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Prescription omega-3-acid ethyl esters reduce fasting and postprandial triglycerides and modestly reduce pancreatic β-cell response in subjects with primary hypertriglyceridemia

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ABSTRACT

Treatment with prescription omega-3-acid ethyl esters (POM3) reduces triglycerides (TG) and TG-rich lipoprotein particles, but has been associated with increased fasting glucose (2–6 mg/dL). This double-blind, randomized, controlled crossover trial in 19 men and women with hypertriglyceridemia (fasting TG ≥ 150 and ≤ 499 mg/dL) examined lipid responses and indices of insulin sensitivity and secretion following a liquid meal tolerance test. Six weeks treatment with POM3 vs. corn oil resulted in significant lower mean fasting (-50.1 mg/dL, $p < 0.001$) and postprandial TG (-76.1 mg/dL, $p < 0.001$), higher mean fasting glucose (2.8 mg/dL, $p = 0.062$), reduced mean disposition index (2.1 vs. 2.4, $p = 0.037$), and no change in the median Matsuda composite insulin sensitivity index (3.3 vs. 3.2, $p = 0.959$). These results suggest that POM3 slightly reduces pancreatic β-cell responsiveness to plasma glucose elevation, which may contribute to the rise in fasting glucose sometimes observed with POM3.

1. Introduction

Treatment with prescription omega-3-acid ethyl esters (POM3) reduces the circulating concentrations of triglycerides (TG) and TG-rich lipoprotein particles [1–3]. Insulin resistance is commonly associated with hypertriglyceridemia [4–6]. The insulin resistant individual generally has impairments in the ability of a given concentration of insulin to stimulate peripheral glucose uptake, to suppress hepatic glucose output, and to suppress the release of free fatty acids from adipose depots [7,8]. Insulin resistance is a central pathophysiologic factor in the development of type 2 diabetes mellitus [8].

A majority of patients with hypertriglyceridemia treated with POM3 will have glucose intolerance (pre-diabetes or diabetes), or be at risk for its development. Results from several studies have shown that POM3 treatment increases fasting glucose concentration modestly (2–6 mg/dL) in patients with and without type 2 diabetes mellitus [9–12]. This increase in fasting glucose, however, does not appear to be associated with increases in circulating concentrations of glycosylated hemoglobin [9,11,12] or fructosamine [1,3], suggesting that the weighted average daily plasma glucose concentration is not markedly altered.

Although results from a number of clinical studies on omega-3 fatty acid intake and carbohydrate metabolism in individuals with diabetes have been published [9–11], most of these trials were not completed in subjects with hypertriglyceridemia. Treatment of hypertriglyceridemia with POM3 has been shown to lower fasting [3] and postprandial [13,14] free fatty acid concentrations in some studies. This might be expected to improve insulin sensitivity since chronically elevated levels of free fatty acids contribute to the maintenance of an insulin resistant state [8,15].

Most prior trials of omega-3 fatty acids and carbohydrate metabolism have used fish oil in the TG form, which provides approximately 300 mg of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per gram of oil consumed, thus delivering ~600 mg of non-omega-3 fatty acids. The relatively high additional energy content that results from providing therapeutic doses of omega-3 fatty acids in fish oil and the concurrent delivery of significant amounts of non-omega-3 fatty acids along with EPA and DHA bring into question whether the results from fish oil studies are representative of those that might derive from the use of a more concentrated form of EPA+DHA in subjects with hypertriglyceridemia.

This study was designed to assess the effects of 4 g/d POM3 (delivering 3.6 g/d EPA+DHA), compared with a corn oil control, on indices of insulin sensitivity and pancreatic β-cell function, as well as aspects of the fasting and postprandial lipid and lipoprotein profiles, in subjects with hypertriglyceridemia.

2. Patients and methods

2.1. Study design

This study had a double-blind, randomized, controlled crossover design which included two screening/baseline visits (weeks −1

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and 0), four treatment visits (weeks 4, 6, 12, and 14) and a telephone call at the end of a two-week wash-out period (week 8). Subjects were randomly assigned to receive either 4 g/d POM3 (Lovaza®) or 4 g/d control (corn oil) capsules for the first of two six-week treatment phases. After completion of the wash-out period, subjects crossed over to receive the study product that they had not received during the first phase for a second six-week treatment phase. The primary objective of the trial was to examine the difference between treatments in insulin sensitivity. The study was conducted at Provident Clinical Research in Addison, IL according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2000), and the United States 21 Code of Federal Regulations, including approval of the protocol by an institutional review board (Quorum Review, Inc., Seattle, WA). Informed consent for the study was obtained from all subjects before protocol-specific procedures were carried out, and subjects were informed of their right to withdraw from the study at any time.

