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Corn oil improves the plasma lipoprotein lipid profile compared with extra-virgin olive oil consumption in men and women with elevated cholesterol: Results from a randomized controlled feeding trial

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BACKGROUND: Restricted intakes of saturated and trans-fatty acids is emphasized in heart-healthy diets, and replacement with poly- and monounsaturated fatty acids is encouraged.

OBJECTIVE: To compare the effects of polyunsaturated fatty acid–rich corn oil (CO) and monounsaturated fatty acid–rich extra-virgin olive oil (EVOO) on plasma lipids in men and women (N = 54) with fasting low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL and <200 mg/dL and triglycerides (TG) ≤350 mg/dL.

METHODS: In a double-blind, randomized, crossover design (21-day treatments, 21-day washout between), 4 tablespoons/day CO or EVOO were provided in 3 servings study product/day (muffin, roll, yogurt) as part of a weight-maintenance diet (~35% fat, <10% saturated fat, <300 mg cholesterol). Subjects ate breakfast at the clinic every weekday throughout the study. Lunches, dinners, and snacks (and breakfasts on weekends) were provided for consumption away from the clinic.

RESULTS: Baseline mean (standard error) lipids in mg/dL were: LDL-C 153.3 (3.5), total cholesterol (total-C) 225.7 (3.9), non–high-density lipoprotein (non–HDL)-C 178.3 (3.7), HDL-C 47.4 (1.7), total-C/HDL-C 5.0 (0.2), and TG 124.8 (7.2). CO resulted in significantly larger least-squares mean % changes (all $P < .001$ vs EVOO) from baseline in LDL-C −10.9 vs −3.5, total-C −8.2 vs −1.8, non–HDL-C −9.3 vs −1.6, and total-C/HDL-C −4.4 vs 0.5. TG rose a smaller amount with CO, 3.5 vs 13.0% with EVOO ($P = .007$). HDL-C responses were not significantly different between conditions (−3.4 vs −1.7%).

CONCLUSION: Consumption of CO in a weight-maintenance, low saturated fat and cholesterol diet resulted in more favorable changes in LDL-C and other atherogenic lipids vs EVOO.

Trial Registration: ClinicalTrials.gov identifier: NCT01925716.

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Introduction

Corn oil (CO) contains the highest naturally occurring phytosterol levels of the refined vegetable oils (0.97 g/100 g oil per the US Department of Agriculture National Nutrient Database for Standard Reference), and is rich in polyunsaturated fatty acids (PUFA).[1,2] Restriction of intakes of saturated fatty acids (SFA) and trans-fatty acids is emphasized in cholesterol-lowering, heart-healthy diets, whereas consumption of unsaturated fatty acids is emphasized.[3–5]

PUFA, in place of SFA or carbohydrates, has been shown to lower the plasma low-density lipoprotein cholesterol (LDL-C) concentration and to be associated with reduced risk for coronary heart disease (CHD) in prospective cohort studies.[6–8] The Mediterranean dietary pattern, high in monounsaturated fatty acids (MUFA)-rich olive oil, has also been associated with reduced CHD risk in epidemiological and clinical studies,[9–11] and, when substituted for SFA or carbohydrates, MUFA significantly reduces LDL-C without lowering high-density lipoprotein (HDL)-C.[7,12,13] The degree of unsaturation that is most effective for providing beneficial lipid changes and protection from CHD is controversial.[14–16]

It is often underappreciated that, although food sources, including dietary oils, may be rich in 1 type of fatty acid, they are not 100% SFA, MUFA, or PUFA. Thus, it is important to consider the effects of specific food choices, particularly with regard to the effects of substitution of 1 food or food component for another. The present, single-center, randomized, controlled, double-blind, 2-period, crossover feeding trial compared the effects on lipoprotein lipids of 2 mostly unsaturated dietary oils, CO and extra-virgin olive oil (EVOO), incorporated into a weight-maintenance diet containing ~35% of kcal from fat, <10% SFA, and <300 mg/d cholesterol in men and women with hypercholesterolemia at a single clinical research center (Biofortis Clinical Research, Addison, IL).

Methods

Study design

This study was conducted according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2000), and the United States 21 Code of Federal Regulations (ClinicalTrials.gov identifier: NCT01925716). The study protocol and informed consent documents were approved by an institutional review board (Quorum Review IRB, Seattle, WA). A signed informed consent form and authorization for disclosure of protected health information were obtained from all subjects before protocol-specific procedures were carried out. Staff and subjects remained blinded to treatment throughout the trial.

