	NS	NS	-27
Vincent-Baudry et al. (2005) ¹⁵	Mediterranean	3 months	-19	NS	NS	NS
	AHA low-fat		-8	NS	NS	NS
Singh et al. (2002) ¹⁶	Indo-Mediterranean	2 years	-25	1	-32	-27
	NCEP Step I		-19	2	-22	-20
Fahlman et al. (2002) ³⁵	Control	10 weeks	NS	NS	-36	NS
	Aerobic training		NS	9	-21	NS
	Resistance training		NS	10	-29	NS
Wood et al. (1988) ⁴¹	Caloric restriction	1 year	-12	5	-24	-14
	Exercise		-10	4	-14	-10

Bold results represent the most effective strategy within a particular study. NS = non-significant within-group difference from baseline to study completion.