2.2. Subjects

Eligible participants included men and postmenopausal women between 18 and 79 years of age, inclusive, with fasting TG ≥ 150 and ≤ 499 mg/dL and low-density lipoprotein cholesterol (LDL-C) < 200 mg/dL after discontinuation of lipid-altering agents other than stable dose statin therapy (defined as no initiation or dose alteration within four weeks of the screening visit). Persons with diabetes or fasting glucose ≥ 126 mg/dL were not enrolled, nor were individuals with coronary heart disease (CHD), a CHD risk equivalent [16], or those with a history of cancer; clinically important cardiac, renal, hepatic, endocrine, pulmonary, biliary, pancreatic, gastrointestinal, or neurologic disorders; body mass index > 45.0 kg/m^2; elevated serum creatinine, alanine aminotransferase or aspartate aminotransferase levels; or uncontrolled hypertension (≥ 160 mmHg systolic and/or ≥ 100 mmHg diastolic resting blood pressure).

Use of non-study-related lipid-altering drugs, except for stable dose statin therapy, was not allowed within four weeks prior to screening or throughout the trial. Up to two servings of fish per week were allowed, but use of non-study related omega-3 fatty acids with ≥ 1.0 g/d of EPA, DHA, or a combination of EPA and DHA in drug, supplement, or food form within eight weeks of screening was exclusionary. Other dietary supplements known to alter lipid metabolism (e.g., sterol/stanol products, red rice yeast, > 200 mg niacin, and psyllium) were excluded within two weeks of screening. Medications known to affect carbohydrate metabolism were also prohibited. Subjects with extreme habits that, in the opinion of the investigators, had the potential to confound the results were excluded. This included alcohol and substance abuse as well as atypical dietary patterns (e.g., Atkins diet, very high protein/low carbohydrate diet) and exercise habits (e.g., serious athletic training). The use of weight loss drugs, supplements, or programs and corticosteroids, antibiotics, or cyclic hormone therapy was also prohibited, as was unstable use of antihypertensive medications or thyroid hormone replacement.

2.3. Liquid meal tolerance test procedure

At the end of each treatment phase (weeks 6 and 14) subjects completed a liquid meal tolerance test (LMTT) after an overnight fast (9–15 h). Subjects were instructed to avoid engaging in any vigorous physical activity during the 48-h period prior to the LMTT, and to consume at least 150 g/d carbohydrate during the 24 h prior to the LMTT. A 24 h dietary recall was used to verify compliance with carbohydrate intake instructions. Subjects were administered a liquid meal, to be consumed within 10 min, which consisted of two 8 oz servings of Ensure® Creamy Milk Chocolate or Homemade Vanilla Shake (Abbott Nutrition, Columbus, OH) providing 500 kcal, 80 g carbohydrate, 12 g fat and 18 g protein. After consumption of half of the liquid meal, subjects consumed 4 capsules of the study product that they had been taking during that treatment period, and then finished the liquid meal. Venous blood samples were collected from an indwelling intravenous catheter in the antecubital space for analysis of plasma glucose and insulin concentrations at $t = -5, -1, 30, 60, 90, 120, 180$, and 240 min, where $t = 0$ was the start of the liquid meal consumption. In addition, blood samples were analyzed for a lipid profile [total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and TG] at $t = 120$ and 240 min; and free fatty acids at $t = -1, 30, 60, 90, 120$, and 240 min.

Plasma glucose and insulin concentrations were used to determine LMTT indices of insulin sensitivity and secretion. The Matsuda composite insulin sensitivity index (MISI) was calculated as $10{,}000/(G_0 \times I_0 \times G_m \times I_m)^{0.5}$ where G_0 and I_0 were pre-meal values for glucose (G) and insulin (I) and G_m and I_m were mean post-meal values during the first 120 min of the test [17–20]. Total areas under the curve (AUC) from 0 to 120 min and from 0 to 240 min for free fatty acids, glucose and insulin were determined using the trapezoidal rule. The insulin secretion index (ISI) was calculated as the total $AUC_{0-120\ min}$ for plasma insulin divided by the total $AUC_{0-120\ min}$ for plasma glucose [21]. Pancreatic β-cell function was determined by calculation of a disposition index according to the formula: MISI × ISI [21]. Values for homeostasis model assessment (HOMA) of insulin sensitivity (HOMA%S) and β-cell function (HOMA%B) were calculated from fasting glucose and insulin values using the HOMA calculator available at www.dut.ox.ac.uk.