Treatments

The study included 2 21-day treatment periods and a 21-day washout between treatments. During the treatment periods, 4 tablespoons per day (~54 g) of CO (528 mg phytosterols, 29.7 g PUFA) or EVOO (120 mg phytosterols, 5.6 g PUFA) were provided in 3 servings of study products per day (muffin, dinner roll, yogurt) as part of a weight-maintenance diet. The fatty acid and sterol compositions of the CO and EVOO as determined by Covance Laboratories (Madison, WI) are shown in Tables 1 and 2, respectively, and the nutrient compositions of the study products are presented in Table 3. Subjects reported to the clinic on Monday through Friday during both treatment periods for breakfast, including 1 serving of study product, between 0630 and 0930 AM. Subjects were provided lunch, dinner, and a snack, including 2 additional servings of study product, 1 of which was consumed with lunch and 1 with dinner, for consumption away from the clinic. Meals for Saturday and Sunday were dispensed on Fridays for consumption outside the clinic.

Meal plans were determined for the subjects based on energy needs using the Mifflin-St Jeor equation[17] to estimate resting energy expenditure, and summed with the average estimated energy expended in physical activity as assessed by the Stanford 7-day activity questionnaire.[18] A range of menu plans in 200-kcal increments from 1800 to 3600 kcal/d was created. The diets were designed to provide ~35% energy/d from fat (<10% SFA and <300 mg cholesterol), ~15% energy/d from protein, and ~50% energy/d from carbohydrate (with total daily fiber intake ~15 to 20 g/d). All foods in the rotating menus were identical in the 2 treatment conditions with the exception of the oils used to prepare the study foods (dinner roll, muffin, and yogurt). The average daily energy and nutrient intakes for the rotating menus were analyzed using Food Processor SQL Nutrition Analysis and Fitness Software (version 10.4.0, ESHA Research, Salem, OR). Subjects were also given a list of non-caloric beverages for ad libitum consumption. They were instructed to consume all of the study foods in their entirety and to avoid consuming any additional food or nonspecified drink items. In the event that a subject consumed a nonstudy food or caloric beverage, he or she was instructed to record the intake of the food/beverage item in a provided notebook and return to the clinic the uneaten portion of the nonstudy food or the label of the nonstudy item.

Compliance with the dietary instructions was evaluated by the study staff according to the returned food items from the lunch and dinner meals and snack; study product compliance was recorded as the percentage of scheduled intakes of study products consumed. Body weight was assessed weekly during each treatment period, and meal plans were adjusted, as needed, to ensure each subject maintained a stable body weight. Subjects were also instructed to maintain their usual physical activity level

Table 1 Fatty acid composition of CO and EVOO for fatty acids present at levels >0.05 g per 100 g in either oil*

Fatty Acids, calculated as TG	CO g per 100 g	EVOO
Total fatty acids	100	99.9
SFA	13.4	17.0
MUFA	28.1	68.2
PUFA	54.0	10.2
Trans	0.33	<0.02
16:0 Palmitic	11.5	14.4
16:1 Palmitoleic	0.10	1.48
17:0 Heptadecanoic	0.06	0.07
18:0 Stearic	1.74	2.76
9c-18:1 Oleic	28.4	66.8
Total 18:1 cis	29.0	69.6
18:2 Linoleic	55.6	10.0
Total 18:2 trans	0.24	<0.02
18:3 Linolenic	0.95	0.69
Total 18:3 trans	0.07	<0.02
20:0 Arachidic	0.40	0.41
20:1 Eicosenoic	0.27	0.25
22:0 Behenic	0.12	0.12
24:0 Lignoceric	0.16	0.06

CO, corn oil; EVOO, extra-virgin olive oil; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TG, triglycerides.

*Results are from analyses performed by Covance Laboratories (Madison, WI).

Table 2 Sterol composition of CO and EVOO*

Sterol	CO mg per 100 g	EVOO
Total sterols	989	198
Cholesterol	1.7	<1.0
Campesterol	178	7.5
Stigmasterol	68.8	2.0
Beta-sitosterol	617	146
Brassicasterol	<1.0	<1.0
Other sterols/stanols	125	42.7

CO, corn oil; EVOO, extra-virgin olive oil.

*Results are from analyses performed by Covance Laboratories (Madison, WI).

and other habits throughout the trial, and queries regarding compliance with these requests were made at weekly weigh-in visits.

