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Marine Omega-3 Fatty Acid Intake: Associations with Cardiometabolic Risk and Response to Weight Loss Intervention in The Look AHEAD Study

Running title: Marine omega-3 fatty acid intake in Look AHEAD

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Objective- To examine usual marine omega-3 fatty acid (mO-3FA) intake in persons with diabetes, its association with adiposity, lipid and glucose control and its changes with behavioral lifestyle intervention for weight loss.

Research design and methods- Cross-sectional and one-year longitudinal analyses were performed on 2397 Look AHEAD (LA) participants. LA is a cardiovascular-outcome trial evaluating the effects of intensive lifestyle intervention (ILI) for weight loss in overweight/obese subjects with type 2 diabetes.

Results- Baseline mO-3FA intake was 162 ± 138 mg/day. It was inversely associated with triglycerides (B = –0.41, p <0.001) and weakly with HDL (B = 4.14, p = 0.050), after multiple covariate adjustment. One-year mO-3FA and fried/sandwich fish intake decreased with ILI (p <0.001).

Conclusions- mO-3FA intake in LA participants was low but associated favorably with lipids. These results encourage investigation on the potential benefits of increasing mO-3FA intake in lifestyle interventions for weight loss in individuals with diabetes.

Observational studies have suggested that mO-3FA intake may decrease coronary atherosclerosis progression in subjects with diabetes (1). However, only a fraction of participants in cardiovascular event studies have had diabetes. Concerns that high-dose mO-3FA may worsen glucose control have reduced enthusiasm for their use in diabetes (2). Little is known regarding usual dietary mO-3FA intake and its association with metabolic disturbances in diabetes, and much less about the effects of weight loss interventions on mO-3FA consumption.

RESEARCH DESIGN AND METHODS

2397 participants, corresponding to the first half of LA enrollees, completed the LA food frequency questionnaire (LA-FFQ) (3). LA is a multicenter randomized trial in overweight/obese persons with type 2 diabetes, investigating the effects of ILI-induced weight loss on cardiovascular morbidity and mortality. Eligibility required: BMI ≥25 kg/m^2 (≥27 if on insulin), age 45-76, hemoglobin A1c (HbA1c) <11%, blood pressure ≤160/100 mm Hg, and fasting triglycerides ≤600 mg/dl (4).

The LA-FFQ and its analysis were previously described (3). 8 line items inquire about seafood consumption. mO-3FA intake was estimated by adding eicosapentaenoic and docosahexaenoic acid (EPA, DHA) intake from the LA-FFQ.

Statistical analysis. The baseline association between mO-3FA intake and weight, BMI, waist circumference, HbA1c, fasting glucose and lipids was examined using multiple-variable linear regression. The final model included demographics, dietary variables, fitness (exercise capacity on graded exercise test) and class use of medications to control lipids and glucose. Comparisons between race/ethnicity groups were tested with ANCOVA. Differences in variable change at a year between ILI and the usual-care group, Diabetes, Support and Education (DSE), were analyzed with unpaired t-test and Chi-square. Data was available for each variable analyzed in ≥99% of participants. An $\alpha < 0.05$ indicated significance.

RESULTS

Participant baseline characteristics do not differ from those of the overall LA sample (5) with respect to gender, race/ethnicity, adiposity or fitness. Age criteria change during the second year of study recruitment resulted in a slightly younger age in our subgroup (See Online Appendix Table A1 which is available at http://care.diabetesjournals.org).

mO-3 FA intake and metabolic variables at baseline. Mean mO-3FA intake was 162 ± 138 mg/day (median 120 mg/day). Intake was ≤200 mg/day in 75% of LA participants and ≥1000 mg/day in only 1%, with significant race/ethnicity differences (Table 1). mO-3FA intake was inversely associated with triglycerides (log-transformed) ([illegible]1, *p* <0.001) and with a trend for increasing HDL ([illegible]= 4.14, *p* = 0.050), independently of multiple covariates (On-line Appendix, Table A2). No association was found between mO-3FA intake and cholesterol, non-HDL or LDL-cholesterol, or with markers of adiposity or glucose control (*p* >0.05). African Americans, who consumed the most mO-3FA, had the highest HDL-cholesterol and the lowest triglycerides.

mO-3 FA intake, HDL and triglyceride levels with ILI at a year. mO-3FA intake decreased with ILI but not with DSE at a year (*p* <0.001) (Table 1). When investigating changes in type of fish consumed, we found an ILI-induced decrease in fried/sandwich fish consumption (*p* <0.001) but not in lean or mO-3FA-rich fish. The small change in mO-3FA intake with ILI did not explain one-year changes in HDL and triglycerides.