2.4. Additional clinic visit assessments

At each clinic visit, a fasting lipid profile (TC, LDL-C, HDL-C, non-HDL-C, and TG) was obtained, vital signs were measured, adverse events were assessed, and compliance with study product consumption was determined. Lipoprotein lipids were analyzed according to the Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung and Blood Institute. LDL-C concentration in mg/dL was calculated with the Friedewald equation [22] as follows: LDL-C = TC–HDL-C–TG/5. In instances where the TG concentration was ≥ 400 mg/dL, LDL-C was not calculated. Non-HDL-C was calculated as the difference between TC and HDL-C. Additionally, fasting chemistry (including glucose, insulin, and fructosamine) and hematology profiles were measured at screening/baseline and the end of each treatment phase. All clinical laboratory analyses were performed by Medpace Reference Laboratories (Cincinnati, OH) as described previously [3].

2.5. Statistical analyses

Statistical analyses were generated using SAS version 9.2 (SAS Institute, Cary, NC). All tests of statistical significance were completed at the 5% level, two-tailed. Analyses were conducted in both a modified intent-to-treat sample, which included data for all subjects who were randomized and provided at least one post-randomization outcome data point during each treatment phase, and in a per protocol sample which excluded subjects with poor compliance or protocol violations. The modified intent-to-treat and per protocol samples were defined prior to breaking the blind. Safety analyses were completed in all subjects who were randomized and consumed at least one dose of study product. Sample size calculations conducted during planning projected that an evaluable sample of 19 subjects would provide 80% power (5% α-level, two-tailed) to detect a 2.1 unit difference between

control and active treatments in the MISI, assuming a 3.0 unit standard deviation.

Baseline comparability of treatment sequence groups was assessed by analysis of variance (ANOVA; continuous variables) and Fisher's Exact test (categorical variables). Repeated measures ANOVA or analysis of covariance was used to assess responses to treatment. The initial repeated measures models contained terms for treatment, period and sequence as fixed effects, with subject modeled as a random effect. For variables that were measured at baseline as well as at the end of each treatment period, the baseline value was included in the model as a covariate. Models were reduced in a stepwise manner until only significant ($p < 0.05$) terms or treatment remained. The method of last observation carried forward, in which the value of the previous non-baseline visit in the same treatment phase was carried forward to the subsequent visit, was utilized for incomplete data within each treatment phase in the modified intent-to-treat analyses. Only measured values were utilized for the per protocol analysis. Model residuals were examined, and for variables with clear evidence of non-normality, rank transformations were employed and the model rerun. Sensitivity analyses showed that there were no statistically significant or clinically meaningful treatment by sequence or treatment by period interactions. Therefore, outcome variable data, vital signs, body weight, and clinical laboratory results from the two sequence groups were pooled. Frequencies of adverse events in the two treatment conditions were compared using McNemar's test. Values for continuous variables are reported as mean ± standard error of the mean (SEM) except for variables that were not normally distributed, which are presented as medians and interquartile limits.

3. Results

3.1. Subjects

A total of 51 subjects were screened for participation in this trial, and 23 were randomized to treatment with POM3/control ($n=11$) or control/POM3 ($n=12$). Of these, 22 subjects were included in the modified intent-to-treat population [one subject dropped from the study prior to completing both treatment phases due to adverse events of mild lower leg cramping and moderate headache]. Three additional subjects were removed from the per protocol population due to low compliance with study product consumption ($n=1$), a change in medication use (sex hormones; $n=1$), and excessive weight gain (6.2%; $n=1$). The results described herein are for the 19 subjects (POM3/control $n=9$; control/POM3 $n=10$) in the per protocol sample except where otherwise indicated. Based on capsule counts and subject interviews, mean ± SEM compliance was 98.6 ± 0.6% for POM3 and 99.5 ± 1.2% for control. Demographic and baseline characteristics (pooled for both treatment sequences) are presented in Table 1.

