Dietary Intake of Eicosapentaenoic and Docosahexaenoic Acid and Diabetic Nephropathy: Cohort Analysis of the Diabetes Control and Complications Trial

CHEETIN C. LEE, MPHIL[1]
STEPHEN J. SHARP, MSC[1]
DEBORAH J. WEXLER, MD[2]
AMANDA I. ADLER, MD, PHD[1,3]

OBJECTIVE — To investigate the association between dietary n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) and the degree and development of albuminuria in type 1 diabetes.

RESEARCH DESIGN AND METHODS — We analyzed longitudinal data from 1,436 participants in the Diabetes Control and Complications Trial. We defined the average intake of eicosapentaenoic and docosahexaenoic acid from diet histories. Urinary albumin excretion rates (UAERs) were measured over 24 h; incident albuminuria was considered the first occurrence of an UAER >40 mg/24 h sustained for ≥1 year in normoalbuminuric individuals.

RESULTS — In a mean follow-up of 6.5 years, we observed a lower mean UAER (difference 22.7 mg/24 h [95% CI 1.6–43.8)]) in the top versus the bottom third of dietary n-3 LC-PUFAs, but we found no association with incident albuminuria.

CONCLUSIONS — Dietary n-3 LC-PUFAs appear inversely associated with the degree but not with the incidence of albuminuria in type 1 diabetes. These findings require further investigation in prospective studies.

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Fish provides the main dietary source of n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (1). Unlike for macrovascular complications, consumption of fish or fish oils and their associations to diabetic microvascular complications is less well studied. Trials of supplementation with n-3 LC-PUFAs on urinary albumin excretion rate (UAER) in diabetes exist but taken together did not show a significant effect (2). In cross-sectional analyses, fish consumption was associated with a lower risk of macroalbuminuria in type 2 diabetes (3). Whether n-3 LC-PUFAs accounted for these beneficial effects is not clear. No observational study has investigated the association between n-3 LC-PUFAs exclusively from dietary intake and diabetic nephropathy. In this study, we examined the association between dietary n-3 LC-PUFAs and incident albuminuria and changes in UAER over time in type 1 diabetes.

RESEARCH DESIGN AND METHODS

— The study population included 1,436 individuals aged 13 to 39 with type 1 diabetes who participated in the Diabetes Control and Complications Trial (DCCT) between 1983 and 1993 with baseline information on dietary n-3 LC-PUFAs (4). We defined dietary n-3 LC-PUFAs as the sum of the average intake of EPA and DHA in g/day obtained from a modified Burke-type diet history at baseline (5), which provided data on the nutrient composition of a diet instead of food quantities. UAER was measured annually as albumin excretion in a 4-h timed urine specimen. Incident albuminuria was defined as the first occurrence of UAER of >40 mg/24 h sustained for ≥1 year in normoalbuminuric individuals at baseline (6).

We used mixed-effects regression models with random intercepts to estimate the association between thirds of dietary n-3 LC-PUFAs and repeated measurements of UAER (7). We tested for interaction to assess whether this association differed between the primary prevention and the secondary intervention cohorts or between treatment groups. We used proportional hazards regression models to estimate the association between dietary n-3 LC-PUFAs and incident albuminuria. The data for this analysis came from a public domain (8).

RESULTS

— Among the 1,362 normoalbuminuric participants at baseline, 95 people developed albuminuria in a mean follow-up of 6.5 years. Participants with dietary n-3 LC-PUFAs in the upper third were more likely to be male, older, consume alcohol, use dietary supplements, plus have higher BMI and intake of energy and protein but lower UAER, versus participants in the lowest third of intake.

In unadjusted mixed-effects regression analyses, the mean UAER was 28.1 mg/24 h (95% CI 6.1–50.0, $P = 0.01$) lower in participants, comparing the top with the bottom third of dietary n-3 LC-PUFAs. In adjusted analyses, the difference in mean UAER narrowed to 22.7 mg/24 h (1.6–43.8, $P = 0.04$).

We observed a significant interaction between dietary n-3 LC-PUFAs and treatment groups ($P = 0.005$) and a borderline significant interaction by cohort ($P = 0.06$) for the difference in mean UAER. In adjusted stratified analyses, the mean UAER was 40.2 mg/24 h (95% CI 1.3–

From the [1]Medical Research Council Epidemiology Unit, Institute of Metabolic Science, Cambridge, U.K.; the [2]Massachusetts General Hospital Diabetes Center and Harvard Medical School, Boston, Massachusetts; and the [3]Wolfson Diabetes and Endocrine Clinic, Addenbrooke's Hospital, Institute of Metabolic Science, Cambridge, U.K.
Corresponding author: Amanda I. Adler, amanda.adler@addenbrookes.nhs.uk.
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Table 1—*Estimated difference in mean UAER in mg/24 h§ (95% CI) comparing the middle or the upper third of the dietary n-3 LC-PUFA distribution with the lowest third by treatment randomization and cohort*