Subjects

Eligible subjects were normally active men and nonpregnant, nonlactating women 18 to 74 years of age, inclusive, with body mass index ≥18.5 and <35.0 kg/m^2, fasting LDL-C ≥130 mg/dL and <200 mg/dL and fasting triglycerides (TG) ≤350 mg/dL. The subjects were required to have calculated energy needs of ≥1800 kcal/d.[17,18] Individuals who reported using, within 4 weeks before screening, medications intended to alter the lipid profile, or weight-loss drugs or programs, were not included, nor were those who used any foods or dietary supplements that might alter lipid metabolism within 2 weeks of screening. If a subject had an active infection or used antibiotics within 5 days of screening or any of the scheduled lipid blood draws, that visit was rescheduled and, where applicable, was extended until at least 5 days after the infection resolved or the antibiotic use had been completed.

Laboratory measurements

Laboratory measurements were conducted by EMH Reference Laboratory (Elmhurst, IL). Serum chemistry and hematology profiles were measured at screening; fasting (12 ± 2 hours, water only) lipid profiles were measured twice on separate days at baseline and the end of each 21-day treatment period. The lipid profile, including total-C, LDL-C, HDL-C, and TG, was analyzed according to the Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung and Blood Institute.[19] LDL-C concentration in mg/dL was calculated according to the Friedewald equation:[20] LDL-C = total-C – HDL-C –TG/5. Non–HDL-C was calculated as non–HDL-C = total-C – HDL-C.

Statistical analysis

All statistical analyses were conducted using SAS for Windows (version 9.1.3; Cary, NC). Efficacy analyses were performed in the group of randomized subjects who provided at least 1 postrandomization outcome data point during each treatment period (ie, efficacy-evaluable population). Safety analyses were completed for data collected from all subjects who were randomized and consumed at least 1 serving of study product.

An evaluable sample of 47 subjects was expected to provide 85% power (alpha = 0.05, 2-tailed) to detect a difference between treatments of 4% in the change in LDL-C (primary outcome variable) from baseline to the end of the treatment period, assuming a 9% pooled standard deviation. A sample of 57 subjects was randomized to allow for attrition and noncompliance. A randomization list for treatment sequence was generated using SAS with the seed number recorded. The a priori estimated difference in LDL-C response between the CO and EVOO treatments was 5.3%, based on calculations from Yu et al[21] and Demonty et al.[22] Other lipoprotein lipid and hemodynamic variables were considered secondary outcomes.

All tests of significance, unless otherwise stated, were performed at alpha = 0.05, 2-sided. Baseline comparability of treatment sequence groups for demographic, lipid, and blood pressure variables were assessed by analysis of variance, chi-square tests, or Fisher exact tests, as appropriate. The primary outcome variable was the least squares

Table 3 Nutrient composition of study products

Energy or nutrient	Muffin* (99.7 g per item)‡	Dinner roll† (92.2 g per item)‡	Yogurt (21.5 g per item)
Total energy, kcal	338.7	351.7	275.6
Carbohydrate, g	39.1	39.6	16.0
Protein, g	4.3	5.9	5.0
Fat, g	18.7	19.1	21.0
SFA, g (CO/EVOO)	2.4/2.6	2.5/2.7	2.7/2.9
MUFA, g (CO/EVOO)	5.1/13.4	5.2/13.5	5.8/15.3
PUFA, g (CO/EVOO)	10.2/2.1	10.3/2.2	11.5/2.2
Fiber, g	2.0	2.0	0.0
Cholesterol, mg	0.0	0.0	0.0

CO, corn oil; EVOO, extra-virgin olive oil; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

*There were 2 flavors of muffins (carrot cake and pumpkin) that differed slightly in total energy, carbohydrate, protein, PUFA, and fiber contents. The values shown represent an average of the 2 flavors for those nutrients and energy. The differences between flavors were small and unlikely to be material.

†There were 2 flavors of dinner rolls (rosemary garlic and wheat) that differed slightly in total energy, carbohydrate, protein, fat, SFA (differed in EVOO rolls only), MUFA, PUFA, and fiber contents. The values shown represent an average of the 2 flavors for those nutrients and energy. The differences between flavors were small and unlikely to be material.

‡Gram weights of muffin and dinner roll were before baking. Variability in moisture loss during baking resulted in slight differences in postbake weights.

mean (LSM) percent change from baseline (average of values on days −7 and 0) to the end of each treatment period (average of values on days 19 and 21 in each 21-day treatment period) in LDL-C concentration, and secondary outcome variables included LSM percent changes from baseline in total-C, HDL-C, non–HDL-C, TG, and the total-C/HDL-C ratio. Responses to treatment for the primary and secondary outcome variables, resting hemodynamic measurements, and body weight were assessed with repeated measures analysis of variance or covariance using SAS Proc Mixed, as were dietary intakes calculated from each subject's energy level menu. Initial repeated measures models contained terms for treatment, sequence, and treatment by sequence as fixed effects, with subject modeled as a random effect, and baseline (where available) as a covariate. Models were reduced in a stepwise manner until only significant ($P < .05$) terms or treatment remained. There was no evidence of clinically important heterogeneity in treatment response by sequence, thus the data from the 2 sequence groups were pooled, and the efficacy results are presented by treatment. Frequencies of adverse events in the 2 treatment conditions were compared using McNemar's test.