Table 1
Subject demographic and baseline characteristics.[a]

Characteristic	*N*=19
	Number (%)
Male	9 (47.4%)
Female	10 (52.6%)
Race/ethnicity	
Non-Hispanic White	18 (94.7%)
Asian/Pacific Islander	1 (5.3%)
Smoking status	
Non-smoker	13 (68.4%)
Current smoker	2 (10.5%)
Past smoker	4 (21.1%)
Statin user	1 (0.1%)
	Mean (SEM)
Age (years)	56.4 (2.7)
Body mass index (kg/m^2)	29.0 (1.2)
Systolic blood pressure (mmHg)	122.3 (2.6)
Diastolic blood pressure (mmHg)	73.9 (1.6)
Fasting glucose (mg/dL)	103.1 (2.4)
Fasting insulin (μU/mL)	10.8 (2.2)
Fructosamine (μmol/L)	240.7 (3.1)
Fasting lipids (mg/dL)	
LDL-C	131.9 (7.1)
Non-HDL-C	171.7 (6.4)
HDL-C	47.3 (3.2)
TC	219.0 (7.9)
TG	198.7 (13.2)
Alcoholic drinks/week	1.3 (0.4)

Abbreviations: HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, Non-HDL-C=non-high-density lipoprotein cholesterol, SEM=standard error of the mean, TC=total cholesterol, and TG=triglycerides.

[a] There were no significant differences between treatment sequences (POM3/control $n=10$; control/POM3 $n=9$) in these variables. Data presented are for the per protocol analysis population.

3.2. Glucose homeostasis

Measures of insulin sensitivity and secretion from the LMTTs and fasting HOMA, free fatty acid, glucose, insulin, and fructosamine values are shown in Table 2. Glucose, insulin, and free fatty acid concentrations obtained during the LMTT are shown in Fig. 1, Panels A, B, and C, respectively. Mean fasting glucose trended higher at the end of the POM3 vs. control treatments (104.9 ± 2.9 vs. 102.2 ± 2.9 mg/dL, $p=0.062$), but mean fasting insulin concentrations were not significantly different ($p=0.833$). The median MISI did not differ significantly between treatments ($p=0.959$), however the mean disposition index was significantly lower during POM3 treatment compared with control (2.1 ± 0.20 vs. 2.4 ± 0.25, $p=0.037$). There were no statistically significant differences between treatments in fasting or LMTT glucose homeostasis measurements.

3.3. Lipids

Fasting lipid variables and postprandial TG (values averaged over the 240 min of the LMTT) following control and POM3 treatments and differences between treatments are shown in Table 3, and TG concentrations obtained at 120 and 240 min of the LMTT are shown in Fig. 1, Panel D. Mean fasting TG (156.3 ± 9.3 vs. 206.5 ± 15.0 mg/dL, $p<0.001$) and postprandial TG (213.3 ± 14.7 vs. 289.3 ± 22.5 mg/dL, $p<0.001$) were significantly lower during POM3 treatment compared with control. There were no statistically significant differences between treatments in other fasting lipid variables.

3.4. Modified intent-to-treat sample

The results for the modified intent-to-treat sample were generally similar to those in the per protocol analysis set. However, the mean difference between treatments in the disposition index did not reach statistical significance in the modified intent-to-treat sample (POM3 2.3 ± 0.3 vs. control 2.4 ± 0.2, $p=0.148$).

Table 2
Measures of insulin sensitivity and secretion from liquid meal tolerance tests and fasting homeostasis model assessments and free fatty acids, glucose, insulin, and fructosamine concentrations ($N=19$).[a]

