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patient-oriented and epidemiological research

Effects of prescription niacin and omega-3 fatty acids on lipids and vascular function in metabolic syndrome: a randomized controlled trial[S]

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Abstract The metabolic syndrome includes both dyslipidemia and impaired vascular function. Because extended-release niacin (ERN) and prescription omega-3 acid ethyl-esters (P-OM3) independently improve these characteristics, we tested their effects in combination. Sixty metabolic syndrome subjects were randomized to 16 weeks of treatment on dual placebo, P-OM3 (4g/day), ERN (2 g/day), or combination in a double-blind trial. Lipoprotein subfractions and vascular endpoints were measured and tested using ANCOVA. ERN increased HDL cholesterol by 5.4 mg/dl from baseline ($P = 0.04$), decreased triglycerides (TG) by 39 mg/dl (−21%, $P = 0.003$), and decreased the augmentation index, which is a measure of vascular stiffness, by 3.5 units ($P = 0.04$). P-OM3 reduced TG by 26 mg/dl (−13%, $P = 0.04$). Combination treatment increased HDL cholesterol by 7.8 mg/dl ($P = 002$) and decreased TG by 72 mg/dl (−34%) but there was no improvement in vascular stiffness. Detailed analysis of lipoprotein subfractions revealed increased large, bouyant HDL_2 (3.3 mg/dl; $P = 0.002$) and decreased $VLDL_{1+2}$ (−32%; $P < 0.0001$), among subjects treated with combination therapy, that were not present with either therapy alone. ERN and P-OM3 alone improved characteristics of metabolic syndrome; however, whereas subjects on combination therapy did not have improved vascular stiffness, TG and HDL levels improved as did certain lipoprotein subfractions.—Shearer, G. C., J. V. Pottala, S. N. Hansen, V. Brandenburg, and W. S. Harris. **Effects of prescription niacin and omega-3 fatty acids on lipids and vascular function in metabolic syndrome: a randomized controlled trial.** ***J. Lipid Res.*** **2012.** 53: **2429–2435.**

Supplementary key words fish oil • niacin • metabolic syndrome • very low density lipoprotein • high density lipoprotein • arterial stiffness • augmentation index • eicosapentaenoic acid • docosahexaenoic acid

The metabolic syndrome afflicts approximately 25% of the US adult population (1) with a similar prevalence in other populations in rough proportion to their degree of 'Westernization'. Subjects with metabolic syndrome are at increased risk for stroke (2), coronary heart disease (CHD)-death, and death from any cause (3, 4). Metabolic syndrome is defined by central obesity, elevated triglyceride (TG) levels, decreased HDL cholesterol (HDL-C) levels, and mild elevations of glucose and blood pressure; numerous physiologic dysfunctions contribute to the overall pathology. For instance, elevated blood pressure is thought to be the result of dysfunctional endothelium-dependent vasodilation and progressive arterial stiffening (5). Also associated with the metabolic syndrome is a preponderance of small, dense LDL particles (6) and an increased thrombotic tendency (7). Although lifestyle changes (diet and exercise) can improve many of these conditions, pharmacotherapy is often needed to normalize individual components.

Because metabolic syndrome is comprised of multiple relatively mild disturbances instead of a single overt pathology, the best therapeutic strategy for managing it is still emerging. Elevated TG and reduced HDL are two of the three most prevalent factors in both younger men and women, and elevated TG is a primary contributor to the overall risk (8). The ideal intervention would safely and effectively address as many of the components of the syndrome as possible.

Niacin reduces serum TG and LDL-C and raises HDL-C (9). Further, niacin has been shown to reverse atherosclerosis (10) and reduce risk for CHD and mortality (11) [although the AIM-HIGH trial with niacin was stopped

This study was funded by the National Institutes of Health (5 R01 DK061486). Abbott (Niaspan) and GlaxoSmithKline (Lovaza) provided the drugs used in this study. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health or other granting agencies. G.C.S. received research support from GlaxoSmithKline. G.C.S. and W.S.H. received speakership honoraria from GlaxoSmithKline.