Assumptions necessary for application of parametric statistical procedures were investigated for each response measurement, and no marked departures were observed, so raw (untransformed) data were analyzed. Missing data were not imputed; thus, only observed data were included in the statistical models.

Results

Of the 109 subjects screened, 57 met the inclusion criteria and were randomized (Fig. 1) to treatment in the 2 sequences of CO/EVOO (n = 29) and EVOO/CO (n = 28). Dates for first subject screened and final subject visit were March 8, 2013, and August 1, 2013, respectively. A total of 54 subjects completed the study and were included in the efficacy evaluable sample. One subject discontinued because of an intolerance to eggs in the study meals, another discontinued for financial reasons, and a third discontinuation was at the investigator's discretion (subject behaved erratically toward staff and other subjects). Mean compliance with consumption of study products during the CO and EVOO treatments, respectively, was 96.2% (0.5%) and 97.5% (0.2%). The main reasons for missed consumption of study products were missed clinic appointments from a storm with flooding (1 day) and a power outage (1 separate day), each of which caused some subjects to miss a single day of study foods. There were no significant differences in compliance between treatment sequences or CO and EVOO conditions ($P = .208$). Demographic and baseline characteristics of the subjects are presented in Table 4. The mean age of the subjects was 53.8 years; a majority were female (64.8%) and of non-Hispanic white race/ethnicity (75.9%). Average total energy and nutrient intakes according to the rotating menus for each subject's energy level, presented in Table 5, confirmed that during the CO treatment period compared with the EVOO period, subjects consumed a significantly ($P < .001$ for all) larger percentage of energy from PUFA (10.2 vs 3.3%) and less SFA (8.0 vs 8.2%) and MUFA (9.8 vs 16.8%).

Mean fasting lipoprotein lipid levels at baseline, end of treatment, the LSM percent changes from baseline to the end of each treatment as well as differences between conditions in responses are shown in Table 6. Consumption of CO products, compared with EVOO products, resulted in significantly larger reductions in LDL-C (−7.4%), non–HDL-C (−7.7%), and total-C (−6.4%) ($P < .001$ for all). Furthermore, the total-C/HDL-C ratio was significantly reduced by 4.4% with CO compared with a slight 0.5% increase with EVOO ($P < .001$), and consumption of CO resulted

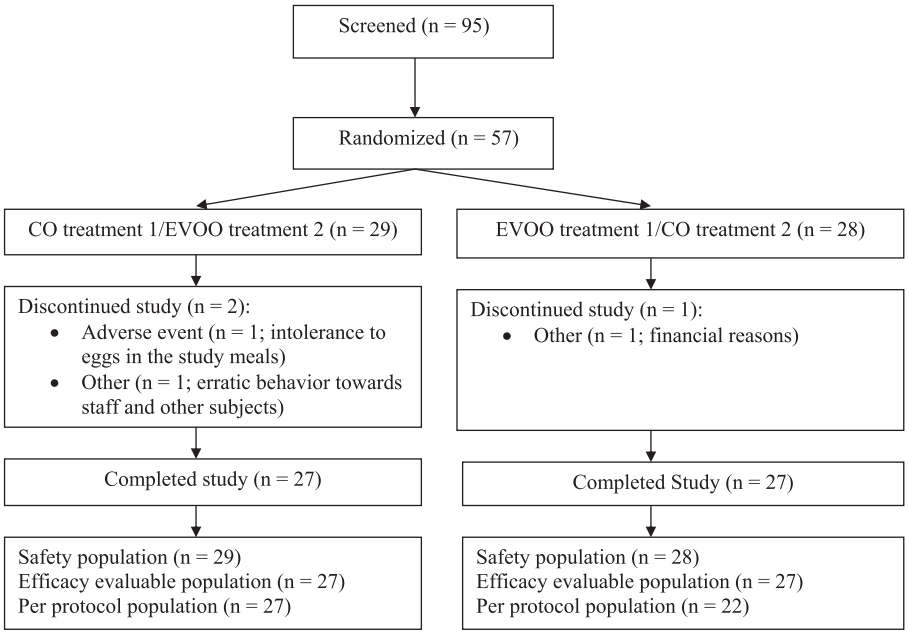


Figure 1 Subject disposition diagram. CO, corn oil; EVOO, extra-virgin olive oil.

in a significantly smaller increase in TG concentration (3.5%) compared with EVOO (13.0%) ($P = .007$). HDL-C responses were not significantly different between conditions (−3.4 vs −1.7% for CO vs EVOO). Figure 2 depicts the percentage of subjects during CO or EVOO conditions with an LDL-C reduction of at least 5%.