Parameter	Control	POM3	Difference POM3 − control	P-value[b]
	Mean (SEM) or median (interquartile limits)			
Matsuda insulin sensitivity index	3.2 (1.9, 7.1)	3.3 (2.0, 7.4)	0.03 (−1.5, 1.8)	0.959
Disposition index	2.4 (0.25)	2.1 (0.20)	−0.32 (0.14)	0.037
Insulin secretion index [(μU/mL)/(mg/dL)]	0.73 (0.09)	0.66 (0.09)	−0.07 (0.04)	0.073
Total FFA $AUC_{0-120\ min}$ (mEq × min/L)	45.6 (3.8)	44.1 (2.7)	−1.6 (3.5)	0.651
Total FFA $AUC_{0-240\ min}$ (mEq × min/L)	82.3 (6.0)	77.8 (4.4)	−4.5 (5.3)	0.411
Total glucose $AUC_{0-120\ min}$ (mg × min/dL)	14,398 (669)	14,394 (612)	−3.6 (426)	0.993
Total glucose $AUC_{0-240\ min}$ (mg × min/dL)	26,181 (935)	25,966 (823)	−215 (757)	0.780
Total insulin $AUC_{0-120\ min}$ (μU × min/mL)	10,550 (1376)	9538 (1369)	−1012 (662)	0.144
Total insulin $AUC_{0-240\ min}$ (μU × min/mL)	15,684 (2033)	14,199 (1973)	−1485 (1145)	0.211
HOMA%S	72.6 (54.1, 176.4)	74.3 (53.5, 155.9)	−0.6 (−38.8, 42.4)	0.744
HOMA%B	89.8 (8.8)	86.1 (9.6)	−3.8 (3.4)	0.285
Fasting FFA (mEq/L)	0.56 (0.05)	0.59 (0.05)	0.03 (0.05)	0.604
Fasting glucose (mg/dL)	102.2 (2.9)	104.9 (2.9)	2.8 (1.4)	0.062
Fasting insulin (μU/mL)	10.8 (1.6)	10.9 (1.7)	0.14 (0.68)	0.833
Fasting fructosamine (μmol/L)	235.4 (5.7)	237.0 (5.1)	1.6 (4.7)	0.809

Abbreviations: $AUC_{0-120\ min}$ = area under the curve from 0 to 120 min, $AUC_{0-240\ min}$ = area under the curve from 0 to 240 min, FFA = free fatty acids, HOMA%B = homeostasis model of β-cell function, HOMA%S = homeostasis model of insulin sensitivity, POM3 = prescription omega-3-acid ethyl esters, and SEM = standard error of the mean.

[a] Data from the two treatment sequences (POM3/control and control/POM3) were pooled. Treatment period I was the average for values at weeks 4 and 6; treatment period II was the average for values at weeks 12 and 14.

[b] P-values are for treatment effect from the final analysis of variance model. For variables that were not normally distributed, analyses were performed on ranked values and medians (interquartile limits) are presented for control and POM3.

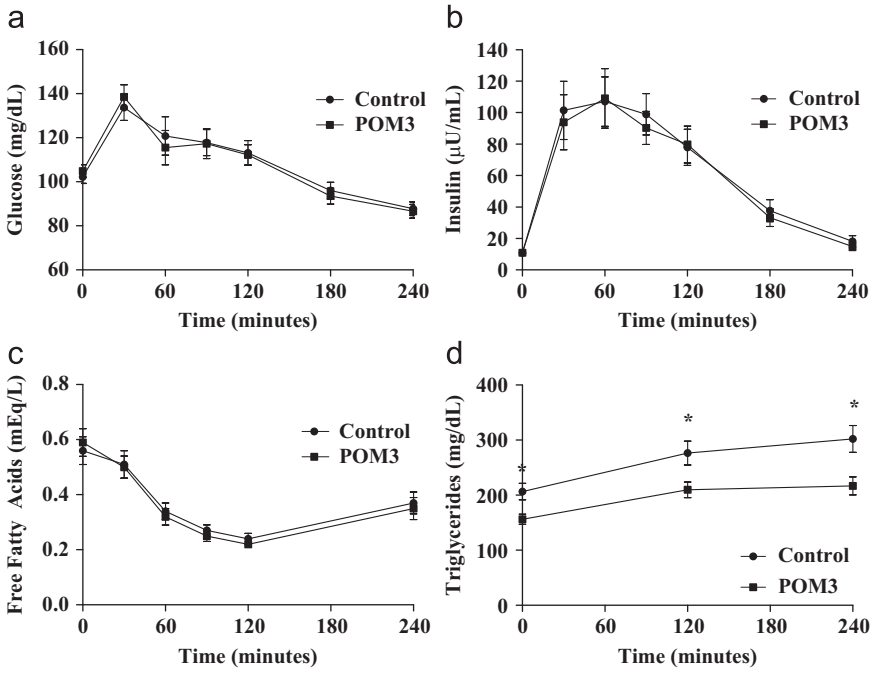

Fig. 1. *Panel A.* Mean ± SEM glucose concentrations during the liquid meal tolerance test. (There were no statistically significant differences between treatments at any timepoint). *Panel B.* Mean ± SEM insulin concentrations during the liquid meal tolerance test. (There were no statistically significant differences between treatments at any timepoint). *Panel C.* Mean ± SEM free fatty acid concentrations during the liquid meal tolerance test. (There were no statistically significant differences between treatments at any timepoint). *Panel D.* Mean ± SEM triglyceride concentrations during the liquid meal tolerance test. *$p < 0.0001$ between treatments at 0 min, $p=0.0005$ between treatments at 120 min, and $p=0.0012$ between treatments at 240 min. *Abbreviations*: POM3 = prescription omega-3-acid ethyl esters, SEM = standard error of the mean.