✤***Author's Choice***—*Final version full access.*

Manuscript received 10 November 2011 and in revised form 10 July 2012.

Published, JLR Papers in Press, August 14, 2012
DOI 10.1194/jlr.P022392

Abbreviations: AI, augmentation index; BMI, body mass indexCHD, coronary heart disease; ERN, extended-release niacin; HLD-C, HDL cholesterol; OMX, omega-3 index; P-OM3, prescription omega-3 acid ethyl-esters; RBC, red blood cell; RHI, reactive hyperemia index; TG, triglyceride; VAP, Vertical Auto Profile.

Clinical trial registration: clinicaltrials.gov (NCT00286234).

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[S] The online version of this article (available at http://www.jlr.org) contains supplementary data in the form of two tables and one figure.

early for inefficacy (12)] Prescription omega-3 acid ethyl esters (P-OM3) are also effective in reducing serum TG (13, 14) and have been shown to reduce risk and improve survival in the setting of CHD (15–17). Both agents have also been reported to improve vascular function (18, 19). Here, we sought to measure the effects of these two agents, separately and in combination, on lipid risk parameters and markers of vascular disease (e.g., endothelial dysfunction and arterial stiffness) in metabolic syndrome patients.

METHODS

Participants and study location

The study was conducted at Sanford Research/USD in cooperation with Sanford Clinic–Clinical Research Services in Sioux Falls, South Dakota. Subjects with metabolic syndrome were recruited by advertisements and from booths at local health fairs. Those expressing interest in participation were screened by a phone interview, and qualifiers were asked to attend a screening visit where informed consent was obtained. Blood pressure, morphometry, and a lipid panel were collected. Inclusion criteria were: age 40 to 69 years; BMI 25 to 40 kg/m^2; fasting TG, 150 to 750 mg/dl; HDL-C > 10 mg/dl; and the ratio of TG/HDL-C > 3.5. Exclusion criteria included: presence of other secondary causes of dyslipidemia or hyperglycemia such as hepatic, renal, thyroid, or other endocrine diseases; history of hypersensitivity to niacin or fish oils; history of gout, hepatitis, peptic ulcer, or cardiovascular disease; presence of diabetes mellitus; use of any dietary supplements providing more than 50 mg of niacin or 100 mg of fish oil omega-3 fatty acids (n-3 FAs); use of any herbal preparations or weight-loss products; use of any lipid-lowering drugs (other than statins) for at least four weeks prior to screening for the study; medically-required treatment with nitrates, calcium channel blockers, or adrenergic blocking agents; hemoglobin < 12 g/dl; LDL-C > 145 mg/dl; or known substance abuse. The protocol was approved by the Institutional Review Board at the University of South Dakota and informed consent was required prior to participation. The study was registered at clinicaltrials.gov (NCT00286234).

Study design

This was a randomized, double-blind, placebo-controlled clinical trial with a 2 × 2 factorial treatment design (Fig. 1). Group size was determined from a pilot study (20) and was originally powered to an alternative outcome (the rate of appearance of nonesterified FAs in the plasma). The power estimates from the pilot study for the lipid endpoints measured here are given in supplementary Table I; vascular data were not collected in the pilot study. Power to detect the main effects of each agent on the primary lipid endpoints was >80% except for that of P-OM3 on HDL-C and nonHDL-C. After initially qualifying for the study, subjects began a 6-week, diet-stabilization, dual-placebo, run-in phase (single-blind) in which noncompliant subjects (i.e., <80% compliant) would have potentially been identified and excluded (but none were). Those subjects completing the run-in phase were randomly assigned using permuted blocks of four (with stratification for gender) to 16 weeks of treatment to either dual placebo, extended-release niacin (ERN, Niaspan, Abbott Labs, 2g/d), P-OM3 (Lovaza, GlaxoSmithKline Pharmaceuticals, 4g/d), or the combination. To improve tolerance, ERN was titrated up over the first month by adding 500 mg to the daily dose each week, to achieve the final 2 g/d (Fig. 1). All subjects (placebo and active) were additionally asked to take aspirin (81 mg) prior to dinner to reduce flushing. In order to improve blinding to ERN, the ERN placebos contained 50 mg rapid-release niacin, which is enough to cause a mild flushing response. The study coordinator assigned each treatment a letter (A–D) and the biostatistician (J.V.P.) generated the randomization schedule using an algorithm as described above. The randomization schedule was then given to the staff at Sanford Clinic who enrolled each participant and blindly assigned them to their treatment group. Subjects were asked at 0, 8, and 16 weeks to report the previous week's flushing frequency and intensity.