Results of the assessments of vital signs (systolic and diastolic blood pressures and heart rate) and body weight at baseline, end of treatment, the LSM changes from baseline to the end of each treatment, and the difference in responses are shown in Table 7. Small declines from baseline in systolic blood pressure and body weight occurred during both treatment conditions, but there were no statistically significant differences in responses between treatments. Diastolic blood pressure rose by a mean of 0.1 mm Hg with CO compared with a mean decline of 1.5 mm Hg with EVOO ($P = .042$). Mean heart rate also increased slightly during the CO condition (1.5 beats/min) compared with a reduction in the EVOO condition (0.6 beats/min) ($P = .022$).

A total of nine subjects (15.8%) reported at least 1 adverse event during the CO treatment and 12 subjects (21.4%) during the EVOO treatment ($P = .467$). Adverse events that were experienced by >3% of subjects in a treatment condition included change in bowel habits (EVOO, n = 2), constipation (EVOO, n = 3), diarrhea (CO, n = 3; EVOO, n = 1), flatulence (CO, n = 2; EVOO, n = 1), nausea (CO, n = 2; EVOO, n = 1), weight decrease (CO, n = 2; EVOO, n = 1), myalgia (CO, n = 1; EVOO, n = 2), rhinitis (CO, n = 2), and upper respiratory tract infection (EVOO, n = 3). None of the adverse events was classified as severe or serious. In terms of relationship to study product, 9 events were classified as probably or definitely related to consumption of EVOO (change in bowel habits [n = 1], constipation [n = 3], dyspepsia [n = 1], weight decrease [n = 1], and weight increase [n = 1]) and 2 events with CO (both weight decrease).

Discussion

The results of this study demonstrate that ∼54 g/d of CO, when consumed as part of a weight-maintenance, low-SFA and cholesterol diet by men and women with hypercholesterolemia resulted in significantly larger reductions

Table 4 Demographic and selected baseline characteristics of subjects*

Characteristic	Value, N = 54
	n (%)
Male	19 (35.2)
Female	35 (64.8)
Race/ethnicity	
Non-Hispanic White	41 (75.9)
Non-Hispanic Black/African American	8 (14.8)
Non-Hispanic Other	3 (5.6)
Hispanic/Latino	2 (3.7)
	Mean (SEM)
Age, y	53.8 (1.3)
Body mass index, kg/m^2	28.2 (0.5)
Fasting plasma glucose, mg/dL	96.7 (1.1)
Physical activity MET score above basal	91.1 (3.5)

MET, metabolic equivalent; SEM, standard error of the mean.
*Baseline for lipids, heart rate, blood pressure, and body weight are shown in Tables 6 and 7, as appropriate.

Table 5 Average daily energy and nutrient intakes for subjects (N = 54) during the CO and EVOO treatment periods (calculated from the menus for each subject's energy level)*,†

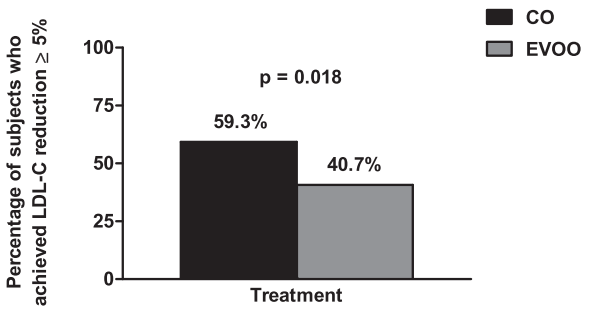
Parameter	CO	EVOO
	Mean (SEM)	
Energy (kcal/d)	2483 (63.1)	2483 (63.1)
Carbohydrate (% energy)	50.0 (0.1)	50.0 (0.1)
Protein (% energy)	16.9 (0.1)	16.9 (0.1)
Total fat (% energy)	34.0 (0.1)	34.0 (0.1)
SFA (% energy)	8.0 (0.1)	8.2 (0.1)‡
MUFA (% energy)	9.8 (0.3)	16.8 (0.4)‡
PUFA (% energy)	10.2 (0.2)	3.3 (0.1)‡
Ratio of PUFA/SFA	1.3 (0.1)	0.4 (0.0)‡
Dietary fiber (g/d)	22.7 (0.4)	22.7 (0.4)
Cholesterol (mg/d)	132.4 (4.4)	132.4 (4.4)

CO, corn oil; EVOO, extra-virgin olive oil; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SEM, standard error of the mean; SFA, saturated fatty acids.