Exposures	Distribution of dietary n-3 LC-PUFAs: Middle vs. lowest thirds*	Upper vs. lowest thirds*	*P*†
	Conventional treatment (n = 727)		
Unadjusted model	−54.7 (−94.1 to −15.2)¶	−51.6 (−91.4 to −11.8)	0.01
Adjusted model	−55.1 (−92.4 to −17.9)	−40.2 (−79.2 to −1.3)	0.04
	Intensive treatment (n = 709)		
Unadjusted model	−3.3 (−22.0 to 15.3)	−3.9 (−21.9 to 14.0)	0.7
Adjusted model	7.9 (−7.9 to 23.6)	−1.1 (−16.8 to 14.5)	0.9
	Primary prevention cohort (n = 724)		
Unadjusted model	−4.4 (−17.2 to 8.3)	−3.2 (−15.3 to 9.0)	0.6
Adjusted model	−3.4 (−16.3 to 9.4)	2.5 (−10.2 to 15.1)	0.7
	Secondary intervention cohort (n = 712)		
Unadjusted model	−53.8 (−95.4 to −12.3)	−49.1 (−91.7 to −6.6)	0.02
Adjusted model	−38.2 (−76.5 to −0.2)	−45.5 (−86.2 to −4.8)	0.03

Adjusted for age, sex, duration of follow-up, baseline variables (duration of diabetes, systolic blood pressure, creatinine clearance, UAER‡, serum triglyceride, BMI), A1C at year 1 follow-up, smoking, alcohol intake, exercise, use of dietary supplements, energy intake, and protein intake. §Difference in mean UAER (mg/24 h) was calculated by modeling the repeated measurements of UAER over the 9-year study period as an outcome in a mixed-effects regression model with random intercepts allowing for the correlation of repeated measures of the same individual. ¶The negative values reflect that the middle and upper third of dietary n-3 LC-PUFAs deteriorated less than the reference group (lowest third). *Reference group. †*P* is for a linear trend across thirds of the distribution of dietary n-3 LC-PUFAs. ‡Baseline UAER is defined as the average of UAER between year 0 and year 1.

79.2) lower in the conventional (vs. intensive) treatment group and was 45.5 mg/24 h (4.8–86.2) lower in the secondary intervention (vs. primary prevention) cohort, comparing extreme thirds of dietary n-3 LC-PUFAs (Table 1). We found no significant associations between dietary n-3 LC-PUFAs and incident albuminuria in unadjusted (hazard ratio [HR] 0.76 [95% CI 0.47–1.23]) or adjusted proportional hazard regression analyses (1.19 [0.72–2.00]).

CONCLUSIONS — In this cohort, consumption of dietary n-3 LC-PUFAs was associated with a slower deterioration of albumin excretion, but not with incident albuminuria in type 1 diabetes. We observed an association only in the conventional treatment group, which may reflect a chance finding or intensive glycemic control may obscure an effect of n-3 LC-PUFAs on albuminuria (6). Dietary counseling is unlikely to have accounted for this, since it was not focused on specific food choices (4). In further support, we observed no difference between treatment groups in n-3 LC-PUFAs consumed per kcal at baseline and at year 2 of follow-up. If dietary n-3 LC-PUFAs improves albuminuria, the effect may differ by level of glycemia. We observed that a higher intake of n-3 LC-PUFAs was associated with lower levels of UAER only in participants with values of A1C above the median (7.7%) (data not shown). Inflammation perhaps accounts for this, since advanced glycated end products activate nuclear factor-κB (NF-κB), which stimulates production of chemokine monocyte chemoattractant protein (MCP)-1 (9). As support, n-3 LC-PUFAs decrease lipopolysaccharide-induced NF-κB activation and MCP-1 expression in human renal tubular cells (10).

We show that dietary n-3 LC-PUFAs are associated with a slower deterioration of UAER only in the secondary intervention cohort. We have previously reported an inverse association between fish consumption and macroalbuminuria—but not microalbuminuria—in type 2 diabetes (3). Urinary MCP-1 is higher in macroalbuminuric diabetic patients than in those with normoalbuminuria or microalbuminuria (11). If dietary n-3 LC-PUFAs decrease UAER via anti-inflammatory mechanisms, one might expect the association to be greater in more advanced stages of nephropathy. This may also explain, in part, why dietary n-3 LC-PUFAs are not associated with incident albuminuria.

The strengths of the DCCT include its design and repeated measurements of UAER. Because of missing values during follow-up, we confined our analyses to dietary data at baseline, a decision unlikely to have biased our results given that the Burke-type diet history is highly reproducible (12). We did not have information on plasma n-3 LC-PUFAs, an objective biomarker of fish consumption (13). However, the use of the Burke-type diet history increases the validity of our measurement of exposure. We observed no change in the results when restricting data to the first 4 years of follow-up with few missing values of UAER. We had no information on the use of ACE inhibitors, which we assume few participants took before 1993.

The current study provides a basis for further prospective studies that examine the effects of dietary n-3 LC-PUFAs on albuminuria, measuring biomarkers including plasma n-3 LC-PUFAs, and exploring potential mechanisms of inflammation. At present, we recommend that clinicians promote current guidance on fish consumption of two portions per week (14).

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