Lipid and vascular data collection took place at weeks 0 and 16. Subjects were asked to fast for at least 8 h prior to each visit. Upon arriving at the dedicated study room, the digital tonometry test (below) was administered first (~40 minutes) followed by a blood draw for fasting lipids. Blood samples were drawn, plasma was separated within 30 min, and samples were stored at −70°C. Compliance to treatment was assessed by pill count for both treatments and also (for P-OM3 treatment) by changes in the omega-3 index (OMX), which is the red blood cell (RBC) FA weight percent of EPA and DHA. All subjects were >80% compliant by pill count. The efficacy of blinding was assessed by a questionnaire after the study ended.

Plasma lipids

Plasma lipids and lipoproteins for study eligibility were measured using standard hospital laboratory techniques, but for endpoint analysis (weeks 0 and 16), these were assessed by ultracentrifugation-based Vertical Auto Profile (VAP; Atherotech, Birmingham, AL). The correlation between the hospital and VAP methods for TG was 0.95 with a Deming regression slope (95% CI) = 1.02 (0.93, 1.12).

Digital tonometry

Reactive hyperemia index (RHI) was measured using an Endo-PAT2000 (Itamar Medical Ltd., Caesarea, Israel). The Endo-PAT uses pneumatic probes placed on the subject's fingertips to estimate pulsatile arterial volume and thus, changes in blood flow. Probes were placed on symmetrical fingertips, generally the index finger of each hand, a blood pressure cuff was loosely placed on the subject's dominant arm, and a baseline reading was obtained. After 3 min, the cuff was inflated to >300 mmHg to occlude blood flow for 5 min and then released. The RHI was obtained by comparing the increase in digital pulse volume in the occluded arm to that in the control arm per the method of Bonetti et al. (21). The Framingham RHI (fRHI), a different approach to analyzing the data than suggested by the manufacturer, was also determined (22). The Endo-PAT2000 also estimates the augmentation index (AI), which is a measure of arterial stiffness. It is defined as the proportion of central pulse pressure due to the late systolic peak, which is in turn attributed to the reflected pulse wave (23). All Endo-PAT measures were made by the same technician trained and certified by Itamar whose specialists reviewed all Endo-PAT tracings to confirm the quality of the data.

RBC FAs

RBC FA composition was measured to document compliance with P-OM3 and was analyzed by the HS-Omega-3 Index® methodology as previously described (24). Fatty acid methyl esters were generated from erythrocytes by acid *trans*-esterification and analyzed by gas chromatography using a GC2010 Gas Chromatograph (Shimadzu, Columbia, MD) equipped with a SP2560, 100-m column (Supelco, Bellefonte, PA) using hydrogen as carrier gas. FAs were identified by comparison with a standard mixture of FAs characteristic of erythrocytes and expressed as a percentage of total identified FAs after response factor correction.

Statistical methods

The changes in responses were modeled as the dependent variables, with adjustment for baseline values due to chance

differences related to the small sample size per group. Because the power to detect interactions was low (<30%), the groups were tested using a one-way ANCOVA with Dunnett adjustment for multiple comparisons to the placebo group. Residuals were examined for normality and homogeneity, and a natural log transformation was used as needed for improved model assumptions. The flushing response was examined using McNemar's exact test from baseline to 8 and 16 weeks for each treatment group. *P*-values < 0.05 were considered statistically significant. Analyses were performed using SAS® software (version 9.2; SAS Institute Inc., Cary, NC) and JMP® software (version 8.0.2.2; SAS Institute Inc., Cary, NC).

RESULTS

Participant flow and blinding

A diagram representing the flow of subjects through the study is given in **Fig. 1**. At the completion of the study, the majority (38; 63%) of subjects guessed they were taking ERN and 22 (37%) guessed they were on active P-OM3 treatment, but there was no difference between the guesses of subjects in the placebo or treatment groups (Fisher $P = 0.43$). Thus, the subjects were effectively blinded to treatment.

Baseline characteristics

Subjects were recruited into the study between August 2007 and October 2008. Seventy-one patients entered the single-blind placebo run-in phase. Three subjects did not return for the baseline visit and seven were lost to follow-up. One subject was included in the study but excluded from analysis when it was recognized that his BMI was greater than the inclusion criterion. One subject had to be excluded from the vascular endpoints due to prior surgery on one index finger that was not appreciated at screening, which prevented him from being tested by EndoPat, and EndoPat data from another was removed as an extreme outlier with problematic baseline measurement. Thus, the final sample included 58 subjects for vascular endpoints and 60 for lipid endpoints. Overall, the subjects demonstrated the characteristics of the metabolic syndrome including high TG, low HDL-C, elevated BMI including waist circumferences of 97 (92, 105) for females and 107 (98, 112) for males, mild hypertension, and mild hyperglycemia, indicating their condition was stable and did not change during the run-in phase (**Tables 1** and **2**). Except for nonHDL-C, subjects were similar at baseline for primary endpoints (Table 2). The

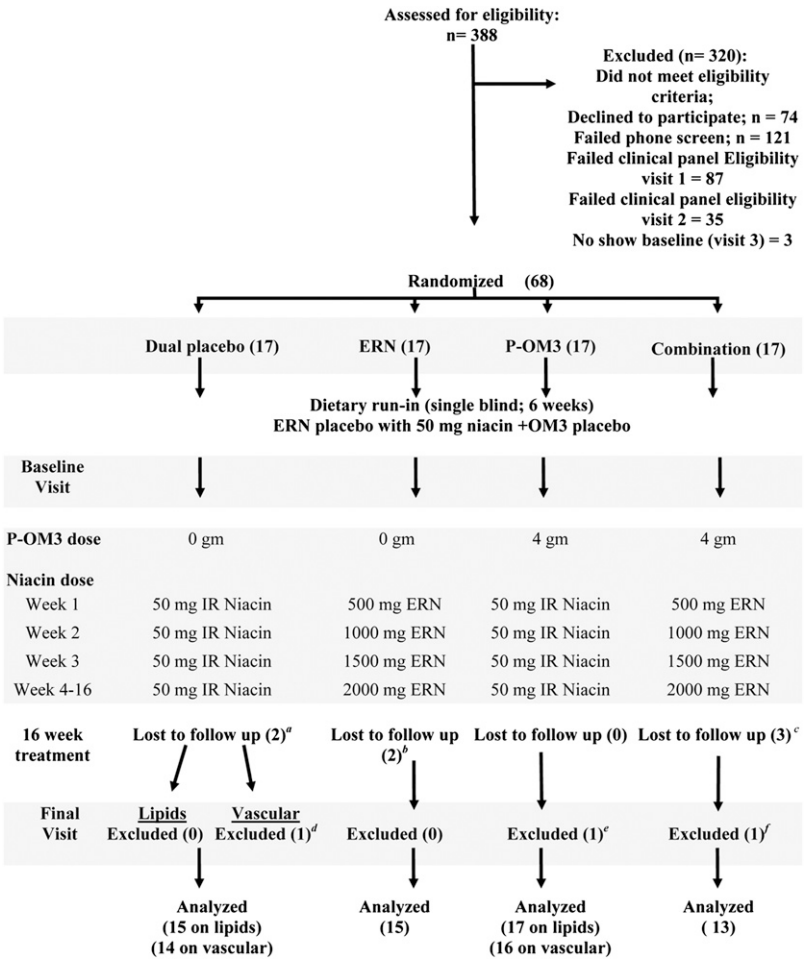

Fig. 1. Flow diagram for the study. [a]safety (elevated CPK), inadequate IV access; [b]rash, flushing; [c]inadequate IV access, time constraints, migraine headache; [d]without index finger, problematic RHI measurement at baseline; [e]error, subject should have been excluded for high BMI.

TABLE 1. Baseline characteristics by treatment group

Variable[a]	Dual Placebo (n = 15)	ERN (n = 15)	P-OM3 (n = 17)	Combination (n = 13)
Age (years)	45(39,65)[b]	49(41,56)	44(40,49)	48(44,54)
Sex male: n(%)	9(60%)	8(53%)	10(59%)	9(69%)
Current Smoker: n(%)	2(13%)	2(13%)	1(6%)	1(8%)
Resting Heart Rate (bpm)	68(60,76)	62(59,73)	72(63,78)	67(61,72)
BMI (kg/m^2)	30(28,33)	33(28,36)	34(32,36)	31(30,35)
Systolic BP (mm Hg)	124(121,132)	141(124,144)	133(130,139)	131(128,139)
Diastolic BP (mm Hg)	81(76,87)	81(74,89)	86(79,90)	82(80,85)
Mean Arterial Pressure (mm Hg)	96(93,102)	97(94,108)	102(96,106)	100(95,103)
Glucose (mmol/L)	5.5(4.9,5.8)[c]	5.4(5.1,5.7)	5.4(5.3,5.9)	5.8(5.3,6.1)
Insulin (uU/ml)	15(10,19)[c]	11(9,17)	11(5,16)	15(10,19)
Anti-hypertensive medication: n(%)	3(20%)	4(27%)	4(24%)	3(23%)
Statin use: n(%)	3(20%)	2(13%)	3(18%)	0(0%)

[a]Kruskal-Wallis test and Chi-squared test for continuous and categorical data, respectively, all $P > 0.05$.
[b]Median (Q1, Q3) unless otherwise indicated.
[c]n = 13 (2 invalid assays).

inclusion criteria used here were shown by McLaughlin et al. (25, 26) to be highly predictive of insulin resistance. The OMX increased significantly in the P-OM3 groups indicating good compliance with treatment (supplementary Fig. I).

Effects on lipid and lipoprotein levels

Table 2 reports the baseline levels for lipid and vascular endpoints along with details of the lipoprotein profile from the VAP analysis. **Table 3** reports the treatment effects adjusted for baseline. In order to satisfy test assumptions, TG and other indicated secondary endpoints were log-transformed, meaning that the effects of treatment are best interpreted as proportional instead of absolute changes; however, for simplicity, the absolute changes from baseline are also indicated. ERN increased HDL-C by 5.4 mg/dl, and reduced TG by 21% (39 mg/dl) and VLDL-C by 19% (5.3 mg/dl). The effect of P-OM3 was to reduce serum TG by 13% (26 mg/dl) and VLDL-C by 12% (3.5 mg/dl). Combination treatment increased HDL-C by 7.8 mg/dl, and decreased TG by 33% (72 mg/dl) and VLDL-C by 27% (8.9 mg/dl). The TG reduction with combination treatment was greater than P-OM3 alone but was not greater than ERN ($P = 0.09$).

Combination treatment had the greatest impact on lipoprotein subfractions, where improvements in particle density were observed. Subjects on combination therapy and on ERN had increased levels of small, dense HDL_3; however, only subjects on combination therapy received the benefit of increased larger, buoyant HDL_2. $VLDL_{1+2}$-C decreased more with combination treatment that with either monotherapy. Similar improvements were observed for LDL, which were shifted toward a greater proportion of large, buoyant particles reflected by an increased LDL_1 +

TABLE 2. Baseline values on lipid (N = 60) and vascular (N = 58) endpoints by treatment group

	Mean (SD)			
[mg/dL] unless otherwise indicated	Dual Placebo	ERN	P-OM3	Combination
Primary Endpoints				
Non HDL-Cholesterol (C)	151 (24)	178[a] (49)	144 (37)	177[a] (38)
HDL-C	40 (8)	44 (10)	43 (8)	40 (8)
Triglyceride	251 (174)	196 (65)	203 (72)	228 (82)
Augmentation Index (units)	2.6 (9.9)	3.9 (9.0)	3.8 (19.0)	0.9 (8.5)
Reactive Hyperemia Index (units)	1.99 (0.48)	1.55[b] (0.14)	1.55[b] (0.28)	1.58[b] (0.22)
Secondary Endpoints				
TG:HDL	6.8 (5.6)	4.6 (1.6)	4.9 (2.0)	5.8 (2.0)
Total-C	191 (28)	222[a,b] (54)	186 (40)	217 (41)
LDL-C	121 (23)	149[a,b] (44)	114 (35)	141[a] (29)
VLDL-C	30 (11)	29 (8)	29 (9)	36 (14)
VAP Lipoprotein Subfractions				
HDL_2-C	7.2 (2.1)	8.6 (2.7)	8.2 (3.2)	7.6 (2.7)
HDL_3-C	32.3 (6.4)	35.5 (7.0)	34.5 (5.2)	32.5 (6.0)
Small, Dense LDL-C (LDL_3+LDL_4)	65.8 (17.2)	72.7 (25.3)	57.6 (22.6)	78.5 (21.1)
Large Buoyant LDL-C (LDL_1+LDL_2)	33.3 (15.6)	50.3[a,b,c] (24.3)	33.8 (16.3)	33.3 (10.5)
Large Buoyant LDL-C [%]	33 (13)	40 (15)	37 (14)	30 (8)
Time to Peak LDL-C [Secs]	112 (5)	114 (4)	114 (7)	111 (3)
Lp(a)-C	7.3 (3.5)	6.0 (3.4)	4.9 (2.0)	6.7 (3.8)
IDL-C	14.9 (8.6)	20.1 (10.0)	18.1 (10.2)	22.5 (12.9)
Remnant Lipoproteins-C	29.9 (11.9)	35.1 (13.0)	34.2 (14.6)	41.8 (20.7)
$VLDL_{1+2}$-C	15.1 (7.7)	13.4 (5.4)	13.3 (4.7)	16.2 (6.5)
$VLDL_3$-C	14.9 (4.1)	15.0 (3.4)	16.1 (5.2)	19.2 (8.2)

Different at baseline (p-value <0.05) compared with: [a] P-OM3, [b] Dual Placebo, [c] Combination group.

TABLE 3. Treatment effects on lipid (N = 60) and vascular (N = 58) endpoints with ERN and P-OM3

[mg/dL] unless otherwise indicated	Least Squares Mean Changes, Adjusted for Baseline[a]			
	Dual Placebo	ERN	P-OM3	Combination
Primary Endpoints				
Non HDL-Cholesterol (C)	−5.9	−23*	−11	−7.3
HDL-C	0.2	5.4*	−0.8	7.8**
Triglyceride[b]	19 (8.8%)	−39 (−21%)**	−26 (−13%)*	−72 (−33%)***c
Augmentation Index (units)	3.1	−3.5*	3.8	−1.9
Reactive Hyperemia Index (units)	0.03	−0.04	0.08	0.14
Secondary Endpoints				
TG:HDL[b]	0.40 (8.2%)	−1.51 (−30%)***	−0.47 (−11%)	−2.38 (−44%)***
Total-C	−6.1	−17	−12	−0.3
LDL-C	−6.3	−17	−7.5	2.9
VLDL-C[b]	0.8 (2.8%)	−5.3 (−19%)**	−3.5 (−12%)*	−8.9 (−27%)***c
VAP Lipoprotein Subfractions				
HDL_2-C	0.4	1.7	0.3	3.3**
HDL_3-C	−0.3	3.8*	−1.1	4.4**
Small, Dense LDL-C (LDL_3+LDL_4)	−4.7	−18*	−6.7	−13
Large, Buoyant LDL-C (LDL_1+LDL_2)	0.2	2.9	2.3	20**
Large, Buoyant LDL-C [%]	0.9	9.2	2.2	16**
Time to Peak LDL-C [Secs]	−0.3	2.4*	0.6	4.5***
Lp(a)-C[b]	1.3 (20%)	0.8 (16%)	−0.1 (−1.1%)	1.3 (22%)
IDL-C	−2.1	−4.5	−3.6	−1.4
Remnant Lipoproteins-C	−2.3	−7.2	−5.4	−5.6
$VLDL_{1+2}$-C[b]	0.8 (5.6%)	−2.4 (−19%)**	−1.7 (−14%)*	−4.8 (−32%)***c,d
$VLDL_3$-C[b]	0.1 (1.0%)	−2.5 (−17%)**	−1.6 (−10%)	−4.0 (−22%)***

[a]Dunnett adjusted *p*-value compared with dual placebo, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.
[b]Natural-logarithm transformed for improved normality and homoscedasticity of residuals. The % change effect (shown in parenthesis) was converted back into original units by multiplying it by the groups' geometric mean at week 0.
[c]Different than P-OM3 group change, $P < 0.05$.
[d]Different than ERN group change, $P < 0.05$.

LDL_2 in subjects on combination therapy, and time to peak LDL in the combination group.

Effects on vascular function

Table 3 also shows the adjusted treatment effects on vascular function. ERN significantly reduced the AI, a marker of vascular stiffness, by 3.5 units. No effect on this measure was observed in either P-OM3 or combination treatments. No significant effect of either agent (singly or combined) was observed on endothelial function measured by RHI or on blood pressure (data not shown). The effects of treatment on flushing are shown in supplementary Table II. The expected flushing effect of niacin was noted with combination therapy at the 8 and 16 week visits; P-OM3 did not prevent it.

Effects on endpoints as a function of changes in RBC n-3 FAs

Robust biomarkers of tissue incorporation exist for P-OM3 therapy (i.e., OMX). Use of this marker allowed us to (potentially) reduce some heterogeneity in response to this agent. To determine the relations between change in major endpoints and n-3 FA incorporation into tissues, we repeated the analyses using the OMX_{final} / $OMX_{initial}$ (i.e., the percent changes in the OMX) instead of P-OM3 treatment assignment (**Fig. 2**). TG reductions were significantly related to the increase in OMX (similar results for EPA or DHA alone were also seen), and the model fit was improved using this metric. This demonstrates that the TG response to therapy was better explained by the change in tissue n-3 FA levels than it was by group assignment.

DISCUSSION

We compared the single and combined effects of ERN and P-OM3 on the dyslipidemia and vascular dysfunction characteristic of the metabolic syndrome. We found that ERN broadly improved dyslipidemia and vascular stiffness whereas P-OM3 improved hypertriglyceridemia. The combination had additive effects on TG beyond that of P-OM3 alone but not beyond ERN alone. Combination therapy

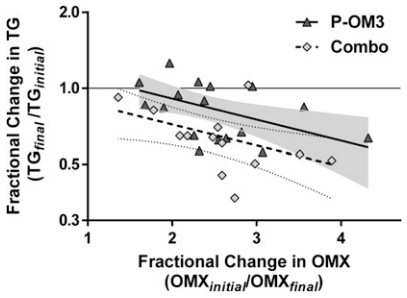

Fig. 2. Changes in triglycerides (TG) (including 95% CI bands) as a function of the change in omega-3 index (OMX) levels in the two groups that received P-OM3. For each group, the extent of TG lowering was in proportion to the relative increase in OMX (P = 02). The greater TG lowering with combination therapy is reflected in the step function between treatment groups (P = 0.001). The line at *y*=1 represents identity, or no change from baseline. The results are shown as the least-squares fit of the semi-log line, note the log-scale of the *y*-axis. Using the ratios of DHA and of EPA (as final/baseline) gave similar results. N = 30; because there was no change in OMX or TG levels for subjects on placebo P-OM3, they were not included in the analysis.

was the only group that had an increase in large, buoyant HDL. Combination treatment did not affect LDL-C levels but it did shift the LDL profile away from the more atherogenic, small, dense LDL particles toward the less atherogenic, large, buoyant particles. Considering all lipid and lipoprotein classes, subjects on combination therapy had the greatest improvements.

ERN had a profound effect across the lipoprotein spectrum. It increased HDL to a similar extent to that reported in the ARBITER 6-HALTS trial (10) where the increase was associated with reduced carotid intima-media thickness. Whereas ERN therapy alone increased HDL_3, combination therapy increased the abundance of the more atheroprotective HDL_2 particles. This is of particular interest because it suggests a qualitative improvement in HDL that is present only with both treatments.

One endpoint for which combination therapy was not better than the individual agents was LDL-C (and nonHDL-C and total-C). For these endpoints, the addition of P-OM3 essentially cancelled the LDL-C lowering effect of ERN. Increased LDL-C has been observed previously with interventions that improve TG metabolism (27); however, it has not been previously reported for this combination and needs to be confirmed. Regardless, we did not find that LDL-C was increased, and we found a shift in buoyancy that is consistent with less atherosclerotic risk (28). Kuvin et al. (29) report ERN increased the size and buoyancy of LDL, theoretically rendering them less atherogenic. This effect was large enough among subjects on combination therapy that it likely explains unchanged LDL-C. Although these endpoints are not components of metabolic syndrome dyslipidemia, they are well established components of cardiovascular risk.

Finally, ERN decreased TG and VLDL-C by roughly 20%. The 12% reduction in these markers by P-OM3 is on the low end of that observed in previous studies in hypertriglyceridemic patients (30), and it is smaller than the effect reported in more severe hypertriglyceridemia (−45%) (14) or in mild hypertriglyceridemia of statin-treated subjects who were not selected for metabolic syndrome (−29%) (13).

The primary finding on vascular endpoints was a reduction by ERN in the AI, which is a measure of vascular stiffness. Given the time allowed for adjusting to ERN (4 months), the gap between the time when the subjects took their final dose of ERN, and when AI was measured (several hours), it does not seem likely that the change in AI was an acute response to niacin-induced vasodilation; however, this cannot be ruled out.

Using the change in OMX (or EPA or DHA) instead of group assignment, the relations between TG and P-OM3 treatment were more clearly discerned. Subjects having the greatest increase in RBC n-3 FA levels also had the largest improvements in lipids, suggesting that tissue n-3 FA levels are more closely related to physiological parameters than group assignment. If true, titrating to a target tissue level may be more effective than giving a fixed dose (31).

Limitations

The sample size was relatively small and treatment duration short (i.e., months instead of years). Accordingly, although the study was well-powered to detect main effects on most lipid endpoints, there was little power to detect interactions. In other words, we were unlikely to detect effects of combination therapy beyond those that were simply additive. We also note that although we did not detect an effect of P-OM3 on nonHDL-C, our study was not powered to detect this endpoint and this should be considered in light of findings from larger studies (13). Despite randomization, baseline values for some endpoints (nonHDL-C and LDL-C in the P-OM3 group and RHI in the placebo group) were not uniform, due again to the small sample size. These imbalances may have confounded the results despite adjustment for baseline values.

In conclusion, combination therapy with ERN and POM-3 produced additive effects on serum TG and on HDL and LDL size and buoyancy. These changes are consistent with a decrease in risk for coronary events; however, further prospective trials are necessary to confirm this.

The authors acknowledge the assistance of Brenda Collison-Schmidt, Kristi Fillaus, Karla Riley, and Marilyn Ruhlman for their excellent study coordination and execution of study protocols.

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