*Food Processor® SQL Nutrition Analysis and Fitness Software (version 10.4.0, ESHA Research, Salem, OR). Calculations were based on the menus during the final week of participation and assumed 100% compliance with study food consumption. The number of subjects at each kcal level was: 1800 (n = 5), 2000 (n = 6), 2200 (n = 10), 2400 (n = 10), 2600 (n = 11), 2800 (n = 4), 3000 (n = 2), 3200 (n = 3), 3400 (n = 2), 3600 (n = 4).

†Values differed between treatments only for the nutrients which differed between study products.

‡$P < .001$ between CO and EVOO.



[a]N = 54 subjects.

Figure 2 Percentage of subjects with reductions from baseline in low-density lipoprotein cholesterol (LDL-C) of ≥5% according to corn oil (CO) or extra-virgin olive oil (EVOO) treatment.

from baseline in LDL-C, non–HDL-C, and the total-C/HDL-C ratio compared with EVOO. These results are consistent with those from a crossover study conducted in 28 healthy young men (19 to 31 years of age) who, for 2 weeks, consumed a diet with 80 g CO/d vs a MUFA-rich mixture of 68 g olive oil plus 12 g sunflower oil/d as the main fat source in a normal, balanced diet. In that trial, the PUFA-rich diet, but not the MUFA-rich diet, resulted in significant decreases from baseline in total-C, LDL-C, and very-low-density lipoprotein-C levels ($P < .01$).[23] However, another previously published comparison of CO, olive oil, and canola oil failed to demonstrate a significant difference in LDL-C responses between oils when consumed as two-thirds of the total daily fat for 32 days by 15 men and women with hypercholesterolemia and a mean age of 61 years, as part of the National Cholesterol Education Program Step 2 diet (<30% kcal from fat, <7% kcal from SFA, cholesterol < 200 mg/d).[24]

HDL-C responses were not significantly different between CO and EVOO conditions in the present trial. Some studies have shown that PUFA-rich, but not MUFA-rich, oils decrease HDL-C,[25] and olive oil consumption has also been reported to maintain, or increase, levels of HDL-C when compared with carbohydrates.[13] When compared directly with PUFA-rich oils, the effects of olive oil on HDL-C have been inconsistent. In Lichtenstein et al's comparison of CO, olive oil, and canola oil, HDL-C increased significantly from baseline with CO and canola oil consumption (9% and 7%, respectively), whereas a rise in HDL-C of 4% with olive oil did not reach statistical significance.[24] Howell et al's examination of lipid responses to CO and olive oil alone or with supplemental phytosterols indicated no significant difference in HDL-C between treatments.[26] TG concentrations in the present trial increased with both the CO and EVOO conditions, possibly as a result of increasing carbohydrate content as a percentage of energy consumed, compared with the subjects' habitual diets. However, the

Table 6 Fasting lipoprotein lipids at baseline, EOT, LSM percent changes from baseline, and differences between treatments in responses (N = 54)

Parameter	Baseline, mg/dL	CO EOT, mg/dL	EVOO EOT, mg/dL	CO, %Δ	EVOO, %Δ	% Diff.	
	Mean (SEM)			LSM (SEM)			*P* value
LDL-C	153.3 (3.5)	136.1 (3.3)	147.1 (3.4)	−10.9 (1.5)	−3.5 (1.5)	−7.4	<.001
Non–HDL-C	178.3 (3.7)	161.4 (3.9)	174.7 (3.8)	−9.3 (1.4)	−1.6 (1.4)	−7.7	<.001
Total-C	225.7 (3.9)	206.8 (4.0)	221.1 (4.0)	−8.2 (1.1)	−1.8 (1.1)	−6.4	<.001
HDL-C	47.4 (1.7)	45.5 (1.5)	46.3 (1.6)	−3.4 (1.2)	−1.7 (1.2)	−1.7	.192
TG	124.8 (7.2)	126.6 (8.7)	138.0 (9.5)	3.5 (4.2)	13.0 (4.2)	−9.5	.007
Total-C/HDL-C	5.0 (0.2)	4.8 (0.2)	5.0 (0.2)	−4.4 (1.5)	0.5 (1.5)	−4.9	<.001

CO, corn oil; Diff, difference; EOT, end of treatment; EVOO, extra-virgin olive oil; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LSM, least squares mean; non–HDL-C, non–high-density lipoprotein cholesterol; SEM, standard error of the mean; Total-C, total cholesterol; TG, triglycerides.

Table 7 Vital signs and body weight at baseline, EOT, LSM changes from baseline, and differences between treatments in responses (N = 54)

	Baseline	CO EOT	EVOO EOT	CO, Δ	EVOO, Δ	Diff.	
Parameter	Mean (SEM)			LSM (SEM)			*P* value
SBP, mm Hg	119.5 (1.6)	118.3 (1.6)	117.7 (1.6)	−1.2 (1.0)	−1.9 (1.0)	0.7	.443
DBP, mm Hg	75.3 (1.2)	75.4 (1.3)	73.8 (1.2)	0.1 (0.8)	−1.5 (0.8)	1.6	.042
Heart rate, beats/min	68.7 (1.1)	70.2 (1.2)	68.1 (1.0)	1.5 (0.7)	−0.6 (0.7)	2.1	.022
Body weight, kg	79.5 (1.9)	78.9 (1.9)	79.0 (1.8)	−0.6 (0.2)	−0.5 (0.2)	−0.1	.746

CO, corn oil; DBP, diastolic blood pressure; Diff, difference; EOT, end of treatment; EVOO, extra-virgin olive oil; LSM, least squares mean; SBP, systolic blood pressure; SEM, standard error of the mean.

degree of TG elevation was smaller with CO compared with EVOO. Although the subjects in this trial were generally not hypertriglyceridemic, these results suggest a potential benefit of CO for minimizing TG elevations.

One potential factor contributing to the lipid effects of CO is its higher phytosterol content relative to EVOO (528 mg vs 120 mg in the 4 tablespoons of oil administered per day). Phytosterols have been shown to alter intestinal cholesterol metabolism through several mechanisms, including competition with cholesterol for incorporation into mixed micelles; modulation of the effects of Niemann-Pick C1–like 1 transporters and scavenger class B type 1 receptors to lower intestinal sterol uptake. Also, absorption of sterols into enterocytes triggers upregulation of adenosine triphosphate binding cassette G5 and G8 transporters, thereby increasing the efflux of sterols into the intestinal lumen for excretion.[27–29]

Ostlund and colleagues evaluated cholesterol absorption after a single meal test with native CO and CO stripped of phytosterols, and showed significantly greater cholesterol absorption after consumption of the phytosterol-free CO ($P = .005$).[30] Howell et al addressed the hypothesis that phytosterols in CO accounted for the differential action on lipoprotein lipids compared with OO by administering 10-day diets containing CO, olive oil, and olive oil supplemented with phytosterols at twice the level found naturally in CO to 16 normolipidemic men and women.[26] Total-C levels were higher after both olive oil treatments vs CO, and nonsupplemented olive oil also resulted in significantly greater LDL-C compared with CO. Inclusion of the phytosterol mixture with olive oil appeared to suppress the LDL-C difference between olive oil and CO. These results suggested that phytosterols were responsible for at least part of the lipid effects of CO compared with olive oil.

The higher PUFA content of CO vs EVOO (29.7 g vs 5.6 g PUFA in the 4 tablespoons of oil administered per day) would also be expected to contribute to the difference in lipoprotein lipid responses between treatments. Because EVOO contains a slightly higher proportion of SFA than CO, the daily intake of SFA was expected to be 7.2 g for CO and 9.2 g for EVOO, resulting in a 0.7% difference in energy intake based on the average energy intake of 2483 kcal/d. However, analysis of study menus indicated that the mean difference between treatments was 0.2% of energy, which is likely to be attributable to rounding error and slight differences in percentages of energy contributed by different fatty acids across energy intake categories. Using the equations from Yu et al,[21] which predict the amount of cholesterol lowering attributable to differences in dietary intakes of MUFA, PUFA, and specific SFA (12:0, 14:0, 16:0, 18:0), consumption of CO, compared with EVOO, was predicted to result in a difference in LDL-C of −2.4% at the average energy intake of the subjects. The observed difference between CO and EVOO conditions for LDL-C was −7.4%, leaving 5.0% of the effect, which might be attributable to other components of the CO and EVOO, including the higher phytosterol content of CO.

Research regarding the effects of CO vs olive oil on cardiovascular outcomes has been limited to date. An early randomized, controlled trial suggested a possible adverse effect of CO consumption on cardiovascular disease, but several issues suggest that those results should be interpreted with caution.[31] Rose et al examined the effects on lipids and cardiovascular events of consumption of CO or olive oil in a restricted fat diet compared with a control group that received no advice on dietary fat in 80 patients with a history of myocardial infarction or angina. Serum cholesterol levels declined significantly in the CO group throughout the study, whereas cholesterol rose slightly (but not significantly) in the control and olive oil groups.[31] Among the proportion of patients still enrolled at 2 years of follow-up, fewer remained free from major cardiac events in the olive oil (57%) and CO groups (52%) vs the control group (75%). Many of the patients complained of side effects (distaste, nausea, diarrhea) with the prescribed oil supplements. This led to substantially diminished compliance with oil consumption; by the end of the study, the estimated amount of oil consumed was ∼50 g/d compared with the 80 g/d prescribed. Also, there was a relatively large number of dropouts for noncardiac reasons, which was the rationale for expressing cardiovascular outcomes as a proportion of only those subjects still in the trial (approximately half of the original participants).

The Minnesota Coronary Survey was a randomized trial that compared the effects of a 39% fat control diet (18% SFA, 5% PUFA, 16% MUFA, 446 mg/d cholesterol) with a 38% fat treatment diet (9% SFA, 15% PUFA, 14% MUFA,

166 mg/d cholesterol) on serum cholesterol and incidence of myocardial infarction, sudden death, and all-cause mortality among 9057 patients in 6 mental hospitals and one nursing home.[32] The mean duration on each diet was 384 days, although some subjects were followed as long as 4.5 years, and mean serum cholesterol declined an average of 14.5% for the treatment group and was essentially unchanged in the control group (decline of 0.7%). There were no significant differences between groups in the primary endpoints of acute and silent myocardial infarctions and sudden deaths. The authors proposed that a reduction might have been detected if the treatment period had been longer, and/or if the population was limited to persons in the age range most likely to benefit (35 to 55 years of age), in whom there appeared to be a trend toward benefit.

In the present study, systolic blood pressure declined with both treatments (no difference between CO and EVOO); however, both diastolic blood pressure and heart rate rose slightly during the CO condition compared with modest declines in the EVOO condition (both $P < .05$ for CO vs EVOO). Results from prior investigations have shown that olive oil consumption decreases blood pressure and is associated with a reduced risk for developing hypertension.[33–36] In a 4-year follow-up of the Prevention with Mediterranean Diet study, a randomized clinical trial of the Mediterranean diet in 7447 men and women in Spain, participants who followed a Mediterranean diet supplemented with either EVOO or with nuts experienced significantly larger reductions in diastolic blood pressure than subjects who received counseling to follow a low-fat diet.[11,36] The blood pressure-lowering effect of olive oil may be due to its high oleic acid content.[37] Soybean oil, which, like CO, is low in oleic acid, has not been shown to affect blood pressure.[37] The small reduction in heart rate with EVOO would also be considered potentially beneficial, because lower heart rate is associated with lower risk for cardiovascular disease.[38] However, the authors are not aware of any study that has been specifically designed to investigate the effects of olive oil vs CO on heart rate. Therefore, this finding is of uncertain clinical relevance and possible effects of EVOO on heart rate and other hemodynamic variables should be investigated further.

Subjects had excellent compliance with consumption of the study products and meals, which were provided by the clinic. The inclusion of the study oils in food products that individuals would be likely to consume in everyday life (ie, muffins, dinner rolls, and yogurt) allow generalizability of these results to a free-living hypercholesterolemic population. Although there were a few isolated instances of changes in body weight, with increases and decreases observed during both treatment conditions, mean body weight changed from baseline by ≤0.6 kg, and there were no differences in body weight changes between conditions, suggesting that the meal plan design and monitoring were generally successful at maintaining stable body weights.

A limitation of this trial was the inclusion of only one level of intake for each oil. The dose-response profiles with regard to the lipid-altering effects of PUFA and MUFA have not been fully described. The dose-response to phytosterol consumption, 1 purported explanation for the LDL-C–lowering effect of CO, has been investigated.[24,39] Another limitation of the trial was the relatively homogeneous sample with regard to type of dyslipidemia. Although all subjects had elevated LDL-C, the mean baseline TG concentration was in the normal range (<150 mg/dL). Additional research will be needed to evaluate the effects of CO vs EVOO in subjects with other dyslipidemias.

Conclusion

The results of this study demonstrated that consumption of CO, as part of a weight-maintenance, low-SFA, and low-cholesterol diet, by men and women with hypercholesterolemia, resulted in significantly larger reductions in total-C, LDL-C, and non–HDL-C compared with EVOO.

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