3.5. Clinical laboratory analyses and adverse events

Alkaline phosphatase was reduced from baseline by both POM3 and control treatments but the mean reduction with POM3 was statistically significantly greater than control (mean difference between treatments of −4.11 U/L, $p=0.038$). Total bilirubin was also reduced by both treatments, but the reduction with POM3 was not as large as that associated with control (mean difference between treatments of 0.05 mg/dL, $p=0.025$). Lymphocyte concentration ($10^3/\mu L$) was increased with both treatments, and the elevation associated with POM3 was statistically significantly greater than that with control (mean difference between treatments of 0.09, $p=0.038$). Other clinical laboratory chemistry and hematology measures were not statistically significantly

Table 3
Fasting and postprandial lipid variables following control and POM3 treatments and differences between treatments ($N=19$).[a]

Parameter (mg/dL)	Control	POM3	Difference POM3 − control	*P*-value[b]
	Mean (SEM)			
Fasting LDL-C	129.5 (7.4)	134.6 (6.7)	5.1 (3.8)	0.195
Fasting Non-HDL-C	170.7 (8.1)	165.9 (6.3)	−4.8 (4.8)	0.330
Fasting HDL-C	45.7 (2.8)	47.4 (3.3)	1.7 (1.1)	0.140
Fasting TC	216.5 (8.4)	213.3 (7.7)	−3.1 (4.7)	0.511
Fasting TG	206.5 (15.0)	156.3 (9.3)	−50.1 (9.5)	<0.001
Postprandial TG[c]	289.3 (22.5)	213.3 (14.7)	−76.1 (18.6)	<0.001

Abbreviations: HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, Non-HDL-C=non-high-density lipoprotein cholesterol, SEM=standard error of the mean, TC=total cholesterol, and TG=triglycerides.

[a] Data from the two treatment sequences (POM3/control and control/POM3) were pooled. Treatment period I was the average for values at weeks 4 and 6; treatment period II was the average for values at weeks 12 and 14 for variables that were measured at more than one visit during a treatment period.

[b] *P*-values are for treatment effect from the final analysis of variance model or analysis of covariance model for variables that were measured at baseline before treatment (baseline value as a covariate).

[c] Postprandial TG is for the average of the 240 min during the liquid meal tolerance test.

different between treatments. Mean body weight changed by <0.5 kg during the study and changes were not statistically significantly different between treatments. POM3 and control changes from baseline for systolic blood pressure (0.0 and −1.8 mmHg, respectively, $p=0.290$) and diastolic blood pressure (−1.4 and 0.5 mmHg, respectively, $p=0.153$) were not statistically significantly different.

Two (4.3%) subjects during the POM3 treatment and 7 (15.2%) during control experienced at least one adverse event ($p=0.070$). The majority of these adverse events were associated with the respiratory system (bronchitis, $n=1$ POM3; pharyngitis, $n=1$ control; sinusitis, $n=1$ control; and upper respiratory tract infection, $n=2$ control) and the liver and biliary system (elevated alanine aminotransferase, $n=3$ control and elevated aspartate aminotransferase, $n=1$ control). Three events during the control phase [elevated alanine aminotransferase ($n=2$) and gastroesophageal reflux ($n=1$)] were judged by the study physicians to be possibly related to treatment. All other events were judged as unlikely to be, or not related to, treatment. There were no serious adverse events during the study, and none of the adverse events was classified as severe. One subject discontinued the study prior to completion, citing adverse events of mild lower leg cramping and moderate headache during control treatment (both recorded by the investigator as possibly related to treatment) as the reason for leaving the study.

4. Discussion and conclusions

The results of the present study suggest that 4 g/d of POM3 (delivering 3.6 g/d of EPA+DHA) was associated with a modest reduction in insulin secretion, as indicated by a 13% lower value for the disposition index in hypertriglyceridemic subjects. Insulin sensitivity and the postprandial glucose responses from 0 to 120 and 0 to 240 min were unaltered by POM3 treatment. These results are consistent with those from Holness et al. [23] who showed in rats that replacement of 7% of energy in a high-fat diet with EPA+DHA did not alter insulin sensitivity, but shifted the relationship towards reduced insulin secretion for a given level of insulin sensitivity. The level of intake of EPA+DHA in the present study represents ~1.0% of energy, which is a fraction of the relative dose provided by Holness et al. [24] in rats. Compared with control, fasting insulin and HOMA%B were not significantly altered with POM3 treatment in the present study, and there was no evidence of clinically important deterioration from normal glucose tolerance, as indicated by postprandial glucose levels and fructosamine concentrations. Giacco and colleagues [25] found no effect of 3.6 g/d of omega-3 fatty acids from fish oil on insulin secretion (first phase insulin response to intravenous glucose) in healthy subjects. It is not certain why our results differed from theirs, although it is possible that the effects of EPA+DHA on insulin secretion are more apparent in the second phase of insulin secretion, or after absorption of glucose from the gastrointestinal tract, rather than through intravenous delivery.

Fasting glucose increased by 2.8 mg/dL ($p=0.062$) in the present trial, which, while not statistically significant, is consistent with the rise observed in other studies the authors have conducted with POM3 [1,26,27]. It is possible that a reduced sensitivity of pancreatic β-cells to glucose-stimulated insulin secretion and reduced suppression of hepatic glucose output by insulin [24] contribute to the rise in fasting glucose observed in studies of POM3. The present study showed no indication of a material change in HOMA%S, which reflects both hepatic and peripheral insulin sensitivity in the fasting state, but this may have been due to the relatively small number of subjects studied.

In a prior study we observed reduced fasting free fatty acids with 4 g/d POM3 plus 20 mg/d simvastatin compared with a corn oil control plus 20 mg/d of simvastatin [26], and hypothesized that reduced free fatty acids might improve insulin sensitivity in hypertriglyceridemic subjects. However, in the present study, neither fasting nor postprandial free fatty acids were reduced significantly during POM3 therapy, and the MISI was unaltered by POM3 treatment. These results are consistent with those of several investigators [25,28–30], but are in contrast to those of Mostad et al. [31] who found a statistically significant ($p=0.049$) reduction in insulin sensitivity in subjects with type 2 diabetes mellitus who received omega-3 polyunsaturated fatty acids from fish oil vs. a corn oil control. Given the small size of the effect in that study and the number of other investigations suggesting no change, the authors believe that the preponderance of evidence favors a neutral effect of EPA+DHA.

Fasting and postprandial TG levels were significantly reduced with POM3 vs. control by ~25% in the present investigation. These effects align with expectations based on results from numerous previous studies [32–36]. Although changes in other lipoprotein lipid parameters did not reach statistical significance, the directionalities and magnitudes of the differences between treatment conditions were consistent with those reported in previous trials [35,36]. POM3 treatment was well tolerated in the present study and no unanticipated safety concerns arose.

In contrast to most prior studies, this placebo-controlled crossover study enrolled hypertriglyceridemic subjects who, as a group, had moderate to high-risk for developing diabetes mellitus, which enhances the applicability of these results to the subset of subjects receiving POM3 for whom potential elevations in glucose would be of greatest concern. According to the clinical diabetes risk model published by Stern et al. [37], the mean 7.5-year risk for development of diabetes of the participants was 35%. A potential limitation of the trial was the relatively small sample size which was sufficient to rule out large effects, but insufficient to detect smaller changes that could still be clinically important. The relatively short length of the wash-out period may also be considered a potential limitation, however, the eight weeks between the end of the first treatment period and the outcome measurements for the second period should have been a sufficient time to establish a new steady state. Also, no statistical

evidence was present of carryover from the first to the second treatment period in sensitivity analyses.

In conclusion, the results from this trial demonstrated that POM3 treatment lowered fasting and postprandial TG and was associated with a small, but statistically significant reduction in the disposition index (13%), with no change in insulin sensitivity. These results support the hypothesis that POM3 modestly reduces pancreatic β-cell responsiveness to plasma glucose elevation, compared to a corn oil control, which may contribute to the rise in fasting glucose concentration sometimes observed with POM3 therapy.

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