CONCLUSION

LA offers a large sample of persons with diabetes in whom a validated tool was used to estimate usual mO-3FA intake. mO-3FA consumption was found to be very low. An intake of ≥1000 mg/ day is recommended for people with diabetes (6-8). Despite the low levels, mO-3FA consumption was associated with lower triglycerides and with a trend for higher HDL. The relationship between mO-3FA and each of HDL and triglycerides was independent of adiposity, fitness, lipid medications (including fibrates), glycemic control, and of dietary variables that impact lipid levels, such as carbohydrate, fiber, and saturated fat. Likewise, the intake of linolenic acid, a precursor of EPA and DHA, and of its metabolic competitor linoleic acid, did not alter the relationship between mO-3FA intake, HDL and triglycerides.

Contrary to reports with high-dose mO-3FA (9,10), we did not find an unfavorable association between mO-3FA consumption and LDL-cholesterol or glucose control. These findings encourage future outcome studies in persons with diabetes evaluating lower intakes of mO-3FA than those previously investigated. A large trial with EPA supplementation in high risk subjects found the greatest reduction in cardiovascular events in the subgroup with lower HDL and higher triglycerides (11), raising the possibility that mO-3FA may be of a particular benefit in persons with diabetes, who characteristically display this lipid profile. The race/ethnicity differences in mO-3FA consumption and the question of whether specific groups might specifically benefit from interventions that increase mO-3FA intake are worthy of further study.

The decrease in mO-3FA with ILI is not surprising given that the LA intervention was not targeted at increasing mO-3FA intake. The decrease in mO-3FA intake paralleled a reduction in fried/sandwich fish intake, which is considered favorable (12).

Our results should be interpreted with caution. LA did not evaluate supplement use and is subject to the limitations of information obtained by self-report (3). The favorable association between usual dietary mO-3FA intake and lipids at baseline encourages future research on the potential benefit of increasing consumption of mO-3FA, in addition to modifying fish type, when planning lifestyle interventions for weight loss in persons with diabetes.

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Table 1. Dietary intake of marine omega-3 fatty acids and fried fish, HDL and triglyceride levels at baseline and one year

	mO-3FA (mg/day)	HDL (mg/dl)	Triglycerides (mg/dl)	Subjects with Fried Fish/SF Intake ≥ 1/week (%)
Baseline				
Overall (n=2397)	162 (138)	43 (11.3)	186 (125.6)	
African American (n=331)	205 (186)*	48.2 (13.0)*	127.4 (99.8)*	
Caucasian (n=1552)	160 (130)	41.4 (10.7)	197.6 (127.01)	
Other (n=76)	156 (117)	45.0 (12.1)	156.7 (90.7)	
Hispanic (n=316)	152 (115)	42.4 (10.8)	191.7 (119.7)	
Native American (n=122)	98 (117)	40.9 (9.0)	192.7 (156.1)	
Longitudinal				
ILI (n=1211)				
Baseline	160 (145)	43 (11.2)	189 (127.4)	5.62
Change at One Year	- 20 (137) †	3.5 (7.1) †	-34.9 (11.5) †	-3.56 ‡
DSE (n=1186)				
Baseline	160 (129)	42 (11.3)	182 (123.6)	6.16
Change at One Year	0 (121)	1.4 (6.6)	-14.7 (98.7)	-0.93

mO-3FA: marine omega-3 fatty acids; SF: Sandwich fish; ILI: Intensive Lifestyle Intervention; DSE: Diabetes, Support and Education.
*Differences across race/ethnicity groups were tested by ANOVA after adjusting for age, gender and clinic site. African Americans had higher intake of mO-3FA, higher HDL and lower triglycerides when compared to Caucasians, Hispanics and with the other race/ethnicity group ($p < 0.05$ for all differences).
† Differences between ILI and DSE in variable change from baseline were evaluated using unpaired t-test. ILI participants had lower mO-3FA, higher HDL and lower triglycerides than those in DSE ($p<0.001$ for all differences).
‡ Differences between ILI and DSE in the proportion of subjects eating fried fish/SF ≥ 1/week were tested with Chi-Square. There was a greater decrease of fried fish/SF intake in ILI than in DSE ($p<0.001$). % of subjects eating lean fish >1/week increased by 5.54% with ILI and by 1.27% with DSE ($p=0.012$). Change in % subjects eating fish rich in mO-3FA did not differ between ILI and DSE at a year ($p=